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9th Leipzig Research Festival for Life Sciences

17. Dezember 2010

Veranstalter:

Medizinische Fakultät der Universität Leipzig

Fakultät für Biowissenschaften, Pharmazie und Psychologie der Universität Leipzig

Interdisziplinäres Zentrum für Klinische Forschung (IZKF) der Universität Leipzig

Translational Centre for Regenerative Medicine (TRM-Leipzig)

Impressum:

Konzeption / Organisation:	Prof. Dr. J. Thiery Prof. Dr. A. Beck-Sickinger, Prof. Dr. T. Arendt
Lektorat:	K. Duczek / I. Malerba
Layout / Satz:	K. Plath
Titelbild:	N. Sträter und A. Beck-Sickinger
Auflage:	420 Exemplare
ISBN:	978-3-9810760-6-6

Inhaltsverzeichnis

Ort der Veranstaltung:
Foyer Max-Bürger-Forschungszentrum
Johannisallee 30 · 04103 Leipzig

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Für die Unterstützung der Veranstaltung danken wir:

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Medizinische Fakultät der Universität Leipzig

Bundesministerium für Bildung und Forschung (BMBF)

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LIFE – Leipziger Forschungszentrum für Zivilisationserkrankungen

ICCAS – Innovation Center Computer Assisted Surgery

Vorwort

Liebe Kolleginnen und Kollegen, liebe Gäste,
wir begrüßen Sie sehr herzlich zu unserem neunten *Leipziger Research Festival of Life Sciences* der Universität Leipzig. Die jährliche wissenschaftliche Leistungsschau gibt allen jungen »Life Science« Wissenschaftlern und Ärzten aus der Universitätsregion die Möglichkeit, ihre neuesten Forschungsergebnisse in einer öffentlichen »Wissenschaftswerkstatt« zu präsentieren. Die hohe Zahl von Abstracteinsendungen unterstreicht die Attraktivität dieses weit über die Fächergrenzen reichenden wissenschaftlichen Kommunikationsforums. Der vorliegende Abstract-Band soll auch der interessierten Öffentlichkeit, der Politik und Industrieunternehmen dienen, die facettenreiche Aktivität und die Erfolge der Leipziger Wissenschaftslandschaft gerade im Bereich »Life Science« und der gesamten Medizin kennen zu lernen. Der Band ist mit Stichpunkten zur Forschungskompetenz und email-Verweisen zugleich ein wissenschaftliches »who is who«, um schnelle Problemlösungen durch Zusammenarbeit »next door« zu erleichtern.
Mit besonderer Wertschätzung des wissenschaftlichen Nachwuchses werden auch in diesem Jahr die besten Posterpräsentationen mit den renommierten Forschungspreisen des *Research Festivals Leipzig* ausgezeichnet.
Wir werden in diesem Jahr auch den kompetitiv eingeworbenen Forschungsverbünden in den Lebenswissenschaften an der Universität Leipzig einen besonderen Raum geben, um Vorhaben und Ergebnisse im Rahmen der Landesexzellenzinitiative und Leipziger Forschungszentrums für Zivilisationserkrankungen: LIFE, des Integrierten Forschungs- und Behandlungszentrums: IFB Adipositas Erkrankungen, 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 diesem 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

Erhebung von Blutrichtwerten beim Weißbüschelaffen (Callithrix jacchus)

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Weißbüschelaffen sind unter anderem ein geeignetes Tiermodell für toxikologische, kognitive und Fertilitätsstudien. Es existiert jedoch wenig Information über die klinisch-chemischen Parameter, um ihren Gesundheitsstatus einzuschätzen. Deshalb war das Ziel der vorliegenden Studie, Richtwerte für Blutbild, klinische Chemie und Lipidparameter zu erstellen. Dazu wurden 54 adulte Weißbüschelaffen (28 weibliche, 26 männliche) mit standardisierter Haltung und Fütterung untersucht. Die Blutabnahme erfolgte an nüchternen Tieren mit anschließender Analyse. Dabei zeigte sich, dass alle Parameter der klinischen Chemie für männliche und weibliche Tiere ähnlich sind, bis auf das Gesamt- und LDL- Cholesterol, mittleres Erythrozytenvolumen (MCV) und mittleres Hämoglobin pro Erythrozyt (MCH). Männliche Weißbüschelaffen haben einen signifikant höheren Gesamtcholesterol- (159,62 ± 23,85 mg/dl; p=0,009) und LDL-Cholesterolspiegel (91,18 ± 9,84 mg/dl; p=0,008) als weibliche Weißbüschelaffen (Gesamtcholesterol 136,79 ± 30,03 mg/dl; LDL-Cholesterol 80,67 ± 19,13 mg/dl). Weiterhin haben männliche Tiere sowohl ein signifikant niedrigeres MCV (67,78 ± 7,64 fl; p=0,041) als auch ein signifikant niedrigeres MCH (1,37 ± 0,09 fmol; p=0,031) als weibliche Tiere (MCV 70,60 ± 3,96 fl; MCH 1,42 ± 0,07 fmol).
Somit konnten wir Richtwerte für Blutbild, klinische Chemie und Lipidparameter des Weißbüschelaffen entwickeln, bei denen es interessanterweise Geschlechtsunterschiede gibt, die im Tierexperiment Berücksichtigung finden müssen.

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POSTER 2

Structure and function of a novel dienelactone hydrolase

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Fluoroaromatic compounds are widely used as pesticides or pharmaceuticals and well known environmental pollutants. The bacterium *Cupriavidus necator* is able to degrade such compounds via a modified variant of the ß-ketoadipate pathway. One of the key enzymes is the *trans*-dienelactone hydrolase (t-DLH) which degrades (fluoro)dienelactone leading to maleylacetate. The *t*-DLH from C. necator is a monomeric enzyme with a molecular weight of approximately 38 kDa. The enzyme shows no significant similarity to other known dienelactone hydrolases. Furthermore C. *necator* *t*-DLH shows activity only in the presence of divalent cations like Mn^{2+} or Mg^{2+}.
The gene of *t*-DLH was cloned expressed in *E.coli*. The protein was purified to at least 90 % homogenity. The wildtype was subjected to crystallization trials using sparse matrix screens. Suitable crystallization conditions could not be identified for this variant. Mutants designed based on the principle of surface entropy reduction were created and purified. Crystals, suitable for diffraction experiments, could be obtained for a double mutant. The phase problem was solved using MIRAS and a model of the enzyme was built and the metal center was assigned. We currently try to get a complex structure to study the reaction mechanism of this new class of dienelactone hydrolases.

Assoziation: PbF III

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POSTER 3

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

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G protein-coupled receptors (GPCRs) are membrane spanning proteins, which represent very important drug targets. For any pharmacological interference, detailed knowledge about the structure and dynamics of the molecules are essential, in particular those structural changes are relevant that occur upon ligand binding to the receptor. Here, we have studied the neuropeptide Y receptor type 2 (Y_2R), which belongs to the class A of GPCRs and has a wide variety in function.
We are able to produce large amounts (35 mg/l minimal media) of the receptor in a prokaryotic expression system as inclusion bodies. These protein aggregates were isolated, solubilized in SDS-micelles and purified. Subsequently, the receptor was refolded into its functional state. Our aim is to investigate ligand-specific conformational changes of the receptor by NMR spectroscopy. Therefore, we used the reductive methylation of lysine residues to introduce ^{13}C-methyl groups. Due to their favorable relaxation properties, these methyl groups allow for sensitive NMR-measurements. We detected ^{1}H-^{13}C HSQC NMR spectra, which provide some resolved NMR signals of the respective methyl groups. Chemical shift changes of some signals are observable, which are induced by ligand binding. These chemical shift changes could be related to alterations of salt bridges or ring current effects that occur due to structural changes induced by ligand binding. We are currently working on the assignment of the residues using site-directed mutagenesis.
A very astonishing side effect is that the methylated receptor shows a dramatic increase in the stability.

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POSTER 4

Rapid oxysterol profiling by liquid chromatography-triple quadrupole tandem mass spectrometry

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Oxysterols are oxygenated derivates of cholesterol which can be formed both enzymatically and non-enzymatically. A number of pathophysiological effects in atherogenesis and inflammation are attributed to cholesterol oxidized products. The analysis of free and esterified oxysterols is hampered by low physiological concentrations (approximately 0.01-0.1 μmol/L plasma) and by the susceptibility to in-vitro autoxidation of cholesterol, producing artifactual oxysterols. The aim of our study is to develop a rapid, reliable method for the simultaneous quantification of enzymatically and non-enzymatically derived oxysterols in human plasma and lipoprotein fractions.
An API 5500 QTrap® (AB SCIEX) with atmospheric pressure chemical ionization and multiple reaction monitoring in positive ionization mode was applied. Fast chromatography of oxysterol isomer separation was performed using a monolithic high performance liquid chromatography column RP-18e Chromolith (Merck, Germany). Three sample preparation strategies were compared (with and without sample hydrolysis) to determine oxysterols and cholesterol: protein precipitation and dilution, solid-phase extraction (SPE), and liquid-liquid extraction.
In our LC-MS/MS method we could analyse 6 oxysterols in 6 min at a flow-rate of 1 ml/min. Comparing the sample preparation strategies, SPE from 20 μL low density lipoprotein or 200 μL plasma without sample hydrolysis was advantageous to prevent cholesterol autoxidation. Further experiments are necessary to investigate recovery, reproducibility and accuracy.

Funding: life

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POSTER 5

Quantitative profiling of arachidonic acid metabolism by fast chromatography combined with hybrid triple quadrupole/linear ion trap mass spectrometry

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Objective: Eicosanoids, enzymatically derived arachidonic acid (AA) products, play important functional roles in inflammation, cellular proliferation, and intracellular signaling. Isoprostanes, the non-enzymatically formed metabolites, are linked to oxidative stress. Our aim was to develop a rapid profiling method for quantification of AA metabolites in plasma by combining ultra high performance liquid chromatography (UHPLC) and hybrid triple quadrupole/linear ion trap mass spectrometry (QTrap MS).
Method: Plasma samples (200 μL) were processed by protein precipitation and off-line solid phase extraction (SPE). UHPLC separation was achieved on a Kinetex C-18 UHPLC column with a Shimadzu Prominence UFLC system. MS analysis was performed for 50 analytes on 4000/5500 QTrap® instruments using multiple reaction monitoring (MRM).
Results: The application of a 5500QT® instrument resulted in an increase of sensitivity (x 10-15), reaching the pg/mL concentration range. By use of the UHPLC column the analysis time was reduced to 8 min and chromatographic resolution could be improved for the separation of regioisomers (e.g. PGE_2/PGD_2). Additionally, the sensitivity could be improved for all analytes by factor 2 compared to a regular C-18 column. With this method we were able to detect two cyclooxygenase, one CYP450 epoxygenase, and three lipoxygenase pathway metabolites in plasma of healthy volunteers.
Conclusion: We present a fast LC-QTrap MS method for the profiling of AA metabolites for clinical studies.

Funding: life

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POSTER 6

Protein detection using lanthanide time-resolved luminescence-based immunoassays and dendritic chelating agents

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The development of sensitive and specific assays for proteins is a major challenge for pharmaceutical research and is crucial for early diagnosis and treatment of diseases. Lanthanide-based luminescent dyes are particularly attractive candidates for such assays due to their large Stokes' shifts, narrow emission peaks and extremely long luminescence lifetimes. This latter feature allows the lanthanide luminescence to be measured after the background signal has decayed, greatly increasing assay sensitivity.

We will present the synthesis of a novel dendrimer-based compound bearing metal-chelating groups on the surface along with biotin moieties to allow conjugation of the dendrimer to antibodies via the biotin-streptavidin interaction. Incubation with europium(III) led to coordination of the lanthanide ion by the streptavidin-dendrimer complex. Subsequent addition of a lanthanide-chelating enhancement solution liberated the bound europium and formed a highly luminescent complex in solution allowing measurement by time-resolved luminescence.

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POSTER 7

Structural Investigations of the Interaction of Interleukin-8 with Components of the Extracellular Matrix using NMR Methods

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Glycosaminoglycans (GAGs) are important components of the extracellular matrix that play a crucial role in a variety of cell-cell and cell-matrix interactions. Some of them are known to be involved in the binding and regulation of distinct proteins like chemokines and growth factors. Hence, for the development of artificial matrices the identification of potential binding sites of regulatory proteins is of particular interest.
Because of the ability of the cytokine interleukin-8 (IL-8) to induce inflammation by recruiting and activation of neutrophils, the interaction of IL-8 with GAGs plays a key role in healing processes.
To study this interaction, large amounts of ^{15}N-labeled IL-8 (65 mg/l) were produced in a prokaryotic expressions system. After isolation and purification of the protein, detailed structure and binding analyzes were done using solution NMR spectroscopy.
At first, a ^{1}H-^{15}N HSQC spectrum of IL-8 was recorded, in which each single peak corresponds to a certain amino acid of the protein. With the help of further two dimensional ^{1}H-^{1}H TOCSY and NOESY NMR experiments, full resonance assignment was achieved.
To study the interaction between IL-8 and hyaluronic acid (HA) as well as chondroitin-4-sulphate (C4S) as hexasaccharides, titration studies were done by recording HSQC spectra in the presence of varying GAG concentrations. Changes in the chemical shifts induced by ligand binding can be used to identify the interacting amino acids and to calculate K_D values.
In the presence of C4S several significant chemical shift changes were found, whereas HA shows no interaction with IL-8.

Assoziation: PbF III

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POSTER 8

Lactate profiling of breast cancer cell cultures using GC-MS analysis

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Lactate is a metabolite of anaerobic glycolysis. Cancer cells exhibit an increased rate of glycolysis even under aerobic conditions because they immediately require energy for their enhanced proliferation. The formed lactate is released into the extracellular space, which creates an acidic microenvironment. It is assumed that there is a correlation between lactate and tumor growth and metastasis. For this reason we addressed valid quantitation of lactate in human breast cancer cells using GCMS with minimal sample preparation.The method included methanolic extraction of frozen cell pellets, subsequent derivatization of polar compounds via silylation and, finally, analysis by GC-MS. We found the silylating reagents of different manufacturers to be contaminated with bis(trimethylsilyl) lactate, which is a problem to proper quantitation of lactate with GC-MS after silylation. Within this context, we found the working range of the GC-MS method for lactate was significantly limited to a concentration range of two orders of magnitude. We determined the precision of the GC-MS measurement from injection on, the precision including the extraction and cell matrix effects, the precision including the derivatization step, and the precision over the whole procedure from methanolic extraction. The accuracy was determined by comparing the results of the GC-MS with a reference method using an enzymatic assay. Finally, the method was applied to assess lactate concentration patterns of five different breast cancer cell lines in comparison to the measured pH-value of the corresponding cultivation medium.

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POSTER 9

Sources of variation in metabolite analysis of adherent growing cells

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Investigations on adherent-growing cells are challenging because cell sampling is difficult and routine protocols are not readily applicable. Numerous reports are indicative that proper sampling for multi-selective analyses is expected to be particularly difficult since such protocols envisage non-selective determination of compounds including those that may undergo rapid modification in vivo. Every biological matrix might impact analysis differently and needs to be validated for each analytical method. We set out to investigate the handling of the model cell line MCF-7 using GCMS metabolite profiling.
Metabolite profiling was used to assess robustness of different sample preparation protocols. 191 metabolites identified with the Golm Metabolome Library and 90 abundant unknown peaks were compiled in a customer library and included in further evaluation. Different extraction protocols, harvesting methods and further sample preparation details such as the use of phosphate-buffered saline (PBS) for trypsinization and normalization to dry weight instead of cell number were compared with each other. Analytical parameter such as working range, analytical precision and biological variance were determined for the methanolic extraction protocol.

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POSTER 10

Reproduzierbare Modellierung von acetabulären Knochendefekten nach D'Antonio am Finite-Elemente-Modell des Beckens

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EINLEITUNG: In der Hüftrevisionsendoprothetik bestimmt die Knochendefektsituation die Auswahl der Implantate und die Wahl der Verankerungselemente. In der Literatur finden sich zahlreiche klinische Defektklassifikationen. FEM-Studien zur Vorhersage der erreichbaren Verankerungsstabilität von Hüftrevisionsimplantaten berücksichtigen jedoch bisher noch keine Knochendefekte. Ziel dieser Arbeit ist es, eine reproduzierbare Beschreibung von realistischen Knochendefektsituationen für die Computermodellierung zu formulieren.
METHODIK: Als Grundlage für die Defektmodellierung wird die Klassifizierung nach D'Antonio herangezogen. Ausgehend von einem Geometrie-Datensatz eines gesunden Beckenknochens wird anhand von anatomischen Landmarken ein Kugelkoordinatensystem in das hemisphärische Acetabulum gelegt. Die Knochendefekte werden als Subtraktion eines oder mehrerer Kugelvolumen vom intakten Beckenknochen modelliert.
ERGEBNISSE: Das Defektmodell kann über die Angabe von vier Parametern je Subtraktionsvolumen reproduzierbar im Beckenknochen positioniert werden. Am Acetabulum häufig auftretende Defekttypen nach D'Antonio werden als 3D-CAD-Modelle vorgestellt. Diesen Modellansichten werden Bilder von Defekten an anatomischen Knochenpräparaten gegenübergestellt.
DISKUSSION: Mit der hier beschriebenen Methode können beliebige Knochendefekte reproduzierbar modelliert und beschrieben werden, mit der Einschränkung, dass im Defektareal keine verbleibenden Kontaktinseln vorhanden sind. Reale Knochendefekte haben eine stark zerklüftete Oberfläche. Dies wird bei der FEM-Modellierung durch die Wahl der Kontaktparameter berücksichtigt.

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POSTER 11

Einfluss der Belastungen beim Aufstehen aus verschiedenen Sitzhöhen auf die postoperative Implantatstabilität in der Hüftendoprothetik

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EINLEITUNG: Beim Einwachsen eines Press-Fit-Implantates sollten die Mikrobewegungen im acetabulären Implantat-Knochen-Interface die in der Literatur angegebenen Grenzwerte nicht überschreiten. In Arbeiten zur Stabilität von künstlichen Hüftimplantaten mit Hilfe der Finite-Elemente-Methode (FEM) wurden als Randbedingungen bisher keine Muskelkräfte berücksichtigt. Ziel dieser Studie ist es, die Auswirkungen von Muskelkräften beim Aufstehen aus drei verschiedenen Sitzhöhen auf die Höhe der Mikrobewegungen zu untersuchen.
METHODIK: In der MKS-Software AnyBody wurde ein muskuloskelettales Körpermodell für die Studie modifiziert. Für das Aufstehen aus 46 cm, 53 cm und 60 cm Sitzhöhe wurden die Muskelkräfte berechnet. In der FEM-Software ANSYS wurde ein Modell des Beckenknochens erstellt. Eine Implantatpfanne der Firma ESKA Implants, Lübeck wurde in 45° Ink. und 20° AV eingesetzt. Als Randbedingung für die FEM-Simulation wurden die in AnyBody berechneten Muskelkräfte angesetzt und die Sacroiliacal-Gelenke fest gelagert.
ERGEBNISSE: Die Anteile von mehr oder weniger kritischen Mikrobewegungen an der gesamten Knochen-Implantat-Kontaktfläche werden für das Aufstehen aus den drei Sitzhöhen angegeben. Die größten Mikrobewegungen treten beim Aufstehen aus den einzelnen Sitzhöhen jeweils am Anfang der Bewegung auf.
DISKUSSION: Aus den hier gezeigten Ergebnissen kann geschlussfolgert werden, dass die Höhe, aus der aufgestanden wird, einen erheblichen Einfluss auf die Mikrobewegungen im Implantat-Knochen-Interface hat. Das Aufstehen aus niedrigeren Sitzhöhen hat kritischere Auswirkungen als das Aufstehen aus höheren Sitzhöhen.

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POSTER 12

The Interaction with Membranes or Micelles Induces Structural Changes of Myristoylated GCAP-2

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Guanylate cyclase-activating proteins (GCAPs) are neuronal Ca^{2+} sensors, which play a central role in shaping the photoreceptor light response and in light adaptation through the Ca^{2+}-dependent regulation of the transmembrane retinal guanylate cyclase. GCAPs are N-terminally myristoylated and the role of the myristoyl moiety is yet not fully understood. While protein lipid chains typically represent membrane anchors, the crystal structure of GCAP-1 showed that the myristoyl chain of the protein is completely buried within a hydrophobic pocket of the protein, which stabilizes the protein structure. Therefore, we address the question of the localization of the myristoyl group of GCAP-2 in the absence and in the presence of lipid membranes as well as DPC detergents. We investigate membrane binding of both myristoylated and non-myristoylated GCAP-2 and study the structure and dynamics of the myristoyl moiety of GCAP-2 in the presence of POPC membranes. Further, we address structural changes within the myristoylated N-terminus of GCAP-2 in the presence of membrane mimetics. Our results suggest that upon membrane binding the myristoyl group is released from the protein interior and inserted into the lipid bilayer.

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POSTER 13

The preservation of α1-antitrypsin (AT) inhibitory activity to neutrophil elastase (NE) by means of HOCl-scavengers

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Several diseases of civilisation are accompanied by chronic inflammations, which are characterised by tissue destruction and pain caused by an uncontrolled release of myeloperoxidase (MPO), its highly reactive product HOCl and proteases as NE. In particular, the increased NE concentration destabilises the balance between NE and its inhibitor AT. Therefore, the aim of this study was a controlled NE inhibition by AT in a concentration depended way. Since MPO and HOCl are known to inactivate AT efficacy, several HOCl-scavengers were investigated regarding their AT protective function. A mixture containing optimized concentrations of protease-inhibitors and protecting agents could represent the basis for the reconstitution of homeostasis in an inflamed region by means of drug delivery systems. NE inhibition was investigated at slightly acidic conditions, because inflamed regions are characterised by pH-values between 5-6.
NE activity could be inhibited by physiological concentrations of AT. Moreover, MPO and HOCl addition provoke a reconstituted NE activity indicating an inactivation of AT inhibitory activity towards NE. In order to regain AT activity, the HOCl-scavengers methionine and cefoperazone were additionally applied in a concentration-dependent way. 240μM methionine or 50μM cefoperazone abolished the MPO/HOCl impairing effects towards AT.
Using the supernatant of activated PMN, similar results could be obtained indicating that a combined application of AT, methionine and cefoperazone provide the basis for an effective concept for the therapy of inflammatory processes.

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POSTER 14

Design of a 1H, 13C double tuned NMR Probehead for the Investigation of Tissue Engineered Cartilage

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Inflammatory diseases of the connective tissue are highly relevant in countries with high life expectancy and represent a major socio-economic factor in health care. In particular, cartilage diseases are highly abundant, painful, and cause a significant portion of early retirements. As cartilage has a very limited self-healing capacity, medical research focuses on various aspects of cartilage regeneration. One of which is the ex vivo fabrication of autologous cartilage by means of tissue engineering. In cartilage tissue engineering, chondrocytes are seeded into appropriate scaffolds and cultured in a bioreactor. Non invasive quality control methods for tissue engineered cartilage are needed, that allow to assess the cartilage within the bioreactor in a non destructive manor. In our approach, we use nuclear magnetic resonance to detect the components of the de novo formed extracellular matrix in cartilage and probe their dynamic properties. In order to do this within the sterile bioreactor, a NMR probehead needs to be developed that accommodates the bioreactor and allows for sufficient radio frequency performance of the circuitry to excite and detect the NMR signal. Several coil geometries are conceivable, which feature specific advantages and disadvantages. On the poster, we will present the construction of the aspired resonators for Proton – and Carbon – Spectroscopy and simulations of their B_1 – fields. Further experimental NMR results of chondroitin sulfate solutions in bioreactors will be shown.

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POSTER 15

Interaction of myeloperoxidase with its product hypothiocyanite.

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The heme enzyme myeloperoxidase (MPO) is stored in azurophilic granules of polymorphonuclear leukocytes (PMNs). It oxidizes (pseudo)halides to its corresponding hypo-(pseudo)halous acids. Taking into account reduction potentials and physiological concentrations, Cl^{2+} and SCN^{2+} are the two main substrates of halogenation activity of MPO *in vivo*. Upon two-electron oxidation of thiocyanate hypothiocyanite (HOSCN) is formed.
Investigations regarding the formation of HOSCN revealed spectral changes that were attributed to the formation of compound II, an MPO redox intermediate which is inactive in regard to (pseudo) halide oxidation.
In this study we used stopped-flow measurements to investigate the spectral changes after incubation of MPO with either HOSCN or a mixture of H_2O_2 and SCN^{2+}. Analysis of the spectra as well as experiments with the sequential addition of methionin or (–)-epicatechin revealed that a MPO-HOSCN complex but not compound II is formed. Using exogenous HOSCN we determined a K_D value of 7.3 mM at pH 7.0. For the H_2O_2/SCN^{2+} mixture a K_D value of 25 μM at pH 7.0 was determined respectively. Yet adding H_2O_2 and SCN^{2+} sequentially the intermediate formation of compound II was observed preceding the complex formation.
The thiocyanate concentration in humans is known to vary in a broad range, depending on e.g. dietary and smoking behaviours and/or different pathological conditions. The enzymatic activity of MPO is nowadays not only attributed to the innate immune response but also to immune regulation. Thus the binding of HOSCN to MPO may be important in respect to chronic inflammations.

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POSTER 16

Analysis of complex phospholipid mixtures by MALDI-TOF MS: The search for the most suitable matrix

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Objectives
The interest in lipid analysis by matrix-assisted laser desorption & ionization time-of-flight mass spectrometry (MALDI-TOF) MS is continuously increasing [1]. Although 2,5-dihydroxybenzoic acid (DHB) is the so far most established matrix, DHB detects the individual lipid classes with strongly different sensitivities [2] and its application to record negative ion spectra is very limited. To overcome this problem, several matrices with improved properties such as 9-aminoacridine (9-AA), 2-mercaptobenzothiazole (MBT) and some others were recently introduced [3]. The characteristics of these matrices will be compared and their potential applicabilities to complex cell and tissue extracts evaluated.

Results and Conclusions
Many different lipid classes, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), sphingomyelin (SM) and different lysolipids are present in cell and tissue extracts. 9-AA offers among all tested matrices the highest sensitivity and is, thus, the matrix of choice. Negative ion detection of some PL classes is an excellent alternative to positive ion detection because negative ion spectra are much simpler to interpret. However, it turned out that the direct detection of acidic PL on a TLC plate by using 9-AA is most likely difficult due to the acidic surface of the silica gel that may lead to protonation of the 9-AA [4]. Additionally, it could also be shown that some zwitterionic PL such as PC and SM are detectable with significanthy different sensitivities although their headgroups are identical.

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POSTER 17

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

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Collagen and glycosaminoglycans (GAGs) such as chondroitin sulphate (CS), hyaluronan (HA) and – to a smaller extent – heparin (Hep) are the main constituents of the extracellular matrix (ECM) of cartilage, bone and skin. As both, collagen and GAGs, fulfil important but different structural functions in the ECM, the detailed assessment of the composition of bioengineered tissues is very important.

The aim of this study is to evaluate the capabilities and limitations of MALDI-TOF MS (matrix-assisted laser desorption ionization time-of-flight mass spectrometry) to determine the amounts of collagen and GAGs in native and bioengineered tissues. For that purpose, collagen is digested by bacterial collagenase resulting in a mixture of tripeptides, the concentrations of which can be quantified by comparison with an internal standard peptide of known concentration. This method was further validated with isolated compounds as well as samples derived from isolated gelatine as well as collagen.

GAGs of ECM can be determined in a similar way subsequent to digestion with chondroitinase ABC that results in the generation of a single unsaturated disaccharide – primarily of the CS type due to the high CS concentration in the ECM. As oversulfated GAGs (for instance, Hep) are rather refractive to enzymatic digestion because the enzyme is inhibited by the sulfate residues, methods of acidic hydrolysis will be also discussed as potential alternatives.

It will be shown that MALDI-TOF MS is a convenient and sensitive method in order to estimate the collagen and GAG contents of ECM.

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POSTER 18

A rapid and simple homogeneous competitive immunoassay based on FRET

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For the detection of antigens, a wide variety of different heterogeneous immunoassay techniques can be used. These assays are sensitive and provide linear ranges spanning three orders of magnitude. Besides these advantages, the drawback remains that multiple incubation and washing steps are required and hence heterogeneous immunoassays are very time-consuming with several hours of assay time. A direct and fast readout of the immunoreaction is possible using homogeneous immunoassays without separation steps.

Here we present a homogeneous competitive immunoassay for the determination of phosphorylated tau peptides. A phosphorylation-specific antibody and the corresponding peptide probe are labeled with two dyes: One linked to the antibody as acceptor and a donor fluorophore coupled to the peptide probe. The immunocomplex of both shows low donor emission intensity due to fluorescence resonance energy transfer. Upon addition of the sample containing the antigen, competitive displacement of the peptide donor probe will increase the donor emission intensity. The resulting signal corresponds to the concentration of the antigen in the sample.

Assoziation: PbF III

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POSTER 19

The Core Unit Fluorescence-Technologies in the IZKF Leipzig

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The Core Unit Fluorescence-Technologies in the IZKF Leipzig provides access to high quality, state of the art flow and slide-based cytometry and high-speed cell sorting as well as the scientific expertise necessary to effectively integrate this technologies into research projects. The Unit is open to all scientists from the Faculty of Medicine and other faculties of the University of Leipzig as well as to external researchers from other institutions.
Currently the Core Unit houses a BD LSR II digital benchtop analyser, a Laser Scanning Cytometer and a FACSVantage SE high-speed cell sorter.
The analytical flow cytometer is equipped with four lasers (355 nm, 405 nm, 488 nm, and 633 nm) and up to 12 parameters (upgradable) can be measured at the same time.
The sorter has three lasers for the excitation (ML UV, 488 nm, 633 nm) and up to 8 parameters are measurable simultaneously. With a special soft- and hardware it is possible to deposit a predefined number of cells onto slides, filters or in individual wells of microtiter plates.
One of the missions of the Core Unit is to train investigators to use analytical flow cytometry to its fullest advantage in their research. The users are provided with validate settings for fluorochromes used in multiparameter cytometry. The high-speed cell sorter is solely staff operated to provide high-quality viable cell sorting experiments.
Another mission is the further training of colleagues. So workshops, hands-on seminars and user seminars are offered.
The goal of the facility is to introduce cytometric methods into new research areas while supporting and extending current research.

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POSTER 20

Identification of glycosaminoglycan oligosaccharides by MALDI-TOF mass spectrometry directly from a standard thin-layer chromatography plate

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Thin-layer chromatography (TLC) is a convenient, fast and inexpensive method to separate complex mixtures. The detection of the analytes is normally based on specific staining but the direct mass spectrometric identification of the analytes on the TLC plate is also possible. We will show here that the detection of glycosaminoglycan (GAG) oligosaccharides derived from chondroitin sulfate (CS) or hyaluronan (HA) can be easily achieved by MALDI-TOF MS. This approach provides much more detailed information in comparison to classical staining.
Intact GAG macromolecules are not detectable by MALDI-TOF MS. Thus, depolymerization of native GAGs was induced by enzymatic or chemical degradation. Although the enzymatic degradation is much more specific and gentle, this digest normally fails if chemically modified GAGs are to be analyzed. Thus, chemical depolymerizations, for instance by HCl, have to be performed although this approach is less specific and results in partial (a) loss of the sulfate and (b) cleavage of the N-acetyl side chain. Both unwanted side reactions can be, however, minimized by careful adjusting the reaction conditions. We will show that combined TLC/MALDI-TOF MS is a particularly simple method to optimize the reaction conditions.
All CS- and HA-derived oligosaccharides can be easily identified in the negative ion mode using 9-AA as matrix and low μg quantities can be detected. However, the used TLC solvent system contains huge amounts of formic acid, formylated carbohydrates are also detectable in small yields. Methods to overcome this problem and to improve the depolymerization of GAG will be discussed.

Assoziation: PbF IV

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POSTER 21

Analysis of Flexible Sidechain Overlaps in Superposed Structures

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A detailed knowledge of enzyme binding sites is crucial for understanding specificity phenomena. Characteristics of binding sites are determined by the physicochemical features of sidechains and their position in 3D space. However, functional similar binding sites don't necessary share structural similarity.Most structural comparison programs use C-alpha positions to superpose residues. But through shifts in the sequence it might occur that functional corresponding side chains reside at different C-alpha positions. Nevertheless, the chemical properties of these residues might be in place due to the flexibility of there sidechains.Here we present a method to identify residues in superposed structures whose extension of the sidechains overlap. The algorithm employs atom coordinates of possible residue rotamers determined by the rotamer explorer module and has been implemented in SVL of the MOE 2009.10 application. We demonstrate the success of this approach on a set of PLP-depended enzymes, which were analyzed to find substrate specific patterns in the active sites.

Assoziation: PbF III

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POSTER 22

Secondary Structure of Aβ Protofibrils in Complex with an Antibody Fragment revealed by Solid-State NMR

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Aß(1-40) is the major fibril-forming peptide from Alzheimer's disease, which adopts a highly ordered ß-sheet conformation upon aggregation into amyloid fibrils. The complex formation process of mature fibrils is not well understood. Here we use ssNMR spectroscopy to elucidate the structure of Aß protofibrils, which were stabilized by the binding of the antibody B10AP. With 8 peptides with varying isotope labeling schemes, 30 residues distributed over the entire peptide sequence were covered. ^{13}C CPMAS spectra and 2D correlation experiments were recorded for the assignment of all carbons. From the conformation dependent chemical shifts we could identify peptide segments of stable secondary structure. Based on this data, Aß protofibrils encompass residues 16-22 and 30-36 in ß-sheet conformation. Random coil-like chemical shifts are present for residues 23-26 as intermediate segment between the ß-strands and the N- and C- terminus. Obviously the structural elements of mature Aß(1-40) fibrils are already present in protofibrils, but the ß-sheet regions apparently elongate during the fibrils conversion. Further information about the dynamics of these regions is provided by measurement of the strength of dipolar couplings, which are converted into an order parameter. Protofibrils show high order parameters (>0.8) within the ß-strand regions, while the measured *S* values are below 0.8 at the termini. We never observed *S* values below 0.4 that would have indicated very high mobility. Thus, significant structural order exists also within those sequence segments that have chemical shift values corresponding to a random coil.

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POSTER 23

A novel biosensoric screening system for direct chemosensitivity testing on tumour biopsy material

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Today cancer is the second most common cause of death. Due to the fact that each tumour has its own characteristics concerning chemosensitivity, there is a strong demand for personalized therapies. In this context we developed a screening system that allows direct testing of chemotherapeutics on tumour biopsy material.
Using impedance spectroscopy as a non-invasive, label-free detection technique in combination with our self-developed 3D microcavity array we are able to monitor chemotherapeutic efficiency for more than four days. More strikingly, with our developed screening platform we could minimize the needed tumour material. Therefore, we are now able to receive up to 300 samples (less than 0.03 mm^3) from one primary tumour (less than eight mm^3) or metastasis respectively. Starting with biopsies from melanoma, we used the isolated samples to screen a panel of six common used cytostatica in a concentration range from 0.03 μM up to 1000 μM. Additionally, we established protocols for single fragment qRT-PCR as well as detection of b-raf and c-kit mutations for analysis of tumour heterogeneity and target identification of novel active pharmaceutical ingredients like PLX4032 and Imatinib.We already measured about ten metastases and three primary tumours. Our impedimetric analysis revealed a specific response pattern for each tumour.
Regarding the chip-based chemosensitivity screening using viable melanoma biopsies we could quantitatively determine the efficiency of chemotherapeutics reflecting the individual patient dependent response to the tested drugs.

Assoziation: PbF III

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POSTER 24

A fluorimetric assay for high-throughput analysis of enzymatic polyethylene terephthalate hydrolysis

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Several hydrolases capable of hydrolyzing synthetic polyesters such as polyethylene terephthalate (PET) have been isolated from various microorganisms in the past years. The currently employed techniques to analyze enzymatic PET hydrolysis are tedious and inconvenient for high-throughput-screening (HTS) purposes. To circumvent this bottleneck, a fluorimetric assay was developed to determine the amount of released terephthalate, the major water-soluble degradation product of enzymatic PET hydrolysis. Enzymatically released terephthalate was converted to the brightly fluorescent 2-hydroxyl terephathlate by the addition of a Fe(II)-EDTA complex. The fluorescence of hydroxylated terephthalate was stable under the experimental conditions such as pH, ion-strength and reaction time. The assay was successfully used to quantify PET hydrolysis catalyzed by TfCut-2, a hydrolase from *Thermobifida fusca* KW3 allowing a rapid HTS of numerous samples simultaneously in a microplate reader.

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POSTER 25

Surface supercharged human enteropeptidase light chain shows improved solubility and refolding yield

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Enteropeptidase is a membrane-bound highly specific serine protease of the small intestine. It appears as a disulfide-linked heterodimer consisting of a non catalytic heavy chain (86 kDa) and a catalytic light chain (26 kDa). For many different biotechnological applications the smaller light chain can be used to avoid the expression of the rather large holoenzyme. Unfortunately recombinant human enteropeptidase light chain (hEPL) shows high activity but low solubility and refolding yields, currently limiting its use in biotechnological applications. Here we describe several protein modifications that lead to improved solubility and refolding yield of human hEPL whilst retaining the enzyme activity. Protein surface supercharging (N6D, G21D, G22D, N141D, and K209E) of the protein increased the solubility more than 100-fold while the replacement of a free cysteine residue with serine (C112S) improved the refolding yield by 50%. The heat stability of this C112S variant was also significantly improved by supercharging. This study shows that even mild protein surface supercharging can have pronounced effects on protein solubility and stability.

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POSTER 26

Combination of a modified fluorescent labeling method and high-throughput automation technology for faster clonal selection of high-producing hybridoma colonies from semi-solid medium

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Background: Monoclonal antibodies are important tools in research, diagnostics and therapy. In higher passages of antibody-producing hybridoma clones a decrease in productivity and increase in growth rate can be observed. Newly established hybridoma clones tend to develop heterogeneity often associated with loosing antibody production. In order to maintain high-producer clones several recloning steps are strictly recommended. Selection of high-producers is a bottleneck in the establishment of stable hybridoma cell lines as traditional cloning and screening procedures are time-consuming and labor-intensive.
Methods: Cloning in semi-solid medium in combination with an immunoprecipitation-based fluorescent labeling method to detect secreted immunoglobulin has been shown to be suitable for selection of highly productive cell lines. To detect high-producing hybridoma colonies in semi-solid medium a modified technique for in-situ screening is presented. For scanning and picking of colonies the CellCelector, an innovative, automated cell transfer system, was applied.
Results: Characterization of the fluorescent signal by area and intensity allowed distinct detection of high-producers. Results of enzyme-linked immunosorbent assays of culture supernatants confirmed high production rates of obtained subclones.
Conclusion: Using the CellCelector, to automatically screen and harvest fluorescent-dye labeled hybridoma colonies from semi-solid medium provides a time-saving, simple and cost-effective alternative for establishment and maintenance of stable hybridoma cell lines.

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POSTER 27

Automatisierte Identifikation von nichtkodierenden RNAs in Transkriptomdaten

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Bei der Hochdurchsatzsequenzierung (HTS) handelt es sich um eine revolutionäre Technologie, die es erstmalig erlaubt, Genom und Transkriptom genomweit und individuell auf breiter Basis zu erforschen. Bei der Auswertung von Transkriptionsdaten liegt ein Schwerpunkt auf der Identifikation von nicht-kodierenden RNA (ncRNAs), die wichtige regulatorische Funktionen in der Zelle übernehmen. Störungen in der Expression von ncRNAs, oder Mutationen in ihrer Sequenz können zu Zivilisationskrankheiten, wie bereits im Fall der koronaren Herzkrankheit gezeigt, führen.
Es ist uns gelungen, einen Zusammenhang zwischen den Prozessierungs-Mustern von kurzen RNAs, ihrer Sekundärstruktur und ihrer Funktion herzustellen. Sie zeigt exemplarisch, dass die Sequenzierungsprotokolle für kurze RNAs Prozessierungs-, Reifungs- und Degradationsprodukte umfassen, die eine akurate automatisierte Klassifizierung der RNAs erlauben. Die entwickelte Methode ermöglicht uns eine vollautomatische Suche nach neuen ncRNAs.

Funding: life

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POSTER 28

Development of a high yield eukaryotic expression and isolation system optimized for neurotropic factors.

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One of the main focuses of actual research and pharmaceutical industry is the reactivation of the neuronal regeneration activity. Degenerative diseases and injuries in the central nervous system are dramatic impairments that are mostly irreversible. One approach is the activation of neuronal regenerative forces by endogenous neurotrophic factors as well as directed path finding by neurotropic factors like semaphorins and netrins. One of those promising factors is semaphorin 7A (sema7A), which is a membrane associated protein with a molecular weight of 75 kDa. For the investigation of molecular function and mechanism of Sema7A and other guiding molecules, they have to be expressed as native post-translational modified recombinant protein. Therefore, we developed a novel eukaryotic expression system based on the HEK293-FT cell line. For an optimal secretion of the neurotropic factor sema7A, the sequence of the GPI-Anchor was selected; a cleavable c-terminal eYFP-Tag was added. Furthermore, we introduced a Strep-Tag and His-Tag for purification via FPLC. Further optimizations of the culture conditions resulted in an isolation of highly purified Sema7A in a concentration range of 0.8 mg/l. Moreover we could verify the right processing by cleaving the tag off and characterised the glycosylation pattern of the purified protein via glycosidase-treatment followed by western blot analysis. In conclusion we were able to demonstrate the high yield expression and purification of recombinant native and functional semaphorin7A.

Assoziation: PbF III

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POSTER 29

Impedance cytometry for label-free cell identification and cell quality control for regenerative medicine

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Identification and profound characterization of cells is a necessity for their isolation and application in cell therapy for regenerative medicine. Present approaches for isolation of stem and progenitor cells rely on specific labelling, analysis by flow cytometry (FCM) and cell sorting. Impedance flow cytometry (IFC) may be a promising label-free alternative to FCM. We tested IFC (Leister/Axetris) as a new label-free way to identify cells. The impedance signal provides information about cell volume, membrane capacitance and cytoplasmic conductivity parameters directly related to the physiological conditions of single cells.
Hybridoma cells were incubated at various densities to induce cell death. Samples were analyzed by IFC at various frequencies to detect the death from alive. Buffers of different ionic strength improved discrimination between dead/alive cells. FCM was used as gold standard after 7-AAD/AnV staining.
Genes@Work cluster analysis revealed parameters for maximal discrimination between viable/dead cells. Cell death estimation was in agreement with FCM.
In addition, neurospheres obtained from postnatal gut of transgenic Wnt1-YFP mice (reporter mouse strain labelling neural crest-derived cells including all cells of the enteric nervous system) were isolated and analyzed by IFC. As control Wnt1-YFP sorted cells were taken. The results showed the ability to detect two distinct populations present within neurospheres.
IFC could become an alternative to conventional FCM. IFC could be applied for quality control of precious samples such as isolated stem cells and biomedical cell analysis for regenerative therapy.

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POSTER 30

Transkriptomanalyse mit Microarrays: RNA Integrität und Qualitätskontrolle

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Neue Microarray und High-Throughput-Sequencing (HTS) Technologien ermöglichen eine umfassende Genom- und Transkriptomanalyse und bilden Standardmethoden zumsystematischen Screening der molekularen Ursachen von Zivilisationskrankheiten. Die anfallenden komplexen Daten sind teilweise mit systematischen Fehlern behaftet. Ziel des Projektes ist es, die Qualität von Mikroarray- und Sequenzierdaten zu bewerten undsystematische Fehler für weiterführende Sekundärauswertungen zu korrigieren.
Exemplarisch werden hier Aspekte der RNA-Qualitätskontrolle dargestellt. Microarrays erlauben die Quantifizierung tausender RNA Spezies in einem einzigen Experiment. Durchschnittlich 11 am 3' Ende der mRNA angeordnete Sonden messen die Expression eines Genes. Im Mittel sinkt die Intensität dieser Sonden mit grösserer Entfernung zum 3' Ende. Dieser Abfall schwankt von Experiment zu Experiment und lässt sich auf RNA Degradationsprozesse, verwendete Reagenzien und Laborfehler zurückführen. Dies muss im Sinne einer Qualitätskontrolle erkanntund, wenn möglich, korrigiert werden.

Funding: life

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POSTER 31

A novel organotypic, quadruple transgenic tauopathy model for drug screening in Alzheimer's disease and related disorders

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The abnormal hyperphosphorylation of the microtubule-associated protein tau is a basic hallmark of Alzheimer's disease (AD). In recent years, several tau-focused therapy approaches have been established to inhibit disease progression. However, effective drug screening is complicated by the lack of suitable screening platforms and human *in vitro* organotypic cell culture models. Therefore, we developed stable SH-SY5Y neuroblastoma cell lines expressing wildtype, single (P301L) and quadruple (P301L, K257T, R406W, V337M) mutated tau. To achieve a more *in vivo*-like situation, cells were cultured as three-dimensional spheroids.
Neurodegenerative as well as regenerative effects could be quantitatively determined with high sensitivity using microcavity array (MCA)-based electrochemical impedance spectroscopy (EIS). With our impedance platform, we were able to detect an okadaic acid (OA) concentration- and time-dependent decrease of relative impedance caused by AD-like tauopathy features in the 3D SH-SY5Y cell culture model. In contrast, regenerative effects induced by tau-focused therapeutics could be characterized by a time- and mutation-dependent increase of relative impedance. These results suggest a possible application of our human organotypic SH-SY5Y 3D *in vitro* cell culture model in combination with the non-invasive, label-free and real-time impedance screening platform for tau-focused drug development in the field of tauopathies including Alzheimer's disease.

Assoziation: PbF III

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POSTER 32

Highly sensitive protein detection based on a novel Europium based dye

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Protein detection plays an important role for pharmaceutical and clinical research today. Various protein staining techniques exist but are limited regarding their sensitivity and often narrow linear quantification ranges. We here describe a novel class of lanthanide chelatators, which absorb in the lower energy region at 360 nm. The new compound was coupled to different proteins and showed highly sensitive protein detection limits in both sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDSPAGE) (1.5 fmol of bovine serum albumin) as well as Dot Blot (100 amol of lysozyme). Furthermore, the novel compound shows an exceptionally broad linear quantificationrange over 5 orders of magnitude allowing applications that require the highest sensitivity alongside standard sensitivity. In addition, the new compound offers multiplexing capabilities.

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POSTER 33 Determination of protease activity using fluorescence resonance energy transfer

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Protease activities are misregulated in a variety of diseases such as cystic fibosis. The activity as well as the sensitive detection of human Trypsin play an important role for the diagnosis of this hereditary disease. Furthermore, sensitive protein detection is a fundamental issue in terms of medical diagnostics and proteomics. Here we present a technique based on Fluorescence Resonance Energy Transfer (FRET) to determine the activity of proteolytic enzymes like human Trypsin. This method includes a novel fluorophore ([EuL]H) and a quencher molecule which are covalently bound to the protein or peptide, decreasing the fluorescence intensity dramatically. After proteolytic digest, the fluorophore and the quencher are separated, leading to an increased fluorescence response. Additionally, our assay is based on time-resolved fluorescence detection, which results in a reduced background and increased signal to noise ratio. Thus, the application of this technique offers a promising possibility to determine changes in the proteolytic activity of human Trypsin and can help to develop a suitable diagnostic test for several diseases involving misregulated proteolytic enzymes.

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POSTER 34 Open Book Injuries of the Pelvic Ring. Biomechanical Investigation versus FE Simulation

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Summary of Background Data: Little is known about the mechanism of open book fractures of the pelvis (OB) and consecutive instabilities of the pelvic girdle. The extent of ligamentous contribution to pelvic stability is in the focus of recent discussion. The aim of this biomechanical and virtual investigation was to determine the mechanism that leads to OB and its consequences on pelvic ring stability, as regards the standing position. Materials and Methods: 8 human pelves (2 ethanol-fixed, 6 unfixed) were utilized, regarding material deformation. After the tests, the specimens were investigated by means of anatomical preparation, thin-slice plastination, sacroiliac joint arthroscopy and CT imaging. A Finite Elements (FE) model was created, including the pelvic bones and the ligaments. Alterations of pelvic load transfer in the standing position related to OB instability to normal standing were then determined. Results: In the cadaveric tests, cranial parts of the anterior sacroiliac joint ligament (ASL) were affected frequently after disruption of the pubic symphysis. These findings were confirmed with the FE simulation. Here, the ASL contributed to more than 80 % of the overall ligamentous force transmission, as regards the OB mechanism. After symphyseal disruption, load maxima were found for the cranial parts of the ASL. Force redistribution, which was found after ASL injury, was redirected to the iliolumbar ligament, the interosseous sacroiliac ligaments, the sacrotuberous and the sacrospinous ligaments. Conclusions: The OB mechanism can be described by means of FE analysis. Close concordances were found for the biomechanical tests and for the FE simulations. Consecutive instabilities, caused by ASL disruption, are compensated by force distribution to the surrounding ligaments of the pelvic ring. This supports the thesis that the remaining ligaments allow to maintain vertical stability.

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POSTER 35

Scattering and Jittering: Using Real and Illusionary Motion for Better Visual Scatterplot Analysis

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A scatterplot is one of the most popular techniques used for visualizing multidimensional datasets. However, if the number of data points is large, occlusion and overdraw problemsoccur. Thus, it might be difficult to visually differentiate these data points and their clusters. Motion is one of the strongest low-level perceptual cues to draw our visual system's attention to a certain subset of data. In visualization it has been used quite often to highlight information. In particular for time varying flow fields, motion has been exploited to show flow patterns in more abstract representations. For the visualization of non-spatial data, however, it has been used in a surprisingly limited fashion. For the use of motion as an interaction tool several approaches were proposed. More closely related to our approaches is the use of motion as a mapping technique which, in our opinion, has not yet been sufficiently exploited in the field of multidimensional visualization. We use three different kinds of motion to support the identification and the separation of multiple clusters in a high-dimensional dataset. First we present two techniques generating real motion effects by the use of flickering and of different weaving patterns. Furthermore we present a technique using mimic motion by the use of peripheral drift. The jittering moves objects by translation of data points. The alternating weaving patterns only change one attribute of the weaving technique and present alternatively different weaving patterns. The peripheral drift exploits the visual recognition to initialize a mimic motion with a static image.

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POSTER 36

Modular Augmented Reality for the Neuro-Comrade Project

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Background
Surgical interventions of the head rely on careful planning due to the complex anatomy and the close proximity of risk structures, such as blood vessels, functional areas like motor or speech areas, or nerve fibers. This issue is aggravated in minimally-invasive surgery, since the field of view is further limited.

Modular Augmented Reality
One approach to address this situation is augmented reality (AR), where a visual representation of the anatomical structures or functional areas is extracted from tomographic image data (virtuality) and augmented in an intraoperative scenario (reality).
In our poster, we present a modular AR system for neurosurgery, which is designed for use with different hardware components. The system is video-based and can acquire images with high definition or standard resolution video cameras. We therefore can optionally provide high quality images or use standard imaging devices.

Accuracy Issues and Depth Perception in Augmented Reality
Since the correct overlay of a real and virtual scene is very important for medical AR (registration), we also discuss the accuracy issues of the system as a whole and identify error sources in the respective modules. The correct depth perception in the augmented scene is provided through perception corrected visualization techniques, such as transparent overlays.

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POSTER 37

Semi-automatische Segmentierung der Prostata in MRT-Daten

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Die Visualisierung und Modellierung von anatomischen Strukturen findet zunehmend Anwendung in der Therapieplanung und der computerassistierten Chirurgie. Um Strukturen patientenindividuell visualisieren zu können müssen diese in radiologischen Bildern zunächst segmentiert werden. Die detailgetreue manuelle Segmentierung ist jedoch eine sehr zeitaufwändige Angelegenheit.
In dieser Arbeit wird ein modellbasiertes Verfahren zur Segmentierung vorgestellt, mit welchem anatomische Strukturen in wenigen Sekunden und minimaler Benutzerinteraktion erkannt werden können. Die vorgestellte Methode kombiniert ein statistisches Formmodell mit einem lokalen statistischen Erscheinungsmodell, welche aus manuell segmentierten Trainingsdaten generiert wurden. Auf Basis dieser Modelle wird ein robustes Suchverfahren zur Erkennung der Kontur implementiert. Hierbei wird ein deformierbares Modell an die zu suchende Struktur im Bild angepasst. Zur iterativen Anpassung des Modells wird ein Verfahren verwendet, welches den Lagrange'schen Bewegungsgleichungen zugrunde liegt. Dabei wird eine neue, robuste Kostenfunktion für die Anpassung auf Basis eines Shrinkage-Schätzers verwendet.
Das Verfahren wird in dieser Arbeit am Fall der Segmentierung der Prostata validiert. Die vorgestellte Methode wird an 10 Datensätzen evaluiert. Dabei zeigt sich für das Segmentierungsergebnis eine mittlere Oberflächenabweichung von 2,1 – 2,8 mm im Vergleich zur manuellen Segmentierung durch einen Experten.

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POSTER 38

Flexible Implantate

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Purpose
Existing software for planning stenting interventions are presently limited to measurement functions. The vessel surgeon demands a more functional software which can assist him through the hole planning process including implant selection and position determination. In the research project of ICCAS and Fraunhofer IWU the integrability of a physically based simulation model of stentgraft and aorta into the clinical environment was examined.
Methods
The finite element method was used to determine necessary simulation parameters and helpful result values. Referring data support of stentgraft models and extension of the patient´s record with simulation results the DICOM standard was analyzed.
Results
Essential parameters for stentgraft-vessel simulation like blood pressure, intima constitution, plaque occurrence and material properties of vessel and plaque were determined. Helpful output quantities are the radial force of the stentgraft and the gap size between implant and vessel wall which helps the surgeon to evaluate implant fixation and sealing. The DICOM Supplement 132 "Surface Segmentation" object can be used to save the model geometry as well as parameters for describing the bending behaviour of a flexible stentgraft. Simulation results can be stored using the "Structured Report".
Conclusions
Simulation relevant values were determined. At present, there are limitations due to specification of individual vessel material parameters. Existing DICOM supplements are suitable for clinical integration of simulation model parameters and can furthermore be used for supporting a data base of stentgraft surface models.

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POSTER 39

Assessment Concepts for the Man-Machine-Interaction in Surgery

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Automation in surgery creates new risks of man-machine-interaction (MMI). The central objective of the project is the development of assessment concepts for MMI in surgery. These concepts are supposed to facilitate the study planning and execution by using systematic assessment approaches and evidence based decision guidance. The focus concentrates on the investigation of the effects of automation. The concepts shall comprise several human performance consequences, arranged in different modular templates.

The proposed assessment concepts are based on the ISO 14155 standard for clinical investigation of medical devices for human subjects. The extracted contents were modified to comply with the MMI investigation requirements. Further relevant concepts were integrated. An interdisciplinary expert team was involved to consider the different areas of expertise: Medicine and Surgery, Informatics and Computer Assisted Surgery, Psychology and Human Factors, Statistics and Biometrics, Industry and Medical Devices.

An initial model for investigation of the MMI in surgery was created. It is subdivided in modules representing the several aspects of study planning and implementation methodology. To meet the requirements of the MMI assessment in surgery different aspects were integrated. E.g. study subjects are clinicians (surgeons etc.) instead of patients. Furthermore the trade-off between clinical realism and effective control to the parameters was integrated.

In the next step the model will be formalized to specify the relationships and rules within. Thus several templates could be generated concerning different study requirements.

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POSTER 40

Fluoroscopic Assistance System for Transapical Aortic Valve Implantation

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Purpose Transapical aortic valve implantation (TAVI) is a surgical technique to treat severe aortic valve stenosis for high-risk patients. The correct placement of stented aortic valve prosthesis is crucial under fluoroscopic X-ray imaging with a C-arm system. For assisting the TAVI, a new assistance system has been developed to support the physician in finding the exact positioning of prosthesis under live 2D fluoroscopy guidance.

Methods The fluoroscopic assistance system can be connected with an interventional C-arm to import a 3D model of aorta and 2D fluoroscopic images. The developed system defines automatically the exact placement of aortic valve prosthesis as follows. First, 3D aorta model including valve landmarks are overlaid on fluoroscopic images. Second, the position of prosthesis is tracked in fluoroscopic image sequences by using template matching approach and a shape model of the prosthesis. Then, the target area of implantation is calculated such that the prosthesis is placed one-third to one-half above the mid-level of the valve annulus.

Results The developed assistance system has been evaluated on different 3D aorta models and fluoroscopic image sequences for five patients from the clinical routine of the TAVI. The maximum localization errors of aortic model overlay and tracked prosthesis are less than 10.0 mm and 1.0 mm, respectively, and within the clinical accepted range.

Conclusions The results demonstrated the feasibility of using developed system for assisting the TAVI. We are now preparing the fluoroscopic assistance system for clinical evaluation during the TAVI at the Heart Center Leipzig.

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POSTER 41

3D Visualization for Tumor Intervention Planning

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Background

Medical images are the main basis for the planning of complex ENT- and neurosurgical interventions, such as tumor resections. Modern medical imaging techniques allow a precise acquisition of a patient's anatomy. Nevertheless, the actual planning usually still takes place with 2D slice data requiring a good spatial imagination of the surgeon. In complex cases and with an increasing number of datasets, this becomes a challenge. A 3D visualization integrating all relevant diagnostic information is capable of supporting the medical expert in this phase.

3D Visualization for the SPU

One goal of ICCAS is the development of a Surgical Planning Unit (SPU) as an environment for an efficient therapy planning procedure. Here, experts of different medical disciplines discuss and decide about the therapy strategy in critical cases. For that, the SPU provides suitable communication interfaces to integrate medical images and various other information, such as the results of prior examinations or laboratory diagnostics. The patient-specific visualizations are generated in cooperation with a radiologist according to the surgeons' specifications. With modern image processing methods the tumor and the risk structures are identified and transformed into 3D models. After registration, these models can be fused into a multimodal visualization. Supported by an intuitive interaction paradigm this allows the surgeon to easily grasp the spatial relations of the patient anatomy, plan the surgery more efficiently, and by that reduce the risk for the patient.

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POSTER 42

An experimental Setup to evaluate Laparoscopic Instruments by analyzing Surgical Process Models

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In the presented study, we evaluate which access setup is most fit to guarantee a high quality of results concerning minimally invasive laparoscopic pediatric surgery. Today, a new access technique, the Single Incision Laparoscopic Surgery (SILS) is used, which is still less invasive than the conventional 3-Trokar access to the situs. Furthermore, we analyze which instrument design in connection with which access technique is more sensible.

To analyze this kind of surgical intervention, we have devised three different tasks that were derived from standard intervention procedures, these included cutting off, suturing, and anastomosis. These tasks were performed by two populations (experienced vs. inexperienced), who had to perform each of these tasks five times in a mockup scenario using a silicone phantom while their physiological parameters were measured. Also, a questionnaire, the NASA-TLX, had to be filled in by the subjects to be able to assess their stress load. In addition, the quality of the tasks' results was reviewed.

To analyze a complex process, such as a surgical intervention, it is sensible to split it up into single activities. A surgical process model (SPM), recorded with the help of the Surgical Workflow Editor and trained observers, represents this process in a formal or semiformal way including single, temporally extended process steps (activities). These SPMs allow for a multitude of possible analyzing scopes especially with respect to the complex environment of the OR. Not only is it possible to analyze intervention courses with the presented method, but also to evaluate different instruments.

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POSTER 43

Surgical Process Modeling – A Translational Four-Level Approach

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For many applications in surgery, such as teaching, learning, evaluation, quality assessment, requirements analysis, and computer-assisted surgery, the precise and formal specification of surgical interventions is a necessary requirement. At present, surgical processes (SPs) are modeled by following varying approaches. As a result, a commonly agreed-upon conceptual foundation is unavailable and thus the comparability, interoperability, and uniform interpretation of process data are hindered.
But for scientific models sharing one context, would not a coherent conceptual and formal mathematical basis be beneficial? Such a uniform foundation would facilitate and elucidate data acquisition and exchange, the transition and interpretation of study results, and the transfer and adaptation of tools and methods.
Therefore, we present a formal, generic framework to specify surgical processes and the methodology of its design. The latter comprises an ontological foundation based on linguistic theories and follows a four-level translational approach. We demonstrate the expressive power and unifying capacity of the presented framework by applying it to several different approaches to model SPs and by showing how it allows for a uniform representation of process models arising from different techniques.
This approach was designed to gather knowledge about the progression of surgical interventions. It enables a consistent translation of natural language to an implementation-near level, supports various research fields (e.g. the evaluation of surgical assist systems, optimization) and the use of workflow management systems within the OR.

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POSTER 44

Integration of Evoked Potentials into Neurosurgical Navigation for tumour resections near the Motor Cortex

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Background: The primary motor cortex is a complex brain area controlling extremity movements. Thus a safe resection of nearby tumours requires a reliable localisation of various eloquent areas through a small trepanation. Additionally, surgical navigation on preoperative MRI suffers from inaccuracy due to brain shift. Hence the measurement of evoked potentials with a strip electrode applied directly to the cortical surface is a common technique for the intraoperative identification of cortical areas. Since the measurements are not spatially linked to preoperative images and surgical navigation, currently the emerging integration task has to be fulfilled by the surgeon.
Intraoperative Mapping: We developed a modular system called *NeuroMapper* that uses a novel mapping approach for strip electrodes to assist the surgeon with the integration task, intraoperative access planning and objective documentation. Therefore, surgical navigation is extended with patient-specific 3D models, comprehensive visualisation and spatial integration of evoked potentials via tracking data. The mapping procedure can easily be performed with standard OR equipment since the system cooperates with routinely used devices. This is facilitated by a service-oriented architecture based on open communication standards. Implemented technical evaluations and tests in clinical cases showed promising results and moderate additional effort.
Conclusion: The *NeuroMapper* enhances the surgical workflow by integrating evoked potentials and surgical navigation. It is a useful step towards model guided surgical assistance systems with open communication interfaces.

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POSTER 45

Model driven design of workflow schemata and the development of a corresponding test system

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Background:
To facilitate the intraoperative context integration for surgical assistance systems a workflow management system (WFMS) should be used. Such a system uses surgical workflow schemata to provide knowledge of the actual activity of the intervention to all participating systems. A workflow schema describes the process in a model language which is processable by the WFMS.
Method:
A Workflow Schema is generated from a generalized surgical process model (gSPM). Due to the fact of the high variability of surgical interventions, the gSPM is a statically averaged model based on many patient individual process observations (iSPM).
A YAWL Workflow Management Engine works as core unit for the test system. YAWL is a petri-net based Workflow Management Language. The overall test system is composed of a simulation unit, the WFMS, and an administration tool. The WFMS loads a workflow schema which is generated as described before. Then the simulation unit loads an iSPM from the database and sends its task step by step to the WFMS. In the WFMS the task will be received and check whether the workflow schema contains all transitions necessary to attain the next task.
Conclusion:
In this work we could show that it is possible to generate workflow schemata from patient individual process descriptions. The test system was able to track the so generated workflow schemata at any time during the process. Therefore it is feasible to approach the high variability of the surgical process with this method of model generation.

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POSTER 46

Requirements of a DICOM supplement for optical surface scanners regarding the use-case of a rhinoplasty surgery

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Motivation:
In the 1980s the DICOM standard was established, because a common interface was needed for the growing number of devices from different manufacturers, such as CT scanners or x-ray stations. Since optical surface scanners gain importance for today's clinical use, it is a logical next step to consider them as an own modality in the DICOM standard.
Methods:
The new standard for surface scanners must be technically up to date and meet the requirements of the manufacturers of devices and software applications. The use cases and necessary attributes and parameters for the new modality have been discussed in several meetings with manufacturers and clinical stakeholders. To verify the theoretical efforts, a project to measure the shape of the nose before and after a rhinoplasty with help of an optical surface scanner has been initiated.
Results:
The proposal had a successful "First Read" by the DICOM working Base Standard, which decides how the DICOM standard is extended. The requirements of the manufacturers have been analyzed and considered in the first proposal. Two new IODs will be created in DICOM. One to transfer point clouds, the other to transfer surface meshes. Colorization shall be done by UV mapping or by colored vertices.
Within the clinical project, multiple 3D shots from seven patients have been made before and after a nose surgery. The workflow has been considered within the DICOM proposal.

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POSTER 47

The Modular Integrated Operating Room based on Open Standards

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Background: Integration of medical devices and IT systems as well as centralized control of the integrated system in the operating room (OR) has been recognized for its potential to increase the overall surgical efficacy, ergonomics and the clinical workflow.
Methods: We designed an open standards based OR integration system, which is modeled as component-based service-oriented architecture. Each medical device is integrated as independent component and interconnected through an Ethernet network. The integration framework facilitates service discovery, time synchronization, system diagnosis, messaging and event handling as well as streaming of continuous signals. Several core components form the backbone functionality of the integrated system. The central surgical console allows access to the functions of the integrated system. The central managing component supports technical administration and systems supervision. Common electronic patient context is maintained by the context module while the session repository stores all data generated pre- and intraoperatively for postoperative documentation.
Results: As a result, the modular OR system integrates a) data, e.g. preoperative imaging and planning data of surgical target structures (using the DICOM Surface Segmentation SOP Classes), tracking data, and patient context; b) device functions with centralized device control at the surgical console; as well as c) user interfaces (using Universal Remote Console Standard) and applications using display integration and video routing technologies. A prototype setup has been established in a demonstrator OR.

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POSTER 48

IHE in Surgery

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Background: The initiative “Integrating the Healthcare Enterprise” (IHE) gives guidelines on which standards in medicine shall be used in which way to achieve a specific goal.At present, several research institutions and parts of the medical device industry are driving forward a movement towards open, modular systems solutions which are based on open standards. IHE as a quasi-normative body can be used to discuss integration issues among industry members and agree on best practices.IHE current focus is on radiology. Within the Operating Room, there are specific needs regarding the technical infrastructure and communication. Patient model information, device and room control must be integrated. For safety reasons, systems monitoring and diagnosis of OR equipment are required. Extending IHE towards Surgery:We propose three new profiles, which could be the beginning of the Technical Framework Surgery: Surface Segmentation Profile (SSE), Implant Template Distribution Profile (ITD) and Implantation Plan Distribution Profile (IPD). The Profiles are describing how the corresponding recently developed DICOM SOP classes shall be used in order to fulfill clinically relevant use cases. Based on our projects on modular systems architectures for the operating room, we have a set of potential further supplements which could be integrated in the mid-future. Conclusion:We believe that IHE could play a major role for the integration of devices and modules for Image and Model Guided Therapy. The coordinated use of standards within this industry will lead to more reliable systems and foster new applications of this technology.

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POSTER 49

Ligand induced internalization and recycling of the human Y2 receptor is regulated by its C-terminal tail

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Agonist-induced internalization of GPCRs plays an important role in signal regulation. The internalization mechanisms of the human neuropeptide Y_2 receptor (hY_2R), as well as its desensitization, endocytosis and resensitization are mainly unknown. The Y_2R is one of four human neuropeptide Y (NPY) receptor subtypes (Y1R, Y2R, Y4R and Y5R) and belongs to the rhodopsin-like superfamily (class A) of GPCRs. They can be activated by the so called NPY family comprising NPY, pancreatic polypeptide (PP) and peptide YY(PYY). The hY_2R is predominantly expressed in the central nervous system as well as in the periphery and is involved in the inhibition of neurotransmitter release, regulation of memory retention, circadian rhythm and angiogenesis, thus makes it an attractive target for drug development. Since it has been reported that hY_2Rs are expressed in distinct tumors it is a promising target for tumor diagnostics and therapy. In order to successfully treat Y_2R related diseases, it is of fundamental interest to unravel the mechanisms and regulation modalities of Y_2R internalization and subsequent resensitization processes. To address this question, we generated a series of C-terminally truncated hY_2R mutants in order to investigate the impact of C-terminal sequences on receptor internalization properties. We identified novel regulatory motifs within the hY_2R C-terminal domain, which contribute to receptor internalization and arrestin3 association. Interestingly, our findings revealed arrestin3-dependent and -independent hY_2R internalization, and also led to the identification of a sequence that modulates receptor recycling.

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POSTER 50

Inhibition of CamKII, JNK and PKC diminishes Wnt5a induced osteogenesis in embryonic stem cells

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Embryonic stem cells (ESCs) are pluripotent stem cells that are capable of differentiating into various kinds of mature cell types, including osteoblasts. We have previously demonstrated that non-canonical Wnt signaling through Wnt5a stage-specifically enhances osteogenesis by decreasing nuclear levels of beta-catenin (CatnB), the main effector of Wnt signaling. We have further shown that Wnt5a appears to modulate mesoderm and neural crest specification in the early stages of ESC differentiation. However, the molecules that transmit the signal downstream of Wnt5a remain unidentified.

In the current study, Ca^{2+}/calmodulin-dependent kinase II (CamKII), c-jun kinase (JNK), and protein kinase C (PKC) signaling were proven to be involved in Wnt5a downstream regulation using a loss-of-function approach with specific inhibitors. Addition of inhibitors during osteogenic specification up-regulated nuclear CatnB levels leading to a decrease in mineralization efficiency. This decrease in overall mineralization was accompanied by a down-regulation of the ectomesenchyme markers T-Brachyury, Sox-1 and CD271 during early differentiation. Moreover, mRNA analysis of chondrocyte and adipocyte-specific genes suggested that the differentiation of these two cell types was also affected by inhibitor treatment.

In conclusion, our results indicated that CamKII, JNK and PKC may act in concert to regulate Wnt5a induced neural crest-derived osteogenesis in ESCs as well as chondrogenesis and adipogenesis.

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POSTER 51

Transmembrane channel like (TMCs) proteins and their role in calcium homeostasis

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TMCs belong to a new family of 8 genes that encode proteins with predicted 6-8 transmembrane domains and a conserved region which is termed TMC domain. They have no sequence similarities with any known proteins and motifs.
Mutations in TMC1 can cause dominant or recessive hearing loss in humans and mice due to a degeneration of the inner and outer hair cells in the organ of corti. The molecular and cellular functions of TMCs remain unknown.
The topology of mTMC1 resembles that of a large superfamily of proteins that includes TRP channels and voltage-gated K channels but no channel activity could be detected up to now.
Here we show that expression of TMC1 and TMC2 lead to a decreased calcium concentration in the endoplasmic reticulum. Furthermore, we investigated the influence of TMC1 and TMC2 expression on different proteins involved in calcium homeostasis. We could show that expression of TMC1 and TMC2 together with Orai1, the pore of the calcium release activated calcium channel, leads to an accumulation of Orai1 in the ER and a diminished store operated calcium entry.

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POSTER 52

Regulatorische Module aus Transkriptionsfaktoren und miRNA

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Die Genexpression von Maushepatozyten verändert sich während der Kultivierung. Ziel der Arbeit war es, Transkriptionsfaktoren und miRNAs zu identifizieren, die diese Veränderungen regulieren.
Primäre Maushepatozyten wurden über 48 h in kollagenbeschichteten Platten kultiviert und das Genexpressionsmuster wurde nach 24, 27, 30, 36 und 48 h mit Affymetrix Arrays bestimmt. Die Promotorregion der differentiell exprimierten Gene wurde nach überrepresentierten Transkriptionsfaktor-Bindestellen (TFBS) und miRNA Bindungsmotifen durchsucht (1). Aus diesen Daten und deren zeitlicher Veränderung wurden mit Hilfe eines Hidden Markov Modells (2) zwei Datensätze erstellt, die die wichtigsten regulatorischen Veränderungen und die auslösenden Faktoren beschreiben. Die Gene bildeten 7 Cluster: 3 für hochregulierte, 3 für herunterregulierte und einen für Gene mit nur geringen Veränderungen. Diese Cluster wurden mit 20 überrepräsentierten TF assoziiert. Am signifikantesten waren ETF, Elk1, ZF5 und E2F bei den hochregulierten Genen. NF-Y und Stat1 waren signifikant bei den herunterregulierten und MAZR bei den geringfügig veränderten Genen. Diese Cluster wurden auch durch 8 miRNA reguliert. Es zeigte sich, dass die Regulation sowohl durch miRNAs als auch durch TF beschrieben werden konnte. Dieser Befund deutet auf die Existenz von regulatorischen Modulen aus miRNA und TF hin, die gemeinsam die Genexpression regulieren.
(1) Ulitsky et al. Nat Protoc 5, 303-322. (2010), (2) Ernst et al. Nature-EMBO Molecular Systems Biology 3, 74 (2007)

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POSTER 53

The SDF-1 chemokine receptors, CXCR4 and CXCR7, exert dual roles during limb myogenesis

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We previously demonstrated that the chemokine, stromal cell derived factor-1 (SDF-1/CXCL12), and its receptor, CXCR4, are highly expressed in the developing mouse limb and control various steps of limb myogenesis, such as muscle precursor cell/myoblast migration, proliferation, and differentiation. The recent identification of CXCR7 as an alternative SDF-1 receptor now prompted us to analyze the role of this second SDF-1 receptor in limb myogenesis. We demonstrate that CXCR7 expression is relatively low in the limb musculature of late embryonic mice and substantially increases during postnatal development. We further demonstrate that vive versa limb CXCR4 expression is relatively high during embryonic development and decreases with ongoing maturation. To subsequently assess the functional consequences of this adverse regulation of CXCR4 and CXCR7 expression during limb myogenesis, we used C2C12 mouse myoblasts as a model system. Western blot analysis in combination with FACS analysis revealed that C2C12 cells express CXCR4 and CXCR7 to similar levels. Treating C2C12 cells with SDF-1 prevented their myogenic differentiation as assessed by MF20 expression. These inhibitory influences persisted in C2C12 cells in which CXCR7 expression was depleted by RNAi. In contrast, SDF-1 promoted myogenic differentiation of C2C12 cells with depleted CXCR4 expression. Collectively, these findings point to a dual role of SDF-1 during limb myogenesis, in terms that SDF-1-bound CXCR4 inhibits limb myogenesis whereas SDF-1-bound CXCR7 promotes myogenic differentiation.

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POSTER 54

Detection of an Asymmetric Distribution of Cholesterol in the Plasma Membrane of Migrating Cells

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Cell migration contributes to multitude of physiological processes including development, immunology and wound healing. But cell migration plays also a major role in pathological processes like vascular disease, inflammation and tumour dissemination. To migrate directionally, cells develop a polarized shape accompanied by large cytoskeletal reorientation processes. Polarization is also characterized by an unequal cellular distribution of different signalling molecules, including the GTPases Rho, Rac and Cdc42 and of some types of plasma membrane lipids like phosphatidylinositides. Similarly a polarized viscosity of the plasma membrane of migrating endothelial cells has been demonstrated. Cholesterol is known to alter membrane viscosity, but if cholesterol is polarized in the plasma membrane of migrating cells is not quite sure.
We investigated front-to-back asymmetries of the plasma membrane in migrating cells using different fluorescence techniques. Fluorescence lifetime measurement of NBD and filipin staining of cholesterol revealed a polarized cholesterol distribution in migrating keratinocyte-like cells with a decreased cholesterol content in their lamellipodia. In neutrophils it seemed that the cholesterol content is higher at the front compared to the back of the cells. We propose that an optimal viscosity is required at the leading edge, which is adapted by each cell type to enable optimal cell extension and actin polymerisation. We will now investigate how modifications of the cholesterol content influence the cell migration and how this will affect the cholesterol gradient in the plasma membrane of these cells.

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POSTER 55

Protective or damaging effects of adipocytokines and free fatty acids on rat INS-1E β-cells with reference to viability, cytotoxicity and apoptosis.

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*Background and Aims:*The molecular interactions between adipose tissue and β-cells are still not sufficiently known, so that there is an urgent need for research.We asked, if adipocytokines, such as leptin, adiponectin, Nampt or vaspin, and free fatty acids, such as palmitate and oleate, influence proliferation and apoptosis of INS 1E β-cells.
Methods: Changes in proliferation were measured by WST-1 assay. Effects on apoptosis were measured by Annexin V/PI Assay. For further characterization of activated apoptosis mechanisms (p53, caspase-3, NF-κB), Western blot studies were undertaken. Insulin secretion after glucose stimulation was measured by ELISA.
Results: A dose-dependent increase (90%) in insulin secretion was detected after glucose stimulation[20mM] compared to the basal value. Viability was decreased after stimulation with cytokines (IL-1β[10ng/ml]) by 80%. Adipocytokines showed no effect on viability. Palmitate induced cytotoxicity by 70%, oleate by 40%. Apoptosis was increased after stimulation with cytokines (by IL-1β+IFNγ[10ng/ml]) by 40% and palmitate[0,5μM] by 30%. Adipocytokines showed no effect on apoptosis. In addition, adipocytokines showed no protective effect on cytokine-induced apoptosis. Furthermore, no effects on caspase-3, p53 or NF-κB pathways were found after stimulation with adipocytokines.
Conclusion: There must be a link between obesity and the development of diabetes. According to our results, leptin, adiponectin, Nampt and vaspin do not induce β-cell death. However, free fatty acids, particularly palmitate, might play a crucial role in development of diabetes.

Funding: life

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POSTER 56

The effect of nutrient availability and resveratrol as nutriceutical on NAMPT activity

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Background: Nicotinamide phosphoribosyltransferase (NAMPT) is a key enzyme of the mammalian NAD^+- biosynthesis and regulates the activity of the Sirtuin 1 protein (SIRT1). SIRT1 is implicated in modulating cellular energy metabolism and stress response. We aimed to establish a NAMPT enzymatic assay with optimal conditions and asked whether different nutrients and resveratrol are able to modulate NAMPT activity.
Methods: HepG2 cells, primary human and rat hepatocytes were cultured under various conditions. NAMPT and SIRT1 expression was quantified by western blot. NAMPT enzymatic activity was measured using a radioactive filter disc assay.
Results: We established a radioactive NAMPT enzymatic assay with optimal conditions. Resveratrol (10, 25, 50μM) increased NAMPT activity in HepG2 cells (~1.4 fold) and in primary rat hepatocytes (~3.3 fold) without influencing NAMPT protein expression. HepG2 cells exposed to glucose restriction and low glucose levels (5.5mM) showed no changes in NAMPT and SIRT1 protein expression and NAMPT activity. Oleate, palmitate and a oleate/palmitate mix did not lead to changes in NAMPT protein expression and enzymatic activity. After 48h, palmitate (0.5, 1mM) increased NAMPT mRNA expression (~1.2 fold) and NAMPT release (~2 fold) due to cytotoxic effects.
Conclusion: Different nutrients did not effect NAMPT enzymatic activity. We demonstrated that NAMPT activity is increased by the SIRT1 activator resveratrol without influencing NAMPT protein level. The beneficial effects of resveratrol might be an up-regulation of the intracellular NAD^+- levels via elevated NAMPT activity to sustain SIRT1 effects.

Funding: formel1, life

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POSTER 57

MicroRNA-21 directly targets a tumor suppressor and promotes prostate cancer cell proliferation

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MiRNAs are endogenous, short non-coding RNAs. They regulate gene expression by translational repression or degradation of mRNAs. MiRNA binding sites are mostly located within the 3′ untranslated region (3′ UTR) of their targets. It has been shown that aberrant expression of miRNAs is associated with carcinogenesis. Among the miRNAs, miR-21 has been identified as a key molecule of oncogenic processes. MiR-21 is overexpressed in diverse types of tumors such as prostate cancer, glioblastoma as well as B-cell lymphoma and contributes to proliferation, metastasis and invasion. In this study, we identified putative targets of miR-21 in LNCaP prostate cancer cells transfected with miR-21 or negative control using two-dimensional differential in-gel electrophoresis (2D-DIGE). In the presence of miR-21 we found 16 significantly suppressed proteins. Validation of candidate targets showed the direct regulation of a tumor suppressor by miR-21. We detected the regulation of this protein in various cell lines using miR-21 precursor as well as anti-miR-21 oligonucleotides by Western Blot analyses. Finally, overexpression of miR-21 in LNCaP resulted in enhanced cell viability. Knockdown of the identified tumor suppressor by RNA interference mimics the proliferative effect of miR-21 to a comparable extent. We also show that this effect on cell viability is not restricted to prostate cancer as it is observed in A172 glioblastoma cells as well. Thus, these data suggest that the tumor suppressor identified by 2D-DIGE is an important factor that mediates miR-21 function in several cell types.

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POSTER 58

Localisation of Breast Cancer Resistance Protein in pharmacologically relevant tissues of dairy cattle and isolation of primary mammary epithelial cells

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Numerous contaminants in milk pose a health risk for consumers of dairy products and suckling neonates. The Breast Cancer Resistance Protein (BCRP) as a member of the ATP-binding-cassette family (ABC) transporters is known to concentrate certain drugs and xenobiotics into milk. So far, there is little information about subcellular localisation of BCRP in dairy cattle in general. For this purpose, we used the monoclonal antibody BXP-21 in formalin-fixed, paraffin-embedded tissues of goat, sheep and cattle to localize this efflux transporter. Briefly, epithelium of small intestine, bile canaliculi, bronchi, renal tubules as well as glomeruli and endothelium of veins and capillaries showed prominent apical staining. Alveolar pneumocytes, hepatocytes and lobules as well as ducts of mammary gland stained cytoplasmic with some apical accents. This staining pattern is compatible with involvement of BCRP in tissue protection from and elimination of xenobiotics, confirming and extending data from human BCRP. Focussing on mammary gland we yet isolated mammary epithelial cells from goat and sheep and analysed expression of BCRP by immuncytochemical staining and RT-PCR. This was necessary a) to verify epithelial expression of BCRP, because total RNA or mRNA from mammary gland always contains BCRP from endothelium of veins and capillaries and b) to screen for other ABC-transporters involved in milk secretion. Our results demonstrate the contribution of BCRP in eliminating xenobiotics in the mammary gland in dairy cattle.

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POSTER 59

p8-Mangel induziert Reactive Oxygen Species und HO-1 in embryonalen Mausfibroblasten

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Einleitung: Die genauen Aufgaben des Proteins p8 in der Zelle sind nicht bekannt. Es scheint als Transkriptionscofaktor den Zellzyklus zu beeinflussen. Aus p8- knock-out ($^{-/-}$) Tieren weiß man, dass p8 zu einem milderen Verlauf von Sepsis und Pankreatitis führt. An der Initiierung dieser Erkrankungen scheinen auch *Reactive oxygen species* (ROS) beteiligt zu sein.
Ziel der Arbeit: Zu klären, inwiefern die vermittelten p8 Effekte über eine Veränderung des Redoxstatus der Zelle hervorgerufen werden.
Methoden und Materialien: ROS-Messung mit CM-H_2DCFDA. Semiquantitative RT-PCR (Light Cycler, Roche) und Western Blot Analysen von Embryonale Fibroblasten (MEF) aus p8$^{-/-}$ und nativen (p8$^{+/+}$) Mäusen. Zellzyklusarrest mit Nocodazol sowie Verifizierung durch FACS-Analysen.
Ergebnisse: p8$^{-/-}$ MEF zeigen unstimuliert und nach H_2O_2 Stimulation eine erhöhte ROS Produktion. Diese war unter ACC-Gabe nur partiell reversibel. Die ROS Induktion durch H_2O_2 in p8$^{-/-}$ MEF war geringer. Gegenregulatorisch zeigte sich ein vermehrter Gehalt des antioxidativen Enyzmes Hämoxygenase-(HO)-1. Nach Arretierung der Zellen in der G2/M-Phase und HO-1 Induktion blieb dieser Unterschied erhalten. Interessanterweise zeigte sich auch ein unterschiedlicher Anstieg von Zellzyklus-regulierenden Proteinen.
Diskussion:p8$^{-/-}$ MEF haben einen erhöhten Gehalt an ROS und induzieren möglicherweise gegenregulatorisch von HO-1. Diese Veränderungen waren unabhängig vom Zellzyklus. Wir spekulieren, dass die bekannten zellulären Wachstumsunterschiede sowie die schwereren Verläufe von Sepsis und Pankreatitis in p8$^{-/-}$ Mäusen auf einen veränderten Redoxstatus zurückzuführen sind.

Funding: formel1

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POSTER 60

Comparison of differentiated cells generated from IPS cells with primary somatic cells

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Induced pluripotent stem (IPS) cells have become a promising tool for regenerative medicine. One of the aims of this project is to obtain pluripotent cells, which could be used in a clinical setting. IPS cells were derived with the following pluripotency factors: Oct4, Sox2, Klf4, and Nanog.
To determine IPS cells pluripotency qPCR, immunohistochemistry, *in vitro* and *in vivo* differentiation and gene array analysis were performed.
To analyze the aging characteristics of IPS cells they were differentiated into fibroblasts which show senescence morphology after repeated passaging. In order to determine which characteristics differentiated cells have, we analyzed through ß-galatosidase staining senescent cells. p21 and p16 level should be higher in senescent cells compared to young primary somatic cells. Also, apoptosis should be reduced in senescent cells.
In addition, during cell cycle telomere length becomes successive shorter in somatic cells. Pluripotent stem cells have stable telomere lengths. Therefore it's interesting to analyze when telomeres reach a critical length, which induces IPS-cells derived fibroblasts to undergo senescence compared to primary fibroblasts. Telomere length was measured by qPCR. Differentiated fibroblasts and primary fibroblasts were analyzed on the same passage-levels.

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POSTER 61

Non-adherent bone marrow cells facilitate hematopoesis after murine allogeneic and syngeneic hematopoeitic stem cell transplantation

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Non adherent bone marrow cells (NA-BMCs) are a mixed cell population derived from bone marrow cells (BM). They contain progenitors of stem cells as well as maturated cells, which are able to differentiate in mesenchymal and hematopoietic cells. Further characterization of NA-BMCs and experiments concerning the recovery and organ repair of lethally irradiated recipients were conducted. After 4 days of cultivation of BM from C57Bl/6 or Balb/c mice, NA-BMCs were characterized *in vitro* by electron microscopy, cytology, flow cytometry and CFU-f. NA-BMCs and BM were transplanted in C57Bl/6 (huCD4$^+$, muCD4$^{-/-}$, huHLA-DR3$^+$) mice, sorted CD45$^+$ cells (out of NA-BMCs) in Balb/c mice. Survival, weight, hemogram and chimerism were analyzed weekly after transplantation. Organ repair was studied by histology after 50 days. Compared to BM, CD45$^+$ NA-BMCs showed an increase of CD11b$^+$, CD90$^+$ and a decrease of CD117$^+$, CD4$^+$, CD8$^+$, CD19$^+$ cells. In NA-BMCs, CFU-f was significantly declining over the cultivation period but NA-BMCs were still able to form CFU-f after 5 days ($p<0.05$). In comparison to BM cells, the transplantation of $2x10^6$ NA-BMCs lead to significantly faster recovery of hematopoiesis and a higher survival rate. Transplantation of sorted CD45$^+$ cells also leads to hematopoietic recovery. Histopathological examination of organs showed no abnormalities or signs of graft-versus host disease. In contrast to syngeneic NA-BMCs, allogeneic NA-BMCs induced no detectable hematopoietic donor chimerism. NA-BMCs could be a therapeutic approach in hematopoietic stem cell transplantation because of faster hematopoietic recovery and organ repair.

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POSTER 62

Expression and function of a new cell cycle regulator

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In 2003, the successful completion of the Human Genome Project was announced. Now, the challenge is to evaluate the functions of all gene products. Here we describe expression, localization, interaction partners and functions of a new cell cycle protein that was initially identified in a genome-wide siRNA-based screen. siRNA knockdown leads to reduced viability of cultured cells. In contrast, overexpression results in a shortening of G_1-phase of the cell cycle. Therefore, we have named the protein CRISPI (Cell Cycle Regulator Inducing G_1/S Progression).
We provide evidence that the gene is expressed in a cell cycle-dependent manner. mRNA and protein are only detectable in S/G_2/M phases of the cell cycle and in proliferating tissues. Induction of the tumor suppressor p53 leads to a strong transcriptional repression of this new gene. Both cell cycle-dependent expression and p53-dependent repression are mediated through a canonical E2F binding site close to the transcription start. In co-localization studies, we were able to show that CRISPI is localized to the nuclear speckles. To identify interacting proteins, we applied a mass spectrometry-based proteomic approach using the stable isotope labelling with amino acids in cell culture (SILAC) method. Furthermore, we observed that the splicing factor MagoH interacts with CRISPI.
Taken together, these findings indicate that CRISPI is an important factor in cell cycle regulation.

Funding: formel1

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POSTER 63

E2F binding without E2F site: The CHR element is sufficient for binding of E2F4 and DREAM proteins to promoters repressed by CDE/CHR sites.

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Cell cycle genes like *cyclin A, cyclin B, Cdc2 (cdk1)* and *Cdc25C* are regulated on the transcriptional level by CDE and CHR promoter sites through repression in G0. The CDE is related to E2F sites. However, CDEs are distinct from E2F elements as they are always found in conjunction with a CHR four nucleotides downstream. Recently, E2F4 and Lin54 together with other mammalian DREAM protein complex components were shown by ChIP analyses to bind to several CDE/CHR-regulated promoters. Until now the assumption was that E2F4 binding to E2F-like CDE sites is central to cell cycle-dependent transcriptional regulation and this association is only supported by the neighboring CHR stabilizing the interaction. We have looked at protein binding to the mouse and human *cyclin B2* promoters in nuclear extracts from G0 cells and observe that the DREAM complex binds to both promoters. Binding of E2F4, p107, p130, Lin9, Lin37 and Lin54 is decreased to background when the CHR is mutated. Importantly, cell cycle-dependent regulation of the human *cyclin B2* promoter solely depends on the CHR since it does not contain a functional E2F or CDE site. Thus, E2F4 in a complex with other DREAM proteins can bind to the promoter through the CHR. NF-Y-binding CCAAT-boxes are required for most of the transcriptional activity of mouse and human *cyclin B2* promoters throughout the cell cycle. Our data suggest a model, based on the *cyclin B2* promoter, by which E2F4/DREAM components repress transcription in G0 and are primarily bound through the CHR. Activation is mostly dependent on NF-Y proteins binding to CCAAT-boxes.

Assoziation: PbF III

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POSTER 64

Effect of Bisphenol A on dendritic cell maturation and T cell plasticity

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Bisphenol (BPA) is a main xenoestrogen commonly used in the plastic industry. It has been shown that maternal exposure with BPA promotes the development of experimental asthma in mouse pups and that BPA affects the differentiation of naïve T cells (TC). In the present study we investigated the effect of low dose BPA on dendritic cell maturation and TC plasticity.
The effect of BPA on the immune function of monocyte-derived dendritic cells (MoDC) and naïve CD4+ TC was analyzed by flow cytometry. Low dose treatment with BPA did not influence the expression of differentiation and maturation marker on MoDC while the expression of the homing receptor CD62L on naïve CD4+ TC was slightly reduced.
These results demonstrate that BPA does not influence MoDC maturation, however, it may influence TC homing properties.

Assoziation: PbF III

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POSTER 65

Association of CTLA4 with Systemic Sclerosis: new data and meta-analysis

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Systemic sclerosis (SSc) is an autoimmune disorder characterized by collagen depositions in skin and internal organs, vascular alterations, immunological abnormalities and great variability. A polygenetic background is indicated as well.
CTLA4 is a prominent candidate gene for immune diseases like SSc. Five studies examining association of CTLA4 with SSc were published with partly contradicting results. Thus, we analyzed association of SSc with 7 CTLA4 polymorphisms (SNPs) in a German Caucasian SSc case control cohort. A meta-analysis of published data on CTLA4 and SSc was conducted as well.
For this, 217 German patients and 232 controls were enrolled. Disease subtype, antibody status, organ involvement and age of onset was noted. Allelic and genotypic distribution were calculated and subgroup differences assessed.
Association of rs11571317 with SSc was found ($p = 0.018$). The promoter SNPs -1772CT and -318CT were also associated with disease subtypes and -1661CT and CT60 with organ involvement.
Significant influence on age of onset was found for +49AG and rs231723 ($p = 0.015$ each).
Meta-analysis did not confirm association of previously investigated CTLA4 SNPs with SSc. But in rs11571317 we found a new CTLA4 SNP to be associated with SSc and severel subtype associations as well. These SNPs, mostly promoter SNPs, might influence CTLA4 expression levels, or exon splicing. It has been proposed, that low levels of receptor CTLA4 or high levels of soluble CTLA4 might contribute to T cell receptor over-stimulation. In summary, CTLA4 variants might promote autoimmunity and influence patients outcome.

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POSTER 66

Differential Allelic Expression of genes associated with Asthma

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An important question in research of genetic traits in complex diseases is functional relevance of identified associating genetic variants. Differential allelic expression (DAE) is estimated to affect 20–50% of human genes and can be measured by genotyping cSNPs in heterozygous cDNA samples.
SNPs in IL13 and CSF2 associated with asthma were investigated for correlation with cis directed expression of a specific allele. Results may provide a functional link between genetic variants and pathological mechanism related to asthma. One coding SNP per gene was investigated. About 50 immortalized B celllines were screened for heterozygosity. Nucleic acids were won. To identify DAE, quantitative genotyping of the alleles by mass-spectrometry was done. Significant derivation of allelic ratios between cDNA and gDNA samples indicated allelic regulation. Similar direction of intra-sample effects for a given SNP indicated cis-regulation.
Both SNPs showed significant DAE ($p[IL13] = 0.002$, $p[CSF2] = 0.01$). For IL13, average expression of the asthma risk A allele was ~22% above expression of the G allele. Higher expression of IL13 might contribute to the clinical relevant increase of functional IL13 activity. For CSF2, the asthma risk T allele was expressed ~38% more then the C allele. We speculate that genetically entailed elevated CSF2 expression promotes macrophage and neutrophil function during inflammatory reactions which is linked to increased inflammatory events in asthma.
Overall, analysis of DAE of disease-associated markers proves an efficient approach for elucidating functional and possibly pathological relevance of SNPs.

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POSTER 67

Red-On-Tap – Continous Proliferation and Simultaneous Maturation of Haematopoietic Stem Cells into Blood Cell Lineages

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The demand for blood transfusions in Germany is currently about 5 Million units per annum at a unit cost in excess of 300€. Many blood transfusion services already have difficulty providing sufficient quantities of correctly matched units. However, attempts to date to engineer cheaper blood substitutes have been disappointing.

The objective of the EU-funded "REDONTAP" project is the continuous production of large quantities of GMP-grade erythrocytes *via* ex-vivo erythropoiesis. Our strategy is to develop a novel bioreactor system capable of recapitulating and optimising the stages of erythropoiesis in the bone marrow: i) Long term maintenance of stem cells; ii) specification and expansion of committed erythroid progenitor cells and iii) functional maturation of robust, enucleated erythrocytes. Seeded with defined stem cells from umbilical cord blood, this system would provide a non-invasive, quality controlled source of tissue matched erythrocytes to order.

Our recent work within the BmBF-Consortium "NMR Metabolic profiling of the Stem cell Niche" has shown that the proliferation and differentiation of haematopoietic stem and progenitor cells are influenced markedly by their metabolic environment, consistent with the existence of distinct metabolic compartments in the bone marrow tuned to support the various stages of erythropoiesis. We are currently defining the parameters required to support stem cell self-renewal on the one hand and erythroid differentiation on the other, in order to develop novel culture media optimised for the high yield production of end-stage erythrocytes.

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POSTER 68

Changes in metabolic profile of skeletal muscle fibres of ApoE-deficient mice

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It is well documented that elevated levels of angiotensin II (Ang-II) are associated with the development of atherosclerosis and that exercise training (ET) attenuates this development. Nothing is known about metabolic alterations in the skeletal muscle due to Ang-II and ET. Aim of this study was to investigate metabolic changes in skeletal muscle fibres due to Ang-II and ET. Osmotic mini-pumps were used to infuse Ang-II (n=20) or NaCl (n=10) into ApoE deficient mice (n=20). Half of the Ang-II infusion mice (n=10) were also exercise daily on a treadmill during Ang-II infusion. After 4 weeks skeletal muscles were removed and analysed by means of cytophotometry for fibre type specific changes of glycolytic (GPDH) and oxidative (SDH) enzyme activities. The results differed in soleus muscle (SOL) as an endurance muscle and extensor digitorum longus muscle (EDL) as a fast force muscle. In SOL mainly the SDH activity changed while the GPDH activity remained nearly unchanged, in contrast to EDL which showed the opposite effect. In both muscles, the FOG fibres (fast fibres with both oxidative and glycolytic metabolism) were the most affected fibre type. The FOG fibres of untrained ApoE mice with Ang-II infusion showed to 50% decreased enzyme activities compared to ApoE mice without Ang-II infusion, suggesting the muscles of ApoE mice may be stronger diseased after Ang-II infusion. The training antagonized this effect, indicating a beneficial effect of training on muscles of ApoE mice.

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POSTER 69

Impairment of NFκB activity by unsaturated fatty acids

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Polyunsaturated fatty acids (PUFAs) are known to modulate lymphocyte proliferation, antigen presentation, cytokine synthesis, oxidative burst as well as expression of adhesion molecules. In this regard, PUFAs are speculated in part to exert their effects on inflammatory gene expression through direct actions on intracellular signaling pathways. However, concerning the action of PUFAs on NFκB conflicting data do exist. In fact, it is not known if the interrelation between fatty acids and NFκB is restricted to special fatty acid families. In addition, the impact of the degree of saturation of a fatty acid is unidentified so far.

Here we present the first systematic study investigating acute as well as long-term effects of PUFAs from the n-3, the n-6 as well as the n-9 family on NFκB activity by mean of a luciferase reporter cell line.

We identified PUFAs to impair NFκB signaling. Furthermore, we could demonstrate the PUFAs ability to derogate NFκB activity to be independent from the family the fatty acid belongs to. Instead, we found a correlation between the number of bis-allyl-methylene positions of the PUFAs added and the NFκB activity of stimulated, long term supplemented cells.

The data provide new insights into the biological mechanisms PUFAs exert their anti-inflammatory effects. Since suppression of NFκB activity could be of benefit in a number of inflammatory diseases as well as cancer, our findings are of clinical implication. According to our data dietary supplementation with PUFA-containing oils is likely to provide an at least palliative therapy for disorders linked to inappropriate NFκB signaling.

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POSTER 70

Alteration of gene expression in murine macrophages by fatty acid supplementation

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Polyunsaturated fatty acids (PUFAs), have been shown to affect various health-related processes e.g. immune response. These modulating effects are speculated to arise from the incorporation of fatty acids into the phospholipid bilayer of certain immune cells possibly influencing membrane fluidity and the structure of membrane receptors. Moreover, fatty acids have been proposed to alterate the expression of several genes thereby acting as universal cellular regulators.

The effects of PUFA on gene expression of immunoregulation-related genes in the murine macrophage cell line RAW 264.7 should be studied. RAW, supplemented with LNA, EPA, DHA, LA and AA, respectively are going to be subsequently stimulated with one of the following: PMA, LPS, *R. equi* or *P. aeruginosa*. Gene expression analysis will be performed via qPCR.

The study will show whether and to what extend PUFA supplementation of cells will be modify the expression of certain immunoregulatory genes. In particular, new knowledge is expected in the field of macrophage activation by pathogens regarding adapter proteins (MyD88, RICK), surface molecules (MHCII, B7, Fc-receptor), enzymes of respiratory burst (superoxid dismutase, myeloperoxidase) and antimicrobial peptides (lysozyme).

Based on the new findings an assessment of the underlying processes of immunomodulation by PUFA will become possible. At this, the inclusion of pathogens allows new insights into host-pathogen interaction. This is the precondition of a targeted use of PUFA as supportive therapy of chronic diseases caused by *Rhodococcus equi* and *Pseudomonas aeruginosa*.

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POSTER 71

Growth substrates with sulfated glycosaminoglycans induce a proliferating fibroblast phenotype in vitro

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Fibroblasts (Fb) play a crucial role in dermal wound healing. They receive signals from immune cells, keratinocytes and are influenced by the chemical and physical properties of ECM itself which has an impact on cell proliferation, differentiation and ECM metabolism. Here we investigated the effect of selectively designed artificial ECM (aECM) on the physiology of Fb with respect to cell proliferation and ECM synthesis.
The aECM consists of collagen I (ColI) and chemically sulfated glycosaminoglycans (GAGs). These sulfate groups might be feasible binding partners for growth factors and cytokines thus improving acceptance of implants in the recipient tissue.
Primary human Fb from breast and foreskin were cultured on coatings of ColI/GAG mixtures of 1:1 or 10:1 ratio. Higher degrees of GAG-sulfation resulted in 2-3-fold increased proliferation of foreskin Fb and up to 8-fold increase of proliferation of breast skin Fb. Compared to controls hyaluronan (Hya) release and Hya synthase expression were reduced by increasing sulfation levels of GAGs with at least 50% reduction of synthesis.
ColI (α1) mRNA was transiently downregulated in Fb grown on derivates Hya3.0 and CS3.1 at 10:1 ratio for 8h. Coatings with highly sulfated Hya and chondoitin sulfate(CS) at a ColI/GAG ratio of 1:1 resulted in a strong downregulation of coll (α1) mRNA expression after 8h and 24h.
These results indicate that sulfation of GAGs has a positive impact on cell proliferation of Fb from various tissue sources. The data suggest that sulfated aECM induce a highly proliferating, non-synthesizing phenotype of Fb resembling early stages of wound healing.

Assoziation: PbF III

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POSTER 72

Assay of cell lines devoid of mtDNA compared to their parental wild type.

Heller S[1], Schubert S[1], Seibel P[1]
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The mitochondrion, one important organelle of eukaryotic cells harbours important biochemical processes and acts as key-player in the ageing process and the programmed cell death.
The human mitochondrial genome (mtDNA) displays a size of 16569bp and contains 37 genes that are important for normal mitochondrial function. Apart from genes for rRNA and tRNA the mtDNA encodes 13 polypeptides that are essential enzymatic subunits of the respiratory chain. Genes of other mitochondrial peptides are located in the nuclear genome so that these peptides have to be transported into mitochondria.
The respiratory chain consists of the four enzyme complexes NADH:ubiquinoneoxidoreductase(complexI),succinate:ubiquinone oxidoreductase (complex II), ubiquinol:cytochrome c oxidoreductase (complex III) and cytochrome c oxidase (complex IV) that function as electron transport complexes and the ATP synthesising complex ATP synthase respectively. Only complex II is completely encoded by the nuclear genome whereas genes of other respiratory chain complexes are located on the nuclear and mitochondrial genome.
Cells without mtDNA are termed ρ0-cells according to the genetics of yeast. Therefore, cells with ρ0-genotype lack a functional respiratory chain and require metabolic supplementation for cell viability. Cells devoid of mtDNA are generated by cultivating them on growth medium that includes chemicals like ethidiumbromide or ditercalinium that interfere with DNA replication. A new method takes advantage of a restrictionendonuclease directed to the mitochondrial matrix without the toxicological side effects caused by the chemical method.

Assoziation: PbF III

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POSTER 73

The effect of inhibitors of oxidative phosphorylation on eukaryotic cell organelles.

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Eukaryotic cells possess several organelles, e.g. mitochondria and peroxisomes.
Mitochondria are DNA containing organelles (16569 bp in Homo sapiens). Less than 5 % of all mitochondrial proteins are encoded by the genome of these organelles, more than 95 % are encoded by the nuclear genome and have to be transported into the mitochondria. Mitochondrial DNA contains 37 genes that are important for normal mitochondrial function. Thirteen of these genes are coding for essential enzymatic subunits involved in oxidative phosphorylation. Mitochondria contain the primary energy-generating system (ATP). Furthermore they play essential roles in processes such as intermediary metabolism, proliferation, apoptosis and ageing of the cell.
Peroxisomes are vesicle-like packets bounded by a single membrane that surrounds a compartment termed the matrix. They are crucial for lipid metabolism and free radical detoxification. Peroxisomes are able to respond to environmental changes and extracellular stimuli by changing their enzyme content, morphology and abundance.
Both organelles, peroxisomes and mitochondria, are metabolically linked and are cooperating and cross-talking.
We studied the influence of inhibitors of respiratory chain on the morphology of mitochondria and peroxisomes. By transient transfection with subcellular localisation vectors these organelles could visualised by fluorescence microscopy.

Assoziation: PbF III

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POSTER 74

Langzeitbeobachtung von Patienten mit MCAD-Mangel: biochemische, klinische und psychosoziale Aspekte

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Einleitung/Methodik: Zur Analyse der Betreuungsqualität an unserer Klinik führten wir eine retrospektive Erhebung durch. Alle an der Universitätsklinik Leipzig behandelten Patienten mit MCADD wurden eingeschlossen. Die Patienten und die Eltern wurden einem standardisierten Interview unterzogen (u.a. KINDL). Auch erfolgte eine Beurteilung des intellektuellen Entwicklungsstandes (HAWIVA III, HAWIK IV, u.a.). Klinische und biochemische Daten wurden aus den Krankenakten ermittelt. *Ergebnisse:* 14/19 (f:m 10/9) Patienten wurden durch das erweiterte NGS auffällig. Drei Patienten wurden anlässlich einer Stoffwechsel-Entgleisung, zwei im Rahmen der Familiendiagnostik identifiziert. Die homozygot klassische Mutation (K329E) fand sich bei 7 Patienten. Die Konzentration von C8 war bei homozygot klassischer Mutation im Durchschnitt höher als bei compound Heterozygoten, jedoch nicht signifikant (11.3 ± 13.5 vs. 8.4 ± 7.3 μmol/l, t-Test: p=0,16). Eine Erniedrigung des freien Carnitins (C0) zeigte sich in keinem Fall. Die übrigen biochemischen Parameter (C8:1, C8/C10, C8/C16) zeigten keine Unterschiede. Die Urinanalyse erbrachte in 9/10 Fällen den typischen Befund einer Dicarbonazidurie. Die psychologische Diagnostik war bei allen Kindern altersentsprechend. Die Lebensqualität ist insgesamt gut. (KINDL). 11/15 Eltern hatten initial große Angst vor einer Stoffwechselentgleisung, im Verlauf wird der MCADD zunehmend als Besonderheit des Kindes angesehen, nicht als Krankheit (12/19). 2 Familien halten die regelmäßige Betreuung in der Stoffwechselambulanz für übertrieben. 3 niedergelassenen Kinderärzten war die Diagnose geläufig, nur in einem Fall traute die Familie diesem die Betreuung zu. 5/19 Familien möchten aufgrund der Diagnose kein weiteres Kind. *Diskussion:* Die Patienten zeigen einen guten klinischen Verlauf. Problematisch erscheint, dass der MCADD mit zunehmendem Alter nur noch als harmlose Stoffwechselvariante angesehen wird. Andererseits führt die vermehrte Diagnose des MCADD möglicherweise zu „Überdiagnostizierung" mit nicht unerheblichen psychosozialen Folgen. Diese verdienen größere Beachtung.

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POSTER 75

Multiparametrische MR-Bildgebung der Prostata bei 3 Tesla

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Das Prostatacarcinom (PCA) zeichnet sich durch eine hohe Inzidenz bei verhältnismäßig geringer Mortalität aus. Mit Hilfe einer MR-Bildgebung der Prostata kann die diagnostische Genauigkeit für ein PCA deutlich erhöht werden. Im Unterschied zu anderen bildgebenden Verfahren (Ultraschall, Computertomographie) erlaubt die MRT als einzige Methode eine zuverlässige Darstellung der Prostatasubstruktur. Neben einer konventionellen, morphologischen Bildgebung mittels hochaufgelöster T2-gewichteter Sequenzen in drei Ebenen, können zusätzlich funktionelle MR-Techniken (diffusions- und perfusionsgewichtete Bildgebung, MR-Spektroskopie) eingesetzt werden. Letztere erlauben Rückschlüsse auf eine eingeschränkte Diffusion (Zellbarrieren), eine pathologische Kontrastmittel-Dynamik (Neovaskularisation) sowie eine malignomsuspekte Veränderung der Metabolite Cholin (Membranaufbau) und Citrat (gesundes Prostatagewebe). Unter Einsatz einer Endorektalspule ist bei einer Feldstärke von 3 Tesla eine exzellente Bildqualität erreichbar, mit der höhere Detektionsraten, eine genauere anatomische Zuordnung sowie ein besseres Staging des PCAs erzielt wurden.
Unter Verwendung eigener Bildbeispiele bei 3 Tesla werden dem Betrachter zunächst auffällige bildmorphologische Veränderungen eines PCAs anhand der vier Parameter *Morphologie*, *Diffusion*, *Perfusion* und *Stoffwechsel* gezeigt. In Zusammenschau aller Bildinformationen soll der Betrachter mit Hilfe einer Übersicht über maligne und benigne Prostataveränderungen mehr Sicherheit in Bezug auf Diagnose und Differentialdiagnose eines PCAs gewinnen.

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POSTER 76

Effektivität computer- und internetgestützter kognitiver Verhaltenstherapie bei Depression. Ein systematischer Literaturüberblick

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Anliegen Systematischer Überblick zur Wirksamkeit von computergestützter kognitiver Verhaltenstherapie bei depressiven Erkrankungen. *Methode* Literaturrecherche in Medline, Web of Science, Cochrane und PsycINFO. *Ergebnisse* 16 Studien wurden identifiziert. Effekte der Interventionen sind abhängig von der Häufigkeit und Dauer des Therapeutenkontaktes und der Art der Kontrollgruppe. Die Effektstärken erstrecken sich von Cohens d = 0,0 bis d = 1,1. *Schlussfolgerungen* Computergestützte Verhaltenstherapie stellt eine niedrigschwellige Interventionsmethode dar, die vor allem bei Patienten mit leichter und mittelschwerer depressiver Symptomatik wirksam ist. In unterversorgten Gebieten kann sie zur Versorgungsoptimierung beitragen und Baustein eines gestuften Behandlungsplanes („stepped care") sein.

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POSTER 77

Nachweis des LH-Rezeptors (LHR) im Urothel und Veränderungen der Expression bei Interstitieller Zystitis (IC)

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Hintergrund: Humanes Choriongonadotropin-beta (ß-hCG) und sein Rezeptor (LHR) wurden in verschiedenen extragonadalen Geweben nachgewiesen, wobei ihre Funktion jedoch unklar ist. Aufgrund klinischer Beobachtungen vermuten wir eine Rolle von ß-hCG im Sinne eines protektiven Faktors für das Urothel der Harnblase und in der Pathophysiologie der Interstitiellen Zystitis. Daher untersuchten wir die Expression des LHR in Harnblasen von Patienten mit IC und einer Kontrollgruppe.
Material und Methoden: Aus Harnblasenbiopsien und Zystektomien gewonnenes Gewebe wurde mittels indirekter Immunfluoreszenz und real-time PCR untersucht (Kontrolle, n=22; IC, n=20). Die Auswertung konfokaler Bilder (LSM 5 Pascal, Zeiss) erfolgte mit ImageJ, die statistische Analyse mit GraphPad Prism 5.
Ergebnisse: In beiden Patientengruppen fanden wir eine Expression des LHR. Diese war im Urothel von weiblichen IC-Patientinnen signifikant höher als in der Kontrolle. Während wir in der Kontrollgruppe (w: n=13; m: n=9) keine geschlechtsspezifischen Unterschiede fanden, war die Expression bei IC im weiblichen Urothel signifikant höher als im männlichen (w: n=15, m: n=5).
Schlussfolgerung: Erstmals konnte der LHR auch in der männlichen Harnblase nachgewiesen werden. Unterschiede in der urothelialen Expression des LHR bei IC-Patienten legen eine Rolle von ß-hCG und des LHR für die Pathologie der Interstitiellen Zystitis nahe. Die Aufklärung der biologischen Funktion des ß-hCG für die Stabilität und Regeneration des Urothels könnte zu neuen therapeutischen Ansätzen der Interstitiellen Zystitis führen.

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POSTER 78

Effect of oral glucose and fat loading on amino acid metabolism and fatty acid beta oxidation

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Introduction: Dietary factors may affect metabolic pathways of amino acids (AA) and acylcarnitines (AC). Our aim was to investigate the effect of standardized oral glucose and fat loading on the metabolism of branched-chain amino acids, glucose-alanine cycle, urea cycle, carnitine shuttle system, and the mitochondrial fatty acid beta-oxidation.
Method: Analysis of 26 AA and 35 AC in dried blood samples was performed by tandem mass spectrometry. The influences of glucose loading were investigated in 16 male (age 54-79 years, BMI 24-29) and 21 female (age 49-68 years, BMI 19-35) volunteers during an OGTT. The effect of oral fat loading was investigated in 7 volunteers (4/3 m/f, age 23-54 years).
Results: Oral glucose loading significantly decreased gender specific the concentrations of the ketogenic amino acids leucine/isoleucine but not of the final metabolite acetyl-CoA (acetylcarnitine). Same observation was found for valine and the corresponding metabolite propionyl-CoA (propionylcarnitine). Arginine and citrulline (urea cycle) showed significantly lower concentrations. Activated fatty acids (C6-C10 carnitine) were only decreased in female volunteers. Fat loading (triglycerides) decreased phenylalanine concenctrations. The glucose alanine cycle and the carnitine shuttle system were not influenced in both, glucose and fat loading.
Conclusion: Glucose and fat loading induced different alterations of metabolic pathways involved in energy balance. Following studies have to elucidate whether in people with impaired glucose tolerance different metabolic alterations of AA and AC metabolism can be observed.

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POSTER 79

Combined pituitary hormone deficiency (CPHD) in two patients due to gross deletions in PROP1 and POU1F1 (PIT1)

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Development of the pituitary gland depends on a complex cascade of transcription factors and signaling molecules. Mutations in any of the genes involved in pituitary development may cause persistent functional defects which lead to Combined Pituitary Hormone Deficiency (CPHD). Aim of the study was to determine the frequency of copy number variants (CNVs) in genes known to cause CPHD in a cohort of patients with hypopituitarism. We have screened 90 individuals with CPHD employing Multiplex Ligation-dependent Probe Amplification (MLPA) to detect CNVs within the transcription factors *PROP1*, *POU1F1*, *LHX3*, *LHX4*, *HESX1*, *GH1* and *GHRHR*. Breakpoints of deletions were identified by STS mapping, long-range and inverse PCR followed by dideoxy-sequencing. Causative mutations were found in two unrelated consanguineous Turkish families. The affected boy in Family I presented with severe growth retardation (-11.2 SDS at 11 yrs) and showed very low basal levels of GH, TSH and PRL. We identified a homozygous deletion of exons 1 and 2 of the *POU1F1* gene and defined the deleted sequence to ~5 kB including about 1.3 kB of the *POU1F1* proximal region. Four siblings of Family II presented with deficiency in GH, TSH and FSH/LH. In these patients we discovered a homozygous 15 kB deletion including the complete *PROP1* gene. MLPA analysis of 90 CPHD patients revealed the first homozygous *POU1F1* and a novel *PROP1* gross deletion. No CNVs within the other analyzed genes were found. In summary, our data prove MLPA to be a valuable tool for the detection of CNVs as cause of pituitary insufficiencies and to provide a molecular basis for genetic counseling.

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POSTER 80

TiO2 particles may pose a mutagenic risk

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Introduction: TiO_2 is thought to be nonmutagenic but discussed to increase inflammatory responses triggering mutagenesis. We analyzed TiO_2 effects on micronucleus (MN) formation in an OECD-conform MN assay using primary human oropharyngeal epithelial cells (EC). *Methods:* Mucosal biopsies were taken and following tryptic digestion grown in KSFM (keratinocyte serum-free medium with 20 ng/ml of epidermal growth factor) in petri-dishes coated with extracellular matrix proteins (EMP). After two passages, EC were seeded into EMP-coated 24-well plates and cultured 3 days (3.5% CO_2, 36.5°C, 95% relative humidity) until replacement of supernatants by either KSFM (negative control; NC), 100 pM mitomycin C (positive control; PC), or 100 $\mu g/cm^2$ TiO_2. After 24 hours, cytochalasin B was applied to block cytokinesis. 24 hours later and following withdrawal of supernatants, EC were ethanol-fixed, and DNA DAPI-stained MN were counted in 1000 bi-nucleated EC (BN) per well. *Results:* 43/48 EC (89.6%) showed significant MN induction in PC (>130% NC). Neither significant differences in MN formation in NC in comparison to gender nor between donors with differing nicotine consumption (below or above 30 pack years) were found; the medians were the same (20 MN in 1000 BN). Differences of these groups regarding medians and interquartile ranges of MN-formation in PC or TiO_2-treated EC were only insignificant. The *t* test for paired samples revealed a significant induction of MN formation by TiO_2 ($p<0.01$). *Conclusions:* TiO_2 increases MN formation in pEC. This outcome is only slightly influenced by sex and smoking behavior.

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POSTER 81

Einfluss der Gesichtsweichteile auf die Fraktur des Jochbeins – Simulation eines Kopfstoßes mit Hilfe der Finiten-Elemente-Methode

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Auf Grund ihrer großen Häufigkeit liegen Mittelgesichtsfrakturen auf Platz Eins aller Schädelfrakturen. Der Zusammenstoß von zwei Köpfen ist eine mögliche Ursache hierfür und tritt bei sportlichen Aktivitäten und gewalttätigen Auseinandersetzungen auf. Trotz der klinischen Relevanz dieses Themas gibt es keine biomechanischen Finite-Elemente- (FE) Untersuchungen eines Kopfstoßes, um die entstehenden Bruchbilder zu beurteilen. In dieser Studie werden sowohl der Einfluss des den Knochen umgebenden Weichgewebes wie auch der eigentliche knöcherne Impact untersucht. Die FE-Modelle der Schädel sowie des Weichgewebes wurden anhand von segmentierten Oberflächennetzen eines Patienten-CTs erstellt. Für die aktuelle Studie wurde auf die Unterkiefer verzichtet. Die Modellierung wurde mit der FEM-Software ANSYS durchgeführt und explizit dynamisch gelöst. Dazu wurden als Materialmodell für die Schädel ein E-Modul von 13500 MPa und für das Weichgewebe ein E-Modul von 0,5 MPa festgelegt. Die Modelle wurden mit tetraederförmigen 4-Knoten-Elementen vernetzt. Der Kopfstoß wurde mit einer Geschwindigkeit von 6,5 m/s modelliert. Die Ergebnisauswertung wird anhand des Fließkriteriums der von-Mises-Vergleichsspannung vorgenommen. Im Vergleich der beiden modellierten Szenarien zeigt sich kein direkter Einfluss des Weichgewebes auf das entstehende Bruchbild. Bei der Berücksichtigung des Weichgewebes treten ebenso Frakturen auf, die klinischen Frakturverläufen gleichen. Es kann gezeigt werden, dass mit Methoden der Computersimulation biomechanische Probleme wie die Beurteilung von Bruchbildern durch Traumen untersucht werden können.

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POSTER 82

Statistische Beurteilung neuer laparoskopischer Techniken und neuer Techniken mit der Workflow Analyse

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Unter Verwendung eines definierten Modellaufbaus wurde die Workflowanalyse angewandt, um laparoskopische Techniken und laparoskopisches Instrumentarium statistisch zu vergleichen.
Methodik: Unter standardisierten Bedingungen wurden drei verschiedene Arbeitsschritte ausgeführt: 1. Schneiden (=resezierend), 2. Einfache Naht fortlaufend (=verschließend), 3. Anastomosennaht fortlaufend (=rekonstruktiv). Angewandte laparoskopische Techniken sind: – Konventionelle gerade Instrumente in konventioneller Technik (3 Trokarpositionen) und in SILS-Technik (1 Tripeltrokarposition im Nabel). – TEM-Instrumente gekröpft in konventioneller Technik (3 Trokarpositionen) und in SILS Technik (1 Tripeltrokarposition in Nabel). Jeder Arbeitsschritt wurde vom Probanden fünfmal durchgeführt (= 15 Durchgänge pro Technik). Bei vier verschiedenen Techniken ergaben sich pro Proband 60 Datensätze. Dies sind bei 10 Probanden 600 Datensätze.
Ergebnisse: 1. Bei konventioneller 3-Trokar-Technik ist der Ablauf mit gekröpften Instrumenten (TEM) 4mal schneller (=signifikant) als mit geraden Instrumenten, bei gleicher Qualität. 2. Die Übungsdauer mit gekröpften Instrumenten (TEM) in 1-Trokar-Technik ist ca. 3mal länger (=signifikant) als mit geraden Instrumenten in konventioneller 3-Trokar-Technik. Es gibt dabei keinen signifikanten Unterschied in der Qualität. 3. Die Übungsdauer ist in 1-Trokar-Technik mit gekröpften Instrumenten (TEM) deutlich geringer (=signifikant) als mit geraden Instrumenten, bei gleicher Qualität.
Schlussfolgerung: Die Workflowanalyse erlaubt sichere und statistisch fundierte Aussagen über alle registrierten Parameter.

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POSTER 83

Veränderung des Ernährungsverhaltens bei Patienten mit Phenylketonurie unter der Therapie mit Tetrahydrobiopterin (BH4)

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Einleitung In der vorliegenden Studie soll geklärt werden, inwieweit sich bei Patienten mit Phenylketonurie das Ernährungsverhalten, die Phenylalanintoleranz und die Nährstoffversorgung unter der Therapie mit BH4 verändern. Ziel einer Behandlung mit BH4 ist die Erhöhung der Phenylalanintoleranz und damit die Lockerung der strengen eiweißarmen Diät sowie die Reduktion der notwendigen Zufuhr phenylalaninfreier Aminosäuremischungen (ASM).
Patienten und Methoden Einschluss von 18 Patienten mit PKU (9 w, 9 m). Erstellen von Ernährungsprotokollen (EP) über einen Zeitraum von 42 Tagen, parallel zur Bestimmung der Phenylalaninkonzentration im Trockenblut. Beginn der Therapie mit BH4 am Tag 14. Auswertung der EP hinsichtlich des Lebensmittelverzehrs und der Nährstoffversorgung. Vergleich mit Nährstoffempfehlungen der Ernährungsfachgesellschaften von Deutschland, Österreich und Schweiz (D-A-CH).
Ergebnisse Auswertung der Daten von 14 Patienten möglich. Bei 9 Patienten stiegen unter Behandlung mit BH4 die Phenylalanintoleranz sowie die Eiweißzufuhr aus natürlichen Lebensmitteln wie z.B. Milchprodukten an. Dabei Verschlechterung der Versorgung mit Vitamin D, Eisen, Jod und Calcium. Keine signifikanten Unterschiede in der Kohlenhydrat- und Fettzufuhr sowie der Energieversorgung. Bei 5 Patienten konnte keine BH4-Sensitivität nachgewiesen werden. Sie zeigten keine signifikanten Unterschiede in der Nährstoffversorgung.
Diskussion Patienten mit BH4-Sensitivität zeigen unter Therapie mit BH4 Unterschiede in der Nährstoffzufuhr, begründet durch die erhöhte Zufuhr an natürlichem Eiweiß, aber auch durch die reduzierte Einnahme von ASM.

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POSTER 84

PANDA – Klinische, genetische und immunologische Charakterisierung des pankreopriven Diabetes mellitus

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Der pankreoprive Diabetes mellitus (pDM) ist eine schwerwiegende Komplikation der chronischen Pankreatitis (cP). Pathogenetisch ist die verminderte Insulinsekretion durch fortschreitende Zerstörung des endo- wie exokrinen Pankreas vordergründig. Die Zunahme der Extrazellulärmatrix erschwert zusätzlich die perisinusoidale Diffusion von Glukose und Mediatoren und die Stimulation der Insulinsekretion wird beeinträchtigt. Eine periphere Insulinresistenz ist beschrieben, was zunächst pathophysiologisch nicht einleuchten mag. Um ein besseres Verständnis für die Pathogenese zu entwickeln, wurde die PANDA-Studie initiiert. In Phase 1 wurden 80 Patienten mit cP rekrutiert, anamnestiziert, klinisch charakterisiert, Ernährungsprotokolle und Laboranalytik sowie 75g-oGTT durchgeführt. Es wurde DNA isoliert und Serum gewonnen, um auf genetische und immunologische Marker hinsichtlich der prognostischen Bedeutung zu untersuchen. Erste Ergebnisse vergleichender Analysen typischer neuer DM-Typ-II-Adipokine (AFABP, Chemerin, FGF21), die wesentlich zur peripheren Insulinresistenz beitragen, zeigten überraschend für AFABP signifikant niedrige Werte im Vergleich zur Kontrollgruppe aus 60 Nichtdiabetikern. Auf genetischer Ebene werden derzeit 28 aktuelle SNP's, die mit einem DM-Typ-II assoziiert sind, hinsichtlich ihrer Korrelation beim pDM mittels PCR und Sequenzierung untersucht. Zudem werden die Seren auf autoimmune Reaktionen i.R. der chronischen Entzündungsaktivität hin analysiert. Für funktionelle Untersuchungen, die die genetischen und immunologischen Daten in Folge unterstützen können, wurden aufgereinigte Lymphozyten kryokonserviert.

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POSTER 85

Das belastete Kind – Depression bei Kindern krebskranker Eltern

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Einleitung:
Die Erkrankung Krebs zieht in offensichtlichem Maße psychische Begleiterscheinungen nicht nur beim Patienten selbst, sondern auch bei Partnern und Kindern nach sich. Das Auftreten internalisierender Symptome beim Kind, speziell eine depressive Symptomatik, konnte vielfach belegt werden (Romer et al., 2009; Visser et al., 2005). Analysiert werden soll, ob das Vorliegen einer elterlichen Depression für die Symptomentwicklung von Einfluss ist. Darüber hinaus gilt es, die Gruppe jugendlicher Töchter, deren Mütter an Brustkrebs erkrankten, auf möglicherweise erhöhte Belastungen hin zu überprüfen.
Methode:
Im Rahmen des Verbundprojektes *„Psychosoziale Hilfen für Kinder krebskranker Eltern"* (Förderer: Deutsche Krebshilfe e.V.; Leitung: PD Dr. G. Romer) wird mittels des SDQ die emotionale Belastung beim Kind und anhand der CES-DC und der HADS-D die kindliche bzw. elterliche Depressivität erfasst. Elternurteile lagen für Kinder von 3-18 Jahren, zusätzliche Selbsturteile für 11-18-Jährige vor.
Stichprobe:
Die Daten (N=114 Familien) wurden im Rahmen einer Längsschnittstudie am Universitätsklinikum Leipzig (MedPsych, KJP) durch schriftliche Befragung erhoben.Die vorliegende Untersuchung bezieht sich auf den ersten Messzeitpunkt und ist somit eine Querschnittanalyse.
Ergebnisse/Diskussion:
Ein Drittel der Kinder zeigte auffällige Depressionswerte. Der Zusammenhang zur elterlichen Depressivität wurde bestätigt, was den Bedarf an familienorientierter seelischer Gesundheitsfürsorge unterstreicht. Hingegen konnten die jugendlichen Töchter, der an Brustkrebs erkrankten Mütter, nicht als Risikogruppe extrahiert werden.

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POSTER 86

Aktivitätsänderung von Proteinase 3 und Neutrophiler Elastase im Gesamtspeichel von Parodontitispatienten nach scaling and root planing

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Ziel: Bestimmung der Veränd. der Akt. v. Proteinase 3 (PR3) u. neutrophiler Elastase (NE) im stim. Gesamtsp. von PA-Patienten n. SRP.
Materialien/Methoden: 29 Männer u. Frauen zw. 25 u. 64 J. mit chron. u. aggr. PA (n=29, mittl. Alter 55,2±9,3 J.) wurden mitt. SRP innerh. v. 24h, z.T. mit AB, behandelt.
Approximalraum-Plaqueindex (API), Quigley-Hein-Index (QHI) u. Gingivalindex nach Löe u. Silness (GI) wurden bei der Basisuntersuchung (0), sowie n. 5-7 Tagen (1) u. 3 Monaten (2) erhoben. Für den Nachw. v. PR3 u. NE wurde jew. über 5 Min. mitt. Paraffinwachs stim. Gesamtsp. gewonnen. Sondierungstiefe (PD), klin. Attachmentlevel (AL), Bluten auf Sondieren (BOP) wurden in einer 6-Punktmessung pro Zahn z. Zeitpkt. 0 u. 2 erhoben. Für die statist. Ausw. wurden Friedman- u. Wilcoxon-Test angewandt.
Ergebnisse:
0: PD 3,5±0,8mm, AL 3,9±1,3mm, BOP 37±30%, API 28±8%, QHI 1,1±0,6, GI 0,5±0,3, PR3=0,1888U, NE=7,9572U; 1: API 32±4 %, QHI 0,7±0,3, GI 0,4±0,1, PR3=0,0474U, NE=1,4487U, 2: PD 2,9±0,6mm, AL 3,5±1,1mm, BOP 10±7%, API 30±4%, QHI 0,5±0,4, GI 0,2±0,1, PR3=0,0878U, NE=2,5551U.
PD war n. 3 Mon. sign. geringer (p=0,020), der AL-Gewinn war nicht signif. (p=0,359). Signif. war der Rückg. des BOP (Friedman p=0,003, Wilcoxon p=0,008). Der Friedman-Test für NE war nicht signif., für PR3 war eine Tendenz zur Sign. zu sehen (p=0,169 u. 0,053). Die Akt. der PR3 u. der NE waren eine Woche n. SRP signif. geringer (Wilcoxon p=0,009 u. 0,002).
Schlussfolgerung: SRP scheint eine Redukt. der Enzymakt. v. PR3 u. NE im Speichel zu bewirken. Es bleibt abzuklären, ob diese Veränderungen für die Entw. eines Screening-Tests genutzt werden können.

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POSTER 87

Einsatz von Tetrahydrobiopterin bei Patienten mit Phenylketonurie – Veränderungen der diätischen Einstellung und der Lebensqualität

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Hintergrund Die Tetrahydrobiopterin (BH_4)-sensible Phenylketonurie (PKU), eine Sonderform des Phenylalaninhydroxylase-Mangels, kann in Europa seit 2008 mit Sapropterindihydrochlorid behandelt werden. Veränderungen der Stoffwechseleinstellung, des Ernährungsverhaltens und der Lebensqualität (QOL) unter BH_4-Therapie sind Gegenstand aktueller Studien.
Patienten und Methoden Analysiert wurden neonatale BH_4-Belastungstests und molekulargenetische Befunde von 66 PKU-Patienten (2-18 Jahre). Von 18 Patienten (9w, 9m; 4-18 Jahre) wurden ein Jahr vor Therapiebeginn, 18 mal während der 42-tägigen Studie und in einem Nachbeobachtungszeitraum von 3 Monaten Phenylalanin (Phe)-Konzentrationen im Trockenblut (TB) und Ernährungsprotokolle analysiert. Die QOL wurde mit dem KINDL®-Fragebogen für Kinder und Jugendliche erfasst.
Ergebnisse 9 Patienten zeigten eine BH_4-Sensitivität mit erhöhter Phe-Toleranz bei guten Phe-Konzentrationen im TB, einer Reduktion der AS-Substitution und Zufuhr eiweißarmer Spezialprodukte. 5 Patienten zeigten keine eindeutige BH4-Sensitivität. Die Daten von 4 Patienten konnten nicht ausgewertet werden. Die BH_4-responsiven Patienten erzielten im Durchschnitt höhere Werte in der QOL. Die stärksten Veränderungen ergaben sich in den Bereichen Freunde und Selbstwert. Nebenwirkungen wurden nicht beobachtet.
Diskussion Eine BH_4-Therapie ermöglicht bei einigen PKU-Patienten eine erhöhte Phe-Toleranz und eine Diät-Lockerung. Eine Steigerung der bereits vor der Therapie guten QOL konnten wir darstellen. Längere Beobachtungszeiträume und Multicenter-Studien sind erforderlich, um diesen Trend zu bestätigen.

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POSTER 88

Autonomic response to mental stress in patients with rheumatoid arthritis with various disease activities

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Background: Stress is recognised as an important risk factor in the pathogenesis of rheumatoid arthritis (RA). However, it is still incompletely understood how the autonomic nervous system and the immune system interact in patients with RA.
Methods: To characterise the autonomic response to mental stress heart rate variability (HRV) was tested in 30 RA patients and matched healthy controls (ProSciCard III, Version 2.2a, Medi-Syst GmbH, Germany). Arithmetic tasks to induce mental stress were performed. HRV measures, such as high frequency (HF), low frequency (LF), and very low frequency (VLF), are yielding measures of parasympathetic and sympathetic activity.
Results: Patients with RA had an impaired response to mental stress for LF HRV with a paradox increase of HF HRV (1.49 ± 0.1 at rest vs. 2.22 ± 0.1 after stress, $p<0.05$). In patients with higher disease activity (DAS> 3,2 =5,1) LF HRV and LF/HF ratio significantly increased upon stress (1.0 ± 0.2 at rest vs. 2.4 ± 0.2 after stress, and 0.85 ± 0.02 at rest vs. 1.12 ± 0.08 after stress, respectively). In patients with low disease activity (DAS= 3,2>2,3) there was a significant increase for VLF HRV and HF HRV (1.39 ± 0.1 at rest vs. 2.0 ± 0.1 after stress, and 2.7 ± 0.2 at rest vs. 3.5 ± 0.3 after stress, respectively). RA patients in remission (DAS =2,3) exhibited a normal LF/HF ratio at rest, stressed an increase of HF and a tendency to a decrease of LF/HF ratio.
Conclusions: Our findings demonstrate that in RA patients the autonomic response to minor psychological stress is characterised by a reduced sympathetic activity which is associated with disease activity.

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POSTER 89

Evaluation of DNA-Aneuploidy in Oral Cancer

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The aneuploidy-cancer theory proposes that cancer is caused by the abnormal dosage of thousands of normal genes. This is generated by the gain or loss of specific chromosomes or segments of chromosomes; alias aneuploidy. The theory predicts that chromosomal and genetic instability is proportional to the degree of aneuploidy. Therefore an abnormal DNA-Content of epithelial cells was determined by measuring the integrated optical density of abnormal keratinocytes using slide based DNA-Image-Cytometry. The aim of our prospective study was to investigate the diagnostic accuracy of DNA-ICM of minimal-invasive brush biopsies taken from suspicious oral lesions. Therefore we measured 490 smears obtained from 187 cancer patients and 303 patients with benign oral lesions which were compared with histology and/or clinical follow-ups. Nuclear DNA contents were measured after Feulgen, restaining using a TV image analysis system. DNA-aneuploidy was assumed if abnormal DNA-stemlines or cells with DNA-content greater 9c were observed. The prevalence of DNA-aneuploidy in smears of oral squamous cell carcinomas was 98,4 %. Sensitivity of DNA-aneuploidy in oral smears for the detection of cancer cells was 98,40 %, specificity 99,34 %, positive predictive value 98,92 % and negative 99,01 %. Conclusion: The appliance of DNA-ICM with DNA-aneuploidy as a marker for neoplastic transformation in oral smears secures cytologic diagnosis of carcinomas. DNA-Image-Cytometry is a very sensitive and highly specific, objective and reproducible adjuvant tool for identification of neoplastic cells in smears of oral brush biopsies.

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POSTER 90

Neural Basis of Memory Deficits in Herpes Simplex Encephalitis

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Literature reports regions such as the temporal lobes, the orbitofrontal cortex, the insulae as well as the cingulate gyri as characteristically affected after herpes simplex virus encephalitis (HSVE). Moreover, a distinctive pattern of cognitive deficits, including memory and executive dysfunctions as well as behavioral and emotional impairment, has been described. However, studies have not systematically reported cognitive deficits in accordance to the extent of atrophy in affected brain regions within subjects. In this work, we explored the pattern of structural changes in gray matter following HSVE to investigate the neural basis of neuropsychological deficits.
Voxel-based morphometry, based on 3-T structural magnetic resonance images, was used to measure gray matter loss in a sample of 13 chronic HSVE patients in comparison with 13 individually age- and sex-matched control subjects. Gray matter values were correlated with memory scores of the patients to ensure specificity of identified gray matter loss.
Individual analyses showed gray matter atrophy in mesial temporal cortices, amygdalae and insulae in almost all subjects. Due to high regional inter-individual variability in lateralization, these effects could not significantly be replicated in the group comparison. Memory impairment scores correlated significantly with gray matter density loss in the left hippocampal region. The results, consistent with the well-known histopathology of HSVE, contribute to the anatomical validity of VBM. Beyond, they add to the understanding of neuropsychological impairments in patients after HSVE.

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POSTER 91

YMCA Step-Test zur Abschätzung der körperlichen Leistungsfähigkeit

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Wissenschaftlicher Hintergrund:
Körperliche Aktivität und kardiorespiratorische Fitness sind eng korreliert mit der Entstehung von Zivilisationskrankheiten wie Atherosklerose, Diabetes mellitus, Adipositas aber auch psychiatrischen Erkrankungen. Goldstandard zu Messung der kardiovaskulären Fitness ist die maximale Ergospirometrie mit simultaner Messung der maximalen Sauerstoffaufnahme. Im Rahmen von populationsbasierten Assoziationsstudien mit großen Probandenzahlen (z.B. LIFE) ist die Erhebung der körperlichen Fitness als wichtiger Einflussfaktor von großem Interesse, jedoch ist die Spiroergometrie aufgrund des Zeitaufwandes ungeeignet. Diese Arbeit untersucht, inwieweit ein dreiminütiger submaximaler Belastungstest (YMCA-Step-Test) zur Abschätzung der kardiorespiratorischen Fitness geeignet ist. Sie dient als Feasibility-Studie für das LIFE-Projekt B3 und wird finanziell unterstützt von der Landesexzellenzinitiative.

Methoden:
Der YMCA Step-Test und eine Spiroergometrie wurden von 37 Probanden mit und ohne Herzerkrankung absolviert. Der modifizierte YMCA Step-Test besteht aus einer 3-minütigen Belastungsphase, in der die Probanden eine 30 cm hohe Stufe mit einer vorgegebenen Trittfrequenz von 24 steps/min besteigen. Die maximale Spiroergometrie wurde auf einem Laufband nach dem Bruce-Protokoll durchgeführt. Es erfolgte jeweils die kontinuierliche Aufzeichnung der Herzfrequenz sowie Blutentnahmen vor jedem Test, bei maximaler Belastung und eine Minute nach Belastung. Zusätzlich schätzten die Probanden die jeweilige Belastungsintensität anhand der Borg-Skala ein. Eine subjektive Einschätzung der Belastbarkeit im Alltag wurde mit dem VSAQ (veterans specific activity questionnaire) erhoben. Zur Korrelationsbestimmung wurde die Pearson Korrelation verwendet.

Ergebnisse:
Das Alter der Probanden lag im Mittel bei 57 ± 14,3 Jahren (Range), die maximale Sauerstoffaufnahme variierte von 13,4 bis 67,0 ml/min/kg. Die Step-Test-Heart-Rate-Recovery (HRR) nach 1 Minute korrelierte mit der spiroergometrisch bestimmten VO2max mit r= 0,43 (p=0,02) in der Gesamtgruppe. Dies ist auf den hohen

Anteil an Probanden mit Betablocker-Einnahme (n=17) zurückzuführen. In der Gruppe ohne Betablocker (n=20) verbessert sich die Korrelation auf r= 0,66 (p=0,02). Die subjektive Einschätzung der Belastbarkeit nach VSAQ korreliert hochsignifikant mit der VO-2max (alle Probanden: r= 0,82; p<0,01; Probanden ohne Betablocker: r= 0,97; p<0,01).

Schlussfolgerung:
Der modifizierte YMCA Step-Test ist ein einfacher und sicher durchzuführender Belastungstest zur objektiven Abschätzung der körperlichen Leistungsfähigkeit. In einer Kohorte aus Herzkranken und Herzgesunden mit hoher Variablität für Alter und VO2max sind die Anzahl der erreichten Steps und die Heart-Rate-Recovery unabhängige Prädiktoren für die spiroergometrisch bestimmte maximale Sauerstoffaufnahme. Legt man die gute Korrelation bei fehlender Betablockermedikation zugrunde, sollte die anstehende Validierung in der populationsbasierten LIFE-A1 Kohorte ein guter Prädiktor der kardiovaskulären Fitness sein.

Funding: life

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POSTER 92

Leistenkomplikationen nach diagnostischem Herzkatheter und perkutaner Koronarintervention (PCI) bei über 80-jährigen Patienten: Wie hoch ist das Risiko?

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Hintergrund Kardiologische Patienten zeichnen sich zunehmend durch hohes Alter und Multimorbidität aus und profitieren in besonderem Maße von Herzkatheterprozeduren. Am häufigsten werden Femoralgefäße als Zugangsweg genutzt. Komplikationen im Leistenbereich (Pseudoaneurysmen, Hämatome, AV-Fisteln) sind typische klinische Probleme.
Methodik Es wurden 34964 Patienten analysiert, die zwischen 2005 und 2009 am Herzzentrum Leipzig insgesamt 42628 Herzkathetern unterzogen wurden. In drei Altersstraten (<65, 65-79, ≥80) wurden relatives Risiko und Prädiktoren für Leistenkomplikationen ermittelt.
Resultate Bei unter 65jährigen lag die Komplikationsrate bei 1,2% (n=178), bei 65-79jährigen bei 1,9% (n=428) und bei über 80jährigen Patienten bei 3,3% (n=175), insgesamt bei 1,8% (n=781). Die Hospitalisierungszeit erhöhte sich bei Komplikation von 5,3 ± 9,9 Tagen auf 8,2 ± 11,9 Tage (bei über 80jährigen Patienten von 7,3 ± 11,4 auf 12,1 ± 16,6 Tage). Mittels multivariater Regressionsanalyse wurden männliches Geschlecht (OR=1,5; p=<0,0005), Alter (pro Jahr stieg die OR um den Faktor 1,03; p<0,0005), zusätzlicher venöser Zugang (OR= 1,92; p<0,0005) Clopidogrelgabe (OR=1,94; p<0,0005) als Prädiktoren ermittelt. Niereninsuffizienz, Heparingabe, ASS-Gabe und Kontrastmittelmenge haben einen weniger signifikanten Einfluss.
Schlussfolgerung Verglichen mit Patienten <65 liegt das relative Risiko bei 65-79jährigen bei 1,6, bei über 80jährigen bei 2,7. Bei Komplikation steigt die Hospitalisierungszeit. Die Prädiktoren der Analyse ermöglichen, eventuell Maßnahmen zur Vermeidung von Komplikationen zu ergreifen und die Liegezeit zu verringern.

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POSTER 93

MOTOR PERFORMANCE AND PHYSICAL ACTIVITY IN LEAN AND OBESE CHILDREN.

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Objective: The purpose of this prospective study was to determine the relationship between motor performance and the extent of physical activity in daily life, with respect to socioeconomic situation in lean and obese school children in Germany, Leipzig. Design and Methods: We studied 107 obese and 70 lean children. Motor skills (coordination, strength and flexibility) were evaluated with selected test items of the Motorik Modul of the KiGGS-Study. Anthropometric data were measured and physical activity was queried using a physical activity questionnaire. Results: Independent of sex and age, the motor performance was significant decreased in obese compared to lean children. Flexibility was not associated with BMI. Significant correlations with BMI were seen for membership in a sports club and daily hours watching TV, whereas no correlations were detectable for physical education school hours per week and sports in leisure time with BMI. Therefore the extent of motor performance is positive associated with membership in a sports club and negative with daily extent of TV-hours. Participation in a sports team was 60% in lean and 32% in obese subjects. Good marks in physical education were highly correlated with overall motor performance. For socioeconomic aspects, children from low-income families had a significant higher BMI and their motor performance was significant decreased. Conclusion: With association to BMI, we revealed a decline of motor performance and physical activity in obese children, whereas sedentary behaviour was increased. Socioeconomic status is related to these conditions.

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POSTER 94

Leukocytes are a major source of circulating NAMPT/ PBEF/visfatin linking obesity and inflammation

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Background: NAMPT (nicotinamide-phosphoribosyltransferase), is a multifunctional protein potentially involved in obesity and glucose metabolism. Aim: We systematically studied potential associations between circulating NAMPT, obesity, obesity interventions, and glucose metabolism and investigated potential underlying inflammatory mechanisms. Results: Circulating NAMPT was significantly elevated in obese compared to lean children and declined after obesity interventions concomitantly with the decline in BMI, hsCrP and leukocyte counts. Circulating NAMPT significantly correlated with glucose metabolism and cardiovascular parameters in univariate analyses, but only the association with glucose response during an oGTT was independent from BMI. We, therefore, assessed the NAMPT dynamic following an oral glucose load and found a significant decline of NAMPT levels to 77.0±0.1% as a function of time and insulin-to-glucose ratio. Circulating NAMPT was, however, most strongly associated with leukocyte counts ($r=0.46$, $P<0.001$). The leukocyte count determined significantly and independently from BMI insulin resistance in multiple regression analyses ($\beta=0.26$, $P<0.001$). We, thus, systematically evaluated NAMPT expression among several tissues and found that NAMPT was predominantly expressed in leukocytes. In subsequent analyses of leukocyte subpopulations we identified higher NAMPT protein concentrations in lysates of granulocytes and monocytes compared to lymphocytes, while granulocytes secreted highest amounts of NAMPT protein into cell culture supernatants. We confirmed NMN biosynthetic enzymatic activity of NAMPT in all lysates and supernatants. In monocytes, NAMPT release was significantly stimulated by LPS exposure. Conclusions: Leukocytes are a major source of enzymatically active NAMPT, which may serve as a biomarker or even mediator linking obesity, inflammation and insulin resistance.

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POSTER 95

Expression der muskelspezifischen E3-Ligasen bei Patienten mit chronischer Herzinsuffizienz : Altersunabhängige Effekte eines 4-wöchigen aeroben Ausdauertrainings

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Die chronische Herzinsuffizienz (CHI) führt im Spätstadium zu einem ausgeprägten Skelettmuskelschwund, dessen molekulare Ursachen bis heute noch nicht vollständig verstanden sind. Ziel der Studie war daher, die Effekte eines 4-wöch. aeroben Fahrradergometertraining auf das Ubiquitin-Proteasom-System (UPS) als zentralem katabolem Weg in Skelettmuskelbiopsien von CHI-Patienten zu untersuchen.
Methodik: 60 Patienten(30 <55 Jahre, 30>65 J.) wurden in Training-und Kontrollgruppe randomisiert. Vor und nach 4 Wochen Training wurden Skelettmuskelbiopsien aus dem M. vastus lat. Entnommen, in denen die Expression der E3-Ligasen Murf-1 und MafBX gemessen wurde.
Ergebnisse: CHI-Patienten (jung 50±5 J.a.,BMI 29±2,LV-EF 27±2%;alt 72±4J.a.,BMI 28±3,LV-EF 29±2%): Bei CHI war die Expression von MuRF-1 im Vergleich zu gesunden Probanden deutlich erhöht. Nach Training kam es zu einer Reduktion der Murf-1-Ligase auf mRNA-(jung 629±122 auf 423±55 arb. E., alt 621±93 auf 391±83,p<0,05) und auf Proteinebene (jung 0,70±0,09 auf 0,57±0,08 arb. E; alt 0,92±0,26 auf 0,76±0,17,p<0,05). MafBX änderte sich nicht.
Schlußfolgerung: Der Skelettmuskelkatabolismus bei CHI ist wesentlich über eine Aktivierung des UPS mit erhöhter MuRF-1 Expression vermittelt. Training reduziert unabhängig vom Alter die Murf-1 Expression signifikant. Die Ergebnisse unterstreichen die Potentiale der Trainingsinterventionen zur Prävention der kardialen Kachexie und Verbesserung der körperlichen Belastbarkeit bei CHI-Patienten auch im höheren Alter.

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POSTER 96

DIFFERENTIAL EICOSANOID RESPONSE AFTER LPS – WHOLE BLOOD ACTIVATION IN HEALTHY CONTROLS AND SEPSIS PATIENTS

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Objectives:
Eicosanoids are primarily oxidized from arachidonic acid and discussed as central mediators of pro- and antiinflammatory processes in sepsis. To elucidate changes in eicosanoid metabolism and its diagnostic potential in sepsis, we determined the eicosanoid response in healthy subjects and septic patients after LPS whole blood activation, using a multiparametric LC-MS/MS approach.
Material and Methods:
Freshly drawn Li-heparin blood from 15 healthy persons and 25 patients suffering from clinically and laboratory defined acute sepsis was incubated with LPS (1μg/ml) for 24 hours. A second LPS activation was performed after three days. After centrifugation, supernatants were purified by solid phase extraction, followed by LC-MS/MS eicosanoid analysis.
Results:
In contrast to healthy persons, the induction of major representatives of the cyclooxygenase pathway in sepsis patients was reduced by up to 90% after LPS activation. The intensity of the eicosanoid response at baseline and in the course of disease was closely correlated with the clinical prognosis.
Conclusions:
Our data indicate that LPS activation and subsequent eicosanoid analysis allows an assessment of disease severity and prognosis. The differential eicosanoid response in patients with sepsis may be a target for individual therapeutic options.

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POSTER 97

Effects of a high-flow cannula device (HFNC) on pressure amplitude, mean pressure, tidal volume and blood gas analysis in patients with IPF and COPD

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Introduction: Treatment with a high-flow cannula device is able to improve symptoms of chronic respiratory insufficiency. The method uses a warmed and humified high flow of air/ oxygen with 16-24 L per minute. The clinical effects in adults are unknown. *Method:* A water-filled tube connected to a sensitive pressure transducer was used as a sensor. The tube was placed in the nasopharyngeal space. We measured pressure amplitudes during the respiratory cycle and mean pressures in patients with IPF and COPD using HFNC (TNI©) and nasal CPAP (4mbar) respectively. For detection of tidal volume variations we used impedance measure bands. The signal was relayed to a polysomnography device. The capillary blood gas analysis was taking from the hyperemic earlap before and after using HFNC (8 hours). *Results:* HFNC led to an increase in pressure amplitude and mean pressure in healthy volunteers and patients with COPD or IPF in comparison with spontaneous breathing. In COPD the tidal volume was increased, but there were no significant differences in patients with IPF. In healthy volunteers tidal volume was significant decreased. Blood gas analysis revealed a decrease in pCO_2 in patients with IPF and COPD. *Discussion:* HFNC resulted in significant effects on respiratory parameters in patients with COPD and IPF. The rise in pressure amplitude and mean pressure will support inspiratory efforts, may increase ventilation and will contribute to a reduction in the work of breathing. A CO_2 wash-out of the upper airway part of the anatomical dead space may contribute to the beneficial effects of the HFNC instrument.

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POSTER 98

Characterization of BCRP mediated drug transport into the lactating mammary gland of dairy cattle

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The presence of drugs or other potential toxic substances in the milk has enormous toxicological and nutritional consequences for the suckling and the consumers of dairy products. The ATP-binding cassette (ABC) transport protein Breast Cancer Resistance Protein (BCRP, ABCG2) is expressed in alveolar epithelial cells of the mammary gland during lactation and gestation in cows, sheeps and goats. Furthermore it was shown that BCRP plays a major role for the active secretion of a variety of xenobiotics including the antibiotic enrofloxacin, toxins such as aflatoxin B1 and carcinogens e. g. PhIP and Trp-P-1 into human and rat milk. So far, there is little information about the transport activity and the substrat specifity of BCRP from the mammary gland of dairy cattle. Therefore we want to establish an *in vitro* cell culture model expressing the BCRP of dairy cattle. To address this issue, total RNA and mRNA were isolated from the bovine, caprine and ovine mammary gland. After identification of BCRP gene specific primers, full length clones were generated using RACE (rapid amplification of cDNA ends) PCR. The final full-length bovine, ovine and caprine ABCG2 cDNA-clone sequences were submitted to the NCBI genebank (EU570105, GQ141082, GQ241418). Stable transfection in MDCK cells was performed and the transport activity of the transfectants was measured by the BCRP specific substrate Hoechst 33342 in combination with the BCRP inhibitor Ko143. Further transport studies using transwell systems will be done to increase the understanding of carrier mediated drug transport into the milk of dairy cattle.

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POSTER 99

Clemastine potentiates the human P2X7 receptor by sensitizing it to lower ATP concentrations

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P2X7 receptors have emerged as potential drug targets for the treatment of medical conditions such as e.g. rheumatoid arthritis or neuropathic pain. To assess the impact of commonly prescribed pharmaceuticals on P2X7 receptor activity, we screened a compound library comprising 1040 approved or clinically tested drugs. We identified several compounds that augmented $[Ca^{2+}]_i$ signals in response to stimulation with 1 mM ATP. Clemastine on its own had no effect, but potentiated ATP-induced Ca^{2+} entry in HEK293 cells stably expressing human P2X7 by shifting the ATP sensitivity to lower agonist concentrations. Extracellularly but not intracellularly applied clemastine rapidly and reversibly augmented P2X7-mediated whole-cell currents evoked by non-saturating ATP concentrations. Clemastine also accelerated the ATP-induced pore formation, accelerating the uptake of Yo-Pro-1, and increasing the fractional $NMDG^+$ permeability. Thus, clemastine is a novel allosteric modulator of P2X7. To assess the activity of clemastine on native P2X7 receptors, it was tested in human monocyte-derived macrophages. Consistent with the data on recombinant P2X7, clemastine augmented the ATP-induced cation entry and Yo-Pro-1 uptake. In accordance with the observation that P2X7 controls the cytokine release from LPS-primed macrophages, we found that clemastine augmented the release of IL-1β from LPS-primed human macrophages. Collectively, these data point to a sensitisation of the recombinantly or natively expressed human P2X7 receptor towards its physiological activator ATP, possibly leading to a modulation of macrophage-dependent immune responses.

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POSTER 100

Ein neuer mit Fluor-18 markierter Radioligand für die molekulare Bildgebung der Phosphodiesterase 10A im Gehirn

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Die Phosphodiesterase 10A (PDE10A) terminiert die Signalübertragung der Second messenger cAMP und cGMP durch Hydrolyse und wird vorrangig in Gehirn (Striatum) und Schilddrüse exprimiert. Veränderungen der Aktivität der PDE10A werden in Zusammenhang mit Schizophrenie und Psychosen gebracht. Selektive und hirngängige PDE10A-Inhibitoren sind daher Ziel der Entwicklung hochwirksamer Therapeutika und geeigneter Diagnostika für die molekulare Bildgebung, wie unser 7-(2-[^{18}F]Fluorethoxy)-6-methoxychinazolin-Derivat zur Visualisierung der PDE10A mit Positronen-Emissions-Tomographie (PET). Die zur Analytik erforderliche nichtradioaktive Referenzverbindung und die Ausgangsverbindungen für die ^{18}F-Markierung wurden in Mehrstufen-Synthesen dargestellt. Für die ^{18}F-Markierung wurde zunächst ein schneller zugängliches zweistufiges Verfahren entwickelt. Eine verbesserte Darstellung erfolgte anschließend im Einstufenverfahren über die direkte Umsetzung des entsprechenden 7-(2-Tosyloxyethyl)-Präkursors mit trägerfreiem [^{18}F]F^{2+}. Die Markierungsausbeute betrug 42-72%, die chemische und radiochemische Reinheit ≥99% und die spezifische Aktivität 110-1110 GBq/μmol. Die zerfallskorrigierte radiochemische Ausbeute lag nach 3-4 h Gesamtsynthesedauer bei 17-40%. Als Kriterium für die Qualität der Hirnaufnahme wurde die Lipophilie des Radioliganden bei pH 7 bis 7,4 mittels HPLC und extraktiven Methoden bestimmt. Ein log$D_{7,0\text{-}7,4} \approx 2,6$ weist auf eine gute Hirnaufnahme bei ausreichend niedriger unspezifischer Bindung hin. Weiterführende Experimente sind geplant, um die Organverteilung des Radioliganden sowie Bindung *in vitro* und *in vivo* zu untersuchen.

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POSTER 101

Double-edged effects of combined treatment with hyperbaric oxygen and recombinant tissue plasminogen activator after experimental embolic stroke in rats

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Background. Hyperbaric oxygen therapy (HBO) became interesting in the field of ischemic stroke, since numerous preclinical studies applying HBO have shown beneficial effects. The present study focused on the potential benefit of co-administered HBO to recombinant tissue plasminogen activator (tPA), which is in use as recanalization strategy, attenuating toxic effects of tPA. Methods. Twenty Wistar rats underwent embolic middle cerebral artery occlusion (MCAO). Two hours after embolization, 11 rats were treated with HBO (2.4 ATA for 60 minutes) and simultaneously applied tPA (9 mg per kg bodyweight), and 9 rats received tPA alone. Menzies score was used to evaluate neurological impairment after MCAO and at 24 hours; magnet resonance imaging (diffusion-, T2*- and T2-weighted sequences) was performed for infarct size calculation and detection of cerebral hemorrhage. Results. Simultaneous treatment with tPA and HBO led to an improved neurological outcome (effect size, 1.13 vs. 0.80; $p<0.05$ vs. non-significant) and decreased rate of ischemic infarction (54.5 % vs. 100 %; $p<0.05$). Cerebral hemorrhage did not occur in the tPA group, but was found in 27.3 % after combined treatment – failing statistical significance. Combined treatment resulted in a non-significant trend to reduced infarct sizes. Conclusions. During a 24-hour observational period, combined treatment with HBO and tPA after MCAO results in beneficial effects in neurological impairment and rate of recanalization, but also tends to an increased rate of cerebral hemorrhage. Further studies are required to identify underlying key factors and their interactions.

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POSTER 102

Embryonic stem cell-derived 3D cultures as versatile tool for drug testing

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The exclusion of severe side effects of potential drug candidates is an important step in the drug development process. Preclinical studies are carried out on *in vitro* cell culture models and *in vivo* in animal models before the drugs can be applied to humans in clinical trials. To reduce animal testing in these preclinical studies the cell culture models have to be optimized to yield more reliable data. In the last decades three-dimensional cell or tissue structures have evolved as a system of intermediate complexity to overcome the problems of the limited transferability of the results obtained from monolayer or suspension cell experiments to the *in vivo* situation. The use of embryonic stem cells enables the investigation of drug effects on the stem cells themselves, on their differentiation and on various differentiated cell types developed from these cells.
The murine embryonic stem cell line ES-D3 is used to generate three-dimensional multicellular structures that can be analyzed in a special designed microcavity array. Via impedance measurements of the 3D stem cell structures in this microcavity chip compounds can be tested regarding their embryotoxicity. In addition 3D cardiomyocyte clusters can be differentiated from these embryoid bodies. They differentiate to spontaneously contracting cardiomyocytes that can be used to analyze the influence of active pharmaceutical ingredients on cardiac electrophysiology by extracellular recording of action potentials in microcavity arrays. Therefore, stem cell-derived 3D clusters in combination with microcavity arrays represent versatile new tools for *in vitro* drug testing.

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POSTER 103

Synthesis and biological investigation of (bis) intercalator-functionalized cell penetrating peptides

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Bioorganometallic chemistry has become more important in several fields, especially in the development of new drugs for cancer treatment. Numerous promising organometallic lead structures have been developed exhibiting highly active cytostatic properties. However, the efficiency of such chemotherapeutics in the treatment of tumors is often limited by their low bioavailability. Cell-penetrating peptides (CPP) have emerged as potent tools to introduce substances into cells without the need of a receptor or transporter molecule. Thereby they are capable to transport various cargos inside cells.
This work describes the synthesis of (bis-)intercalator-functionalized cell-penetrating peptides based on an antimicrobial peptide cathelicidin CAP18. In previous studies we could show, that this peptide is able to transport covalently coupled organometallic compounds into tumor cell lines, enhancing the cytotoxic properties of the compounds.[1] Here, as metal complex iridium(III)/rhodium(III) polypyridyl complexes were chosen, which showed an intercalative binding with DNA and represent a promising class of potent cytostatic agents.[2] Synthesis of the peptide was achieved by solid phase peptide synthesis. The metal complexes were covalently or non-covalently attached to the peptide and the products were characterized and tested with respect to their cytotoxicity against tumor cells.

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[2] Kokoschka M; Bangert J-A; Stoll R; Sheldrick W S. *European Journal of Inorganic Chemistry*, 2010, *2010*, 1507-1515.

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POSTER 104

Lipid Bilayer and Antibody Functionalization of Biopolymer coated Microcarriers for enhanced Drug Delivery

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Targeted, local, time controlled and low dose drug delivery systems provide a promising approach to reduce side effects caused by many common systemically applied therapeutics.
Layer-by-Layer biopolymer coated colloidal microcarriers combine those advantages due to their modular design. The stepwise adsorption of oppositely charged polymers allows the integration of a defined amount of active agents into the multilayer and core. The release within the targeted cell can be controlled by the biodegradable multilayer.
Our aim is to enhance the uptake of such carriers after specific cell attachment. Such a specific modification of the carriers can be provided by an outermost lipid bilayer, additionally functionalized with specific antibodies.
Here, calcium carbonate microparticles with an average diameter of 5 μm have been used as a template for the coating with protamin sulfate (PRM) and dextran sodium sulfate (DXS) to build up a stable biopolymer multilayer.
Outermost, a phosphatidylserine/phosphatidylcholine – lipid bilayer was applied by liposome spreading. Phosphoethanolamine-PEG-biotin was added to the lipid mixture and, therefore, integrated into the microcarrier lipid bilayer. Based on the strong attraction between biotin and streptavidin, streptavidin was bound to the biotinylated lipid surface to enable the subsequent binding of biotinylated antibodies for targeted drug delivery.
The successful design was verified by secondary antibodies determined with CLSM and FACS.
Finally, those microcarriers will help us to address the desired cell in a highly specific way facilitating the release of the transported agents.

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POSTER 105

ANALYSIS OF HERBAL COMPONENTS CONTRIBUTING TO THE EFFECT OF STW 5 ON RAT COLON

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STW 5 (Iberogast) is a fixed combination of nine herbal extracts used in the therapy of motility-related diseases of the gastrointestinal tract. As STW 5 is a combination of nine herbal extracts, it seems reasonable to study the effects of its herbal components to evaluate the contribution to the effect of the fixed combination.
Studies were conducted using isolated untreated and inflamed rat colon preparations. Inflammation was induced by the intra-luminal installation of 2,4,6-trinitrobenzene sulfonic acid (TNBS, 10mM). ACh (10μM)-induced contractions were measured isometrically and analysed using the software BioSys.
Comparable to ileum/jejunum preparations STW 5 decreased the ACh-induced contractions of untreated and inflamed colon preparations in a concentration-dependent manner (62.7-500.5μg/ml) with a maximum attenuation at the highest concentration of 500.5μg/ml. Analysis of the herbal components containing in STW 5 indicated that the single extracts had no significant effects on contractility in equivalent concentrations. Interestingly, peppermint leaves (*Menthae piperitae folium*, STW KII, 9.7μg/ml) and angelica root (*Angelicae radix*, STW KV, 21.1μg/ml) decreased the ACh-induced contractions in low concentrations whereas high concentrations did not influence the contractions in untreated colon preparations. In inflamed colon preparations only STW KII reduced the ACh-induced contraction in low concentration (19.5μg/ml).
Our results indicate that the combination of the nine herbal extracts is necessary for the effects of STW 5 on rat colon preparations.

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POSTER 106

Effects of STW5 and STW6 on rat ileal and colonic preparations: a comparative study

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The multi-herbal drug STW5 (Iberogast) is successfully used for the treatment of gastrointestinal disorders, like functional dyspesia or irritable bowel syndrome. It is a fixed combination of nine plant extract with *Iberis amara* (STW6) as main component.
This study examines the influence of STW5 and STW6 on tone and acetylcholine (ACh)-induced contractions in-vitro and analyzes region specific differences of the phytomedicine. We used 1-1.5cm long intact and inflamed ileum and colon preparations of male Wistar rats. The inflammation was induced by intraluminal installation of 2,4,6-trinitrobenzene sulfonic acid (TNBS, 10mM). STW5 (128-512µg/ml) concentration dependently reduced the tone and decreased ACh-induced contractions of untreated ileal and colonic preparations. STW6 in equivalent concentrations (3-24.1µg/ml) neither affects the tone nor the contractility. TNBS-induced inflammation was accompanied by a significant reduction of ACh-induced contractions. Co-incubation of TNBS with STW5 (512µg/ml) or STW6 (24.1µg/ml) partially normalized the TNBS-induced attenuation of ACh-induced contractions in ileum preparations. In inflamed colon segments the co-incubation of TNBS with STW6 (24.1µg/ml) enhanced the ACh-induced contractions, while STW5 (512µg/ml) had no effect.
In conclusion, STW5 influences intestinal contractions and tone, whereas STW6 does not contribute to these effects. In TNBS-inflamed ileum preparations STW5 as well as STW6 normalized the reduced ACh-induced contractions, while in colon preparations STW6 but not STW5 is effective. Our study confirm region specific efficacy of STW5 and its main component STW6.

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POSTER 107

Detection of the adenine receptor in human and rat neuronal and non-neuronal cells

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Adenine was identified to be an endogenous ligand of a G-protein coupled receptor in rats. A mouse ortholog but not a human ortholog was described. Preliminary radioligand binding studies using a human neuronal cell line suggest the existence of a human ortholog. The aim of the present study was to detect the adenine receptor on human and rat neuronal (SH-SY5Y; B104) as well as non-neuronal (THP-1; NR8383) cell lines. The influence of adenine (10 µM to 1 mM) on cell viability and cell death was determined using the MTT and LDH test. In rat cells the receptor mRNA was detected using qualitative RT-PCR. Adenine (500 µM; 36 h) increased the cell viability of THP-1 and SH-SY5Y cells up to 132.9±8.7 % and 127.8±17.1 %. In contrast the cell viability of rat NR8383 and B104 cells was decreased to 81.9±6.8 % and 88.4±7.8 %. PSB-08162 was described as an adenine receptor antagonist. In our experiments it antagonized the effect of adenine in all cell types. Interestingly, PSB-08162 (100 µM) itself reduced the cell viability in SH-SY5Y and B104 to 80.8±6.9 % and 84.7±14.2 %. Additionally, an interaction between the adenine and the adenosine A_1 receptor was shown on neuronal cells. Our results indicate that the adenine receptor is expressed on neuronal and non-neuronal cells from both species. The studies represent for the first time the pharmacological evidence of an adenine receptor in human cells. The pharmacological analysis pointed to a partial agonism of PSB-08162 on human and rat cell lines.

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POSTER 108

Cytotoxic and pharmacologic effects of new selective PDE10A ligands

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Phosphodiesterases (PDEs) are essential regulators of cyclic nucleotide signaling. PDE10A is expressed primarily in dopaminoreceptive medium spiny neurons in the striatum. Inhibitors of the PDE10A may be interesting for the treatment of neurodegenerative and psychiatric disorders. A novel approach for clinical diagnosis are selective PDE10A ligands using as PET ligands. The aim of the present study was to screen cytotoxic and pharmacological effects of fluoric substituted derivatives of a lead compound with high affinity and selectivity for the PDE10A. Cytotoxicity was investigate concentration- (1 nM-100 μM) and time- (12 h-48 h) dependently on human cell lines SH-SY5Y, HEK293 and HEPG2 using MTT and LDH test. Pharmacological effects were determined using calcium-imaging and intracellular recordings. In vivo toxicity was investigated using the fish embryo toxicity test with zebra danio. The lead compound and the fluoric substituted derivatives reduced the cell viability and membrane integrity at high concentration (100 μM) after long term incubation (48 h) only. High concentrations (100 μM) of the fluoric substituted derivatives increased the intracellular calcium concentration. Electrophysiological investigations indicated no effect of all tested compounds at 100 μM. Using the in vivo test system an acute fish mortality was found after 48 h at 1μM (LC_{50}= 0.1-1 μM). Our results indicate no toxic effect in concentration relevant for PET-ligands, but suggest a different pharmacological profile of the lead compound and fluoric substituted derivatives maybe by district binding characteristics to the PDE10A enzyme.

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POSTER 109

Effects of aqueous and ethanolic extracts of STW 5 and STW 6 on isolated rat small intestine

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STW 5 (Iberogast®) consists of an aqueous-ethanolic fresh plant extract of Iberis amara (STW 6) and eight other components. In order to study the mode of action aqueous and ethanolic extracts were compared for their activity to influence the ACh-induced contractions using rat ileum/jejunum preparations. Lyophilisates of herbal extracts were dissolved either in water or in ethanol (31 % V/V). Ethanol itself (0.031 % V/V) did not influence the basal tone and the ACh (100 μM)-induced contractions when it was applied directly into the organ bath or after preincubation of the preparation with 0.031 % V/V ethanol for 30 minutes. STW 5 as aqueous or as ethanolic solution inhibited the ACh (100 μM)-induced contractions after application into the organ bath by 12.1±3.2 % and 9.7± 4.5 %, respectively. Under the same condition aqueous STW 6 was without effect on the ACh (100 μM)-induced contractions whereas ethanolic STW 6 increased the contractions by 13.9±3.5 %. TNBS (0.01 M) preincubation for 30 minutes resulted in declined ACh (100 μM) contractions. Ethanol (0.031 % V/V) did not affect the reduced contractions. When aqueous or ethanolic extracts of STW 5 and STW 6 were applied to TNBS preincubated preparations no differences were found between the two applications (TNBS 33.7±4,1 %, STW 5 aq. 49.1±4.8 % eth. 58.2±3.4 %, STW 6 aq. 65.7±6.7 % eth. 62.8±5.8 %). The results indicate that the solvent ethanol did not influence the effects of STW 5 and STW 6 on intestinal contractility.

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POSTER 110

Synthesis of Ghrelin Receptor Inverse Agonists

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The ghrelin receptor is a GPCR mainly distributed in the brain, but also in peripheral tissues like stomach. It shows an unique constitutive activity representing 50 % of its maximal activity. The signaling of the receptor controlled by its endogenous ligand ghrelin considerably contributes to the regulation of appetite, food intake and energy homeostasis. Thus, reducing the constitutive activity can be an approach to decrease body weight and to develop an anti-obesity drug.
Inverse agonists are able to reduce basal signaling of a receptor. Holst et. *al* showed that variants of substance P provide inverse agonistic activity at the ghrelin receptor. Structure activity relationship studies led to the hexapeptide KwFwLL-NH_2 that significantly reduces the constitutive activity. Therefore, we synthesized analogues of this peptide by using solid phase peptide synthesis with Fmoc/tBu-strategy. The activity at the ghrelin receptor was tested by an inositol trisphosphate turnover assay. Some peptides presented inverse agonistic activity with EC_{50} values in the nanomolar range.
Furthermore, modified analogues containing PEG were synthesized. Pegylation should increase bioavailability and biodistribution. PEG2 was introduced at the N-terminus of the peptide either directly or separated by a lysine or a lysine-β-alanine spacer. Interestingly, both, the spacer as well as the pegylation influenced efficacy.

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POSTER 111

Promising Tools for Breast Cancer Therapy: Carbaborane-Containing NPY Analogs

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The human Y_1-receptor subtype was found to be overexpressed in more than 90% of breast cancer patientsand in 100% of breast cancer derived metastases [1].
Peptides that selectively bind to receptors over-expressed in the membrane of cancer cells are a promising tool for tumor diagnosis and therapy. Neuropeptide Y (NPY) as well as pancreatic polypeptide (PP) and peptide YY (PYY) selectively bind at Y-receptors (Y_1, Y_2, Y_4 and Y_5) which belong to the rhodopsin-like G-protein coupled receptors (GPCRs). Binding of ligands to Y-receptors leads to ligand induced internalization of the receptor. Using NPY analogs with high affinity to only one receptor subtype allows to selectively target only one Y-receptor subtype [2].
Boron Neutron Capture Therapy (BNCT) is a binary therapy using nontoxic ^{10}B, which is able to absorb nontoxic thermal neutrons to result in an excited state ^{11}B. ^{11}B decomposes to form highly toxic ^4He particles (alpha particles) and ^7Li with a short radiation range of 9 or 5 μm inside the cell. Using these effects, BNCT can be applied in tumor therapy [3].
In this work the combination of both therapeutic approaches is described. Carbaborane-modified amino acids were introduced into receptor-selective NPY analogs by Fmoc/*t*-butyl solid phase peptide synthesis. The resulting peptides were tested for their affinity towards Y_1-receptors, their ability to induce signal transduction and receptor internalization.

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POSTER 112

Multiple meningioma with different grades of malignancy: case report with genetic analysis applying single-nucleotide polymorphism array and classical cytogenetics

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Multiple meningiomas with synchronous tumor lesions represent only 1-9% of all meningiomas and usually show a uniform histology. The simultaneous occurrence of different grades of malignancy in these nodules is observed in only one third of multiple meningiomas. We report a case of a sporadic multiple meningioma presenting with different histopathological grades (WHO I and II). The tumor genome of both nodules was analyzed by GTG-banding, spectral karyotyping (SKY), locus-specific FISH, and single nucleotide polymorphism array (SNP-A) karyotyping. GTG-banding and SKY revealed 25 structural and 33 numerical aberrations with a slightly increased aberration frequency in the WHO grade II nodule. We could confirm terminal deletions on chromosomes 1p [ish del(1)(q36)(p58-,pter-) 16.5% WHO grade I and 20.9% WHO grade II], partial deletions on 22q, and/or monosomy 22 (monosomy 22 14% WHO grade I and 34% WHO grade II) as the most frequent aberrations in both meningioma nodules. In the meningioma WHO grade II, additionally, a *de novo* paracentric inversion within chromosomal band 1p36 was detectable. Furthermore, for meningiomas *de novo*, dicentric chromosomes 4 could be identified in both tumor nodules. We also detected previously published segmental uniparental disomy regions 1p31.1, 6q14.1, 10q21.1, and 14q23.3 in normal control DNA of the patient and in both tumor nodules. Taken together, we describe a very rare case of multiple meningioma with overlapping but also distinct genetic aberration patterns in two nodules of different WHO grades of malignancy.

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POSTER 113

Allyl isothiocyanate induces a phenotypic modulation and inhibits migration of melanoma cells via TRPA1 activation

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Melanoma is the most dangerous form of skin cancer occurring in Caucasians with rising incidence. They are remarkably resistant to conventional anti-tumour therapies like chemotherapy and radiotherapy. Therefore, new treatment strategies are urgently needed. We demonstrate morphological changes of A375 melanoma cells upon treatment with allyl isothiocyanate. The rounding of cells together with the formation of bleb-like structures was paradoxically associated with a reduced potential of the cells to migrate as we could show in a transwell chamber migration model. Since allyl isothiocyanate is a specific activator of transient receptor potential (TRP) channel A1 we examined its functional expression in melanoma cells, untransformed primary melanocytes and keratinocytes. Functional studies revealed TRPA1-dependent Ca^{2+} signals and whole cell currents in a subset of melanoma cells and, to a lesser extent, in primary melanocytes, making TRPA1 a possible molecular substrate for the anti-tumour effects of mustard oil and cinnamaldehyde.

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POSTER 114

Non-protein coding RNAs in breast cancer initiating cells

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Breast cancer is one of the most frequent types of cancer worldwide. Despite advances in the therapy of this disease, mortality remains high because therapy-resistant cancer cells are able to escape current therapies and lead to recurrence of the tumor. Nowadays the population of breast cancer initiating cells (BCIC) is held responsible for this instance and is considered as one of the major factors in the general process of tumorigenesis. Until now, the population of BCIC has been identified, amongst others, in prostate, pancreatic, head and neckl and breast cancers, but a detailed characterization is still missing.
Using a breast cancer cell line model, our aim is to characterize the BCIC on the bases of non-coding RNAs (ncRNAs). NcRNAs do not exhibit protein-coding potential but are in the focus of research as they might be the hidden layer of cellular complexity. NcRNAs are predominantly expressed in a highly controlled, cell type and state specific manner. Changes within ncRNA expression patterns are often associated with diseases or developmental disorders. Therefore, ncRNAs have a great potential to serve as therapeutic targets and biomarkers for several diseases.
We used the nONCOchip to study ncRNA expression in BCIC compared with non-BCIC. The analysis revealed a number of ncRNA transcripts being differentially expressed. Our small-sized pilot study showed that one can discriminate between the potential BCIC and non-BCIC using ncRNA expression. The characterization of BCIC with the help of ncRNAs might be a powerful tool towards a better understanding of this important cell population.

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POSTER 115

The PIK3/Akt pathway is involved in CD97 enhanced single random cell migration and decreased apoptosis induced by serum-starvation in HT1080 tumor cells

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Scattered tumor cells at the invasion front of colorectal cancer show upregulated expression of CD97. To characterize its role in tumors, stable HT1080 clones overexpressing CD97 were established and examined in various functional assays *in vitro*. Full-length CD97 did not enhance directed cell migration but single random cell migration. Truncation of the CD97 seven-span transmembrane domain (TM7) to TM2 disrupted this increase indicating intracellular signal transduction. To elucidate the involved pathways phospho-array screening (Kinexus) was performed, demonstrating enhanced phosphorylation of GSK3α and β, MEK1/2 and c-src in cells overexpressing CD97/TM7. These kinases are downstream targets of the PI3K/Akt pathway. Data were confirmed by western blotting, showing additionally increased total Akt and pPDK-1. Accordingly, enhanced random single cell migration of CD97/TM7 HT1080 cells was blocked by PI3K/Akt inhibitors, which had only slight effects on CD97/TM2 or mock cells. Albeit Akt is a key regulator of cell proliferation and apoptosis, no differences were found between the HT1080 clones in cell proliferation assays and cell cycle analysis. Hydrogen-peroxide induced apoptosis was also not influenced by CD97. Interestingly, full-length CD97 increased cell viability in serum-starved cells, whereas CD97/TM2 died first. This suggests involvement of CD97 in intrinsic but not extrinsic pathways of apoptosis. In summary, our data demonstrate that CD97 enhanced single random cell migration and decreased apoptosis induced by serum withdrawal. The TM7 part of CD97 is essential for signal transduction, maybe involving PI3K/Akt.

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POSTER 116

CD97 interagiert mit β-catenin, einem Schlüsselmolekül im Wnt-Pathway bei der Entstehung kolorektaler Karzinome (CC)

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CD97 wird in CC überexprimiert. Bei der Entstehung dieser Tumore spielt die Dislokation von β-catenin von der Zellmembran in den Kern eine entscheidende Rolle. CD97 verstärkt im Kolonepithel von Tg(villin-CD97) Mäusen Membran-assoziertes β-catenin und damit Adhärenz-Zellkontakte. Es ist unklar, ob CD97 und β-catenin miteinander interagieren.
Wir haben deshalb detailliert immunhistologisch die Lokalisation beider Moleküle im CC und normalen Kolon verglichen (n=57). CD97 und β-catenin sind in lateralen Zellkontakten normaler Epithel- und Tumorzellen ko-lokalisiert (57/57). Zusätzlich kommt es im CC zu einer nukleären Dislokation von β-catenin bei gleichzeitiger Translokation von CD97 in das Zytoplasma (30/57 $p<0,05$). In DLD-1 CC-Zellen verringert die Hemmung von CD97 durch siRNA die Expression von β-catenin in der Gesamtfraktion. Zum Nachweis der direkten Interaktion CD97- β-catenin wurden Ko-Immunpräzipitation und der Proximity Ligation Assay (PLA) genutzt. Sowohl im Kolon der Tg(villin-CD97) Mäuse als auch in DLD-1 Zellen ko-immunopräzipitiert CD97 mit β-catenin und vice versa. Im PLA interagieren CD97 und β-catenin in $CD97^+$ $\beta\text{-catenin}^+$ CC-Zellen.
Zusammenfassend konnten wir zeigen, dass CD97 β-catenin reguliert und direkt mit diesem Molekül interagiert. Die Interaktion CD97 – β-catenin spielt eine Rolle bei der Entstehung kolorektaler Karzinome.

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POSTER 117

Predicting patient-specific residual disease levels for imatinib-treated CML

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Molecular response to imatinib (IM) therapy in chronic myeloid leukemia (CML) patients is usually associated with a typical biphasic decline of *BCR-ABL* transcript levels in which an initial steep decline is followed by a second moderate decline. Using a mathematical model of hematopoietic stem cell organization, we have previously been able to explain both CML pathogenesis and the biphasic decline in response to IM treatment for a cohort of CML patients. However, the model did only represent a "typical median patient" not accounting for the inter-patient heterogeneity.
Following a comprehensive analysis of the patient-specific 7-year follow-up data from a prospective randomized clinical trial (German IRIS cohort, $n = 69$ patients), we estimated the inter-individual heterogeneity of molecular treatment response within the cohort. Based on the estimated distributions of model parameters we are now able to adequately describe the observed patient heterogeneity within the framework of our previously established CML model. Given a patient's initial decline of *BCR-ABL* transcript levels, our model is able to predict long-term response of the particular patients to IM treatment. Furthermore, the model enables us to estimate the number of residual leukemic stem cells (LSCs), which is important to decide about patient-specific treatment options.
Although developed and validated for IM treatment, the proposed method can in principle also be applied to forthcoming molecular response data from first-line second-generation tyrosine kinase inhibitor therapy.

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POSTER 118

Photodynamic Therapy (PDT) using Tetrahydroporphyrin-Tetratosylat (THPTS). First encouraging results on the treatment of retinoblastoma

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Photodynamic Therapy (PDT) has shown to be a promising technique to treat various forms of malignant neoplasia.
The photodynamic inactivation of the tumor cells is achieved by applying the photo sensitizer either locally or systemically (intravenous) and following local activating through irradiation of the tumor mass with light of a specific wavelength after a certain time of incubation. This procedure allows a very selective inactivation of the malignant tumor while sparing the surrounding tissue to the greatest extent. However, this also requires a good accessibility of the targeted tissue. These features and requirements make the PDT a very attractive therapeutic option for the treatment of retinoblastoma, where enucleation (surgical removal of the eye) is still the only curative option in the majority of the cases.
In this study we initially conducted in-vitro investigations of the new cationic water-soluble photo sensitizer THPTS regarding its photodynamic effect on human Rb-1 and Y79 retinoblastoma cells.
We were able to show, that neither the incubation with THPTS without following illumination, nor the sole illumination showed a considerable effect on the proliferation of the retinoblastoma cells, whereas the incubation with THPTS combined with following illumination led to a maximal (100%) cytotoxic effect on the tumor cells.
The results at hand form an encouraging foundation for further in-vivo studies on the therapeutic potential of this promising photo sensitizer for the eyeball and vision preserving, potentially curative therapy of retinoblastoma.

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POSTER 119

Role of microRNAs 195 and 372 in melanoma progression

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Dysregulation of microRNAs has been reported in both stem cells and in malignant tumors such as malignant melanoma. In particular, miR-195 and miR-372 met the interest of many researches since both are involved in cell cycle regulation and cellular proliferation. In our expression screenings, miR-372 showed a consistent downregulation while miR-195 showed upregulation in metastatic lesions of malignant melanoma as compared with primary tumors. To explain these findings, miRNA data banks were searched for target genes, and Wee1 was found as a top target gene for miR-195. Wee1 is a major gate keeper for premature entry of cells into mitosis. We found an inverse correlation between miR-195 and Wee1 in melanoma tissues, with miR-195 being upregulated in metastases and Wee1 downregulated. In line with this, miR-195 transfection of melanoma cells reduced Wee1 protein levels. We speculate that miR-195-mediated downregulation of Wee-1 might promote uncontrolled cell proliferation and cell cycle progression in malignant melanoma. As a putative target for miR-372, we identified VEGF, a pro-angiogenic and anti-apoptotic factor, which was reported to be upregulated during melanoma metastasis. miR-372 transfection of melanoma cells significantly reduced protein levels of VEGF, indicating that VEGF is indeed a target for miR-372 in melanoma. Reduced miR-372 expression might exert its effects in malignant melanoma via upregulation of VEGF and consecutive VEGF-mediated angiogenesis. Taken together, we provide evidence that both miR-195 and miR-372 might promote tumor progression in malignant melanoma via either Wee1 or VEGF, or both.

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POSTER 120

Hedgehog signalling – a new target for therapy of malignant gliomas?

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Glioblastoma multiforme (GBM) is the most aggressive brain tumor in adults. Medium survival of patients is about 14 month.
Recently, the Hedgehog (Hh) signalling pathway that is aberrantly activated in different tumors was discussed as a potential target in GBM. This consideration was based on immunofluorescence and RT-PCR but it is not known whether Hh target genes are activated in GBM.
Hh signalling is initiated by binding of a Hh ligand to the transmembrane receptor patched and leads finally to the activation of Gli transcription factors. In order to detect Gli activity reporter genes were constructed with the luciferase from *Gaussia princeps* under the control of an HSV tk promoter linked to Gli binding sites. Cells isolated from tumors and cells from glioma lines were transfected with the reporter genes and activity was determined.
In addition, cyclopamine, an inhibitor of Hh signalling, was tested for its ability to influence reporter gene expression, cellular metabolism and cell migration.
The experiments without cyclopamine revealed that 8 cultures exhibited enhanced reporter gene expression, 3 cultures repression and 4 cultures did neither show activation nor repression. Interestingly, only 1 out of 6 cultures responded to cyclopamine with significantly decreased reporter gene activity. On the other hand, 16 out of 19 cultures responded to cyclopamine with reduced ATP production and 7 cultures out of 12 exhibited a suppression of migration.
These results indicate that cyclopamine may be a potential therapeutic agent although its action on ATP production and migration may not be related to Gli transcription factors.

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POSTER 121

MECHANISMS UNDERLYING ACQUIRED RESISTANCE TO TYROSINE KINASE INHIBITORS IN LUNG CANCER

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Background: Lung cancer patients respond variably to tyrosine kinase inhibitors. Some patients eventually acquire resistance to the drugs. The mechanism of this phenomenon is associated with mutations in the epidermal growth factor receptor. Our study aims at establishing other factors which lead to acquired resistance to TKI, erlotinib and gefitinib through the analysis of apoptosis regulators in the Bcl2 family.
Methods: Viability of H1299, A549 and HCC827 was assessed by the MTT test. Caspace 3/7 activity was tested to evaluate apoptosis induction. Cell cycle analysis was done after propidium iodide staining. HCC827 was exposed to the test substances for a period of 3 months to develop a resistant version.
Results: Viability curves showed a concentration depended growth inhibition. HCC827 is more sensitive to the drugs as compared to H1299 and A549 for both drugs. The drugs increased the activity of caspace 3/7 in HCC827 but not in A549 and H1299. Cell cycle analysis revealed subG0/G1 cell cycle arrest. HCC827 developed resistance to the drugs after long term exposure. The growth inhibition of these cells in comparison with the parent cell line increased by 2 fold. The caspace activity decreased significantly in the resistant HCC827 compared to the parent cell line. The cell line also showed a subG0/G1 cell cycle arrest.
Conclusion: The sensitivity of HCC827 is due to mutation in the EGRF unlike A549 and H1299 which carry a wild type EGFR. The same trends as in A549 and H1299 were observed in the resistant HCC827.Secondary resistance is demonstrated in the resistant HCC827 which will be analysed for gene expression.

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POSTER 122

Identification of new signalling pathways for targeted therapy in malignant melanoma

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Malignant melanoma is a highly aggressive tumor with increasing incidence and high mortality rates in the metastatic stage. The molecular mechanisms underlying initial tumor development and further progression are still poorly understood. In the present study, we are trying to identify new intracellular signalling pathways important for melanoma cell growth, which might later serve as targets for therapeutic intervention. For this purpose, a large-scale loss-of-function screen was performed in a series of melanoma cell lines using a genome-wide lentiviral RNAi library. In these experiments, siRNAs that lead to cell death or reduced growth of transduced melanoma cell clones are negatively selected and thereby underrepresented in the final whole siRNA pool. In contrast, siRNAs that target tumor suppressor genes are enriched. Differentially expressed siRNAs were identified by DNA microarray technology. Of 345 significantly differentially expressed siRNAs, 138 were signalling molecules. In further analyses, the bioinformatic tools DAVID and STRING were used to narrow down these results to particular pathways and signalling networks. By this means, the MEKK1-JNK/SAPK-c-Jun pathway was identified as a candidate, together with two major interacting partners of other protein networks. For further validation of these findings, functional experiments were performed using melanoma cells with a transient knock-down of individual pathway components.These experiments may finally lead to the identification of new functionally relevant pathways for melanoma cell growth, which might then be targeted by small molecule inhibitors.

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POSTER 123

ADAM10 mediated shedding of long and short leptin receptor isoforms: Influence of lipotoxicity, apoptosis, ER-stress and effects on leptin action

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The soluble leptin receptor (sOb-R) is the main binding protein for leptin in human blood and modulates the bioavailability of the ligand. sOb-R is generated through ectodomain shedding of membrane-anchored Ob-R in humans. However, the regulatory mechanism of this process and the mediating sheddase(s) are still unknown. Metabolic disorders like type 1 diabetes mellitus (T1DM), obesity or type 2 diabetes mellitus (T2DM) are characterized by disregulated sOb-R concentrations that potentially affect leptin actions. We show that ADAM10 is of major importance for the generation of sOb-R. Additionally, we demonstrate lipotoxicity and apoptosis differential induce activated Ob-R shedding in a cell model with overexpression of the human full length Ob-R isoform (Ob-Rfl) or the human short isoform Ob-R219.3. Increased sOb-R concentrations decreased leptin mediated STAT3 phosphorylation via Ob-Rfl, detected by ELISA. Measurements of sOb-R in the supernatant of Ob-R transfected cells with an in-house immunofunctional assay revealed that high leptin concentrations as well as ER-stress induced by tunicamycin decreased sOb-R concentrations. This decrease was accompanied by an impaired leptin signalling and reduced leptin binding confirmed through P-STAT3 immunodetection and ^{125}I-leptin binding assay. These new insights in regulatory mechanisms of Ob-R shedding may provide new possibilities to affect leptin actions by decreasing or increasing sOb-R concentrations. Additionally, long term measurements of serum sOb-R could be a diagnostic approach to monitor the development of leptin resistance.

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POSTER 124

New key players in adipogenesis? Relevance of genes found associated with obesity in Genome Wide Association studies in human adipocytes.

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Recent Genome Wide Association studies (GWAs) identified new single nucleotide polymorphisms associated with obesity. The relevance of the respective genes for the development of adipose tissue is largely unknown. The aim of our study was to characterize the identified candidate genes in adipocytes by expression- and functional analyses in *vitro*.
We selected eight candidate genes (*BDNF*, *MAF*, *MTCH2*, *NEGR1*, *NPC1*, *PTER SH2B1*, *TMEM18*) from six GWAs. We created human tissue expression arrays to evaluate the expression pattern among in metabolic, endocrine, neural and other tissues. We investigated the regulation of the genes during adipogenesis using the human adipocyte model SGBS and analyzed the effect of insulin, dexamethasone, IGF-1 and isoproterenol on gene expression. To address the question whether the candidate genes play a role in adipogenesis we applied RNA-interference to knock down gene function.
All of the candidate genes were basally expressed in adipose tissue. Analyses of gene expression during adipogenesis revealed a threefold up regulation of *MAF*, *MTCH2*, and *NEGR1* and a threefold down regulation of *BDNF*. All genes except *PTER* and *SH2B1* showed a dose dependent regulation under the influence of insulin. *NEGR1* was threefold up regulated whereas *MAF* was threefold down regulated by dexamethasone. Knock down of *BDNF*, *MTCH2*, *NEGR1* and *TMEM18* gene function resulted in a significantly reduced adipogenesis based on morphologic assessment.
Our findings may indicate a potential role of *BDNF*, *MTCH2*, *NEGR1,* and *TMEM18* in adipocyte differentiation.

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POSTER 125

Konzept einer Forschungsdatenbank für die Translationale Forschung

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Große medizinische Forschungsvorhaben wie der IFB Adipositas erheben im Rahmen klinischer Studien umfangreiche phänotypische und genotypische Datensätze der Probanden. Diese Daten sollen über ihre Primärauswertung hinaus zur Lösung weiterer medizinischer Fragestellungen genutzt werden. Ziel ist es, verschiedene Datenbestände so in einem zentralen Repository zu aggregieren, dass sowohl ihr konzeptuelles Modell als auch ihre Repräsentation im Informationssystem verlustfrei abgebildet werden. Probleme hierbei sind die Heterogenität der Quellsysteme (KIS, CDMS, Biobank, Labor, Körperscanner), die unterschiedliche Qualität der Quelldaten, die Beachtung regulativer Vorschriften (Datenschutz), die semantische Integration und die hohe Anzahl täglich dokumentierter Observationen.
Nach einer gründlichen Systemanalyse mit einem speziellen Planungswerkzeug (3LGM²) wurde eine Informationsarchitektur auf Basis verschiedener frei verfügbarer Komponenten entwickelt. Zentrales Element ist hierbei das Clinical Data Warehouse (i2b2), in welches alle medizinischen Fakten importiert werden. Es ermöglicht die Abfrage und Visualisierung komplexer Abfragen auf heterogenen Datenbeständen. Die Identität der Probanden wird durch eine mehrstufige Pseudonymisierung unter Erhalt einer eindeutigen ID im Patientenregister verborgen. Die semantische Korrektheit der Abfragen wird sichergestellt, in dem die Parameter auf ein zentrales Metadatenverzeichnis von harmonisierten Datenelementen verweisen. Der hier vorgestellte Ansatz unterstützt sowohl klinische Fragestellungen wie Kohorten-Analysen als auch die Patientenrekrutierung mit Feasibility-Anfragen.

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POSTER 126

Casein Kinase 2: A Key Player in Adiponectin Signalling

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Adiponectin is an adipose tissue derived hormone that is involved in the inhibition of metabolic syndrome, protection of hypertension and suppression of atherosclerosis [1, 2]. Adiponectin functions are mediated by its two receptors AdipoR1 and AdipoR2. Both receptors consist of seven transmembrane helices. However, in contrast to classical G-Protein coupled receptors, the N-terminus is located intracellularly and the C-terminus is extracellular [3].
In order to identify further proteins involved in signal transduction, we performed a yeast-two-hybrid screen and found casein kinase 2 as an interaction partner of the AdipoR1 N-terminus. To further investigate the role of CK2 in adiponectin signalling, co-immunoprecipitation, ELISA experiments and co-localization studies were carried out. Thus, we could determine the interaction site of the receptor and identified this interaction to be affected by adiponectin. Inhibition of CK2 activity by 2-dimethylamino-4,5,6,7-tetrabromo-1H-benz-imidazole (DMAT) identified CK2 as a key player in adiponectin signalling.
To utilize adiponectin as a therapeutic target, it is essential to understand adiponectins function in more detail. Until now, only little is known about proteins involved in AdipoR signal transduction. In the present study, we were able to identify CK2 as an interaction partner of the AdipoR1 and found CK2 to be involved in adiponectin signalling cascades.

[1] Kadowaki et al., J Clin Invest, 2006, 116
[2] Matsuzawa et al., Arterioscler Thromb Vasc Biol, 2004, 24
[3] Deckert et al., J Recept Signal Transduct Res, 2006, 26
[4] Heiker et al., Cell Signal, 2009, 21

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POSTER 127

Functional Studies on the Importance of C-terminal Truncation of Chemerin

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Introduction: Recent reports suggest that chemerin acts as an adipokine [1,2]. Serum levels of chemerin correlate with characteristics of the metabolic syndrome. Additionally the expression of chemerin and its receptor chemokine-like receptor 1 (CMKLR1) is upregulated during the differention of 3T3-L1 cells to mature adipocytes.
Methods: Using standard solid phase peptide synthesis (SPPS) Fmoc/tBu- strategy we synthesized C-terminal peptides of chemerin and prochemerin. The activity of the synthesized peptides at the human CMKLR1 was tested in an inositol-phosphate-accumulation assay (IP_3-assay). In addition to the peptides we also tested c wildtype chemerin and prochemerin. Both proteins were produced by recombinant protein expression in E.*coli* BL21 and purified via Ni-NTA affinity-chromatography.
Results: In our studies we could confirm the importance of the C-terminal truncation of the prochemerin- specific C-terminal amino acids. In comparison of C-terminal peptides and the recombinant proteins we could show the influence of these amino acids for activation of CMKLR1.
Conclusion: The truncation of chemerin displays a regulation of the ligand towards the CMKLR1. Understanding this processing may help to understand the molecular mechanisms, which influence diseases like the metabolic syndrome.

[1] Goralski, KB et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. *J. Biol. Chem.* 282: 28175-28188, 2007
[2] Bozaoglu, K et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. *Endocrinology 148*: 4687-4694, 2007

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POSTER 128

Adipokine concentrations in seminal plasma are correlated to semen quality in normal-weight and obese men

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Objective: An inverse relationship between increasing adipose tissue and spermatozoa function has been connected to raising prevalence of obesity in the last decades. So far, the molecular background for this male reproductive dysfunction has not been clarified. Adipokines, proteins secreted by the adipose tissue play a major pathophysiological role in other obesity-related diseases and might be a potential link between obesity and male subfertility.
Methods: To test this hypothesis levels of adipokines like leptin, adiponectin, resistin, progranulin, chemerin, NAMPT and vaspin were analyzed in seminal plasma of overweight/obese (n=27, age 34.3±8.7 years; BMI 30.0±3.7 kg/m²) and normal-weight men (n=27, age 34.1±8.8 years, BMI 22.6±1.7 kg/m²) and correlated to standard semen parameters (WHO).
Results: Overweight/obese men had significantly less motile and normomorph spermatozoa compared to normal-weight men. Moreover, the amount of spermatozoa with intact acrosomes was reduced compared to control subjects. In the seminal plasma of overweight/obese men adiponectin concentrations were significantly lower, whereas levels of chemerin and vaspin were higher than in normal-weight males. Furthermore, seminal plasma levels of adiponectin and progranulin correlated positive ($p<0.05$) and levels of vaspin and chemerin negative ($p<0.05$) with sperm parameters.
Conclusions: Our study showed for the very first time a potential relationship of adipokine levels in the seminal fluid and semen quality based on the individuals' body weight. The molecular pathogenesis of these findings is currently under investigation.

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POSTER 129

Comparison of adipokine concentration in serum and seminal plasma

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Background: There is an increasing prevalence of obesity and its comorbidities in Western countries. Obesity-related impairment of male reproductive function and corresponding changes in semen parameters are complex and not fully understood so far. Adipokines, proteins mainly secreted by the adipose tissue, could be involved in the pathogenesis of sperm disorders in patients with adiposity. Our study aimed to understand the regulatory mechanism of adipokines in male reproductive tract by comparing adipokin levels of seminal plasma and peripheral blood.
Subjects and Methods: 130 male sperm donors of varying age (mean±SD: 37.4±12.7) and body mass index (BMI: 27.8±6.2) were included in the cross-sectional study after informed consent. The adipokines leptin, adiponectin, resistin, chemerin, progranulin, NAMPT and vaspin were measured in seminal plasma of all study donors. The data were compared with the corresponding adipokin levels in their peripheral blood (serum).
Results: Mean concentrations of adiponectin (100-fold), leptin (6-fold) and chemerin (2-fold) were significantly ($p<0.05$) higher in serum than in seminal plasma. In contrast, mean concentrations of vaspin (4-fold), progranulin (50-fold) and NAMPT (100-fold) were significantly higher in seminal plasma. For resistin we found no significant difference between both body fluids. Only seminal plasma levels of adioponectin correlated directly and significantly with serum adiponectin ($p<0.01$).
Conclusion: Our results indicate that adipokines are present in the male reproductive tract where they appear to be regulated independently from levels in peripheral blood. The potential influence of adipokines on the functionality of sperms is currently under investigation.

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POSTER 130

Do copy number variations in monogenic obesity genes contribute to the polygenic background of obesity in children?

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Background: In rare monogenic forms of obesity genetic variants have been found in Leptin, Leptin-receptor, Proopiomelanocortin (POMC), Single-minded 1 (SIM1) and Melanocortin-receptor 4 (MC4R). Among them, variations in MC4R is the most common cause of monogenetic obesity. However, monogenic diseases are causing only a minority of obesity cases, while the majority develops on a polygenic background. We aimed to investigate the frequency of copy number variations (CNV) in obese children for the genes mentioned above.
Methods: We used a multiplex ligation-dependent probe amplification (MLPA) to analyze gene-dosage alterations caused by deletions and/or duplications in gene-loci mentioned above in 194 obese children (mean BMI SDS 2.9).
Results: We did not find CNVs in POMC, LepR, Lept, MC4R in any patient of our cohort. We identified 21 children with potential deletions in exon9 of SIM1. In subsequent molecular analyses we could, however, not confirm a deletion. Instead, we identified a SNP (rs3734354) that is located within the binding site of the ligation fragment in these patients and which most likely affects the binding characteristics of the MLPA-probe and therefore delivers a false-positive result. We subsequently genotyped the polymorphism in 764 obese and 1149 lean children. We could not find an association of rs3734354 with BMI-SDS.
Conclusion: Our data do not provide evidence for a role of CNVs in SIM1, MC4R, POMC, Leptin and LepR in the genetics of obesity in children.

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POSTER 131

Physiologic effects of genetic variants in ADCY5, GIPR, GCKR and VPS13C on glucose metabolism – analyses in children.

Windholz J[1]
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Objective Background: Recent genome-wide association studies have revealed several single nucleotide polymorphisms associated with glucose and insulin levels variations in adults. We aimed to reproduce data on 4 of such loci found to be strongest associated in our cohort of obese and non-obese children.
Methods: Using TaqMan allelic discrimination assays, we characterized those loci in our cohorts of 638 children to clarify their role in regulation of glucose levels and insulin release/effect in children.
Results: rs2877716 (ADCY5) was significantly associated with an increase of fasting plasma insulin (P = 8x10-4), peak insulin (P = 9x10-4), HOMA-B (P = 4x10-4) and a drop of QUICKI (P = 2x10-2) and ISI (P = 1x10-2). rs17271305 (VPS13C) was significantly associated with 120min blood glucose (P = 9x10-4).
Conclusion: Our data shows effects of genetic variation within ADCY5 on early impairment of insulin metabolism and variations of VPS13C on early impairment of blood glucose homeostasis in children.

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POSTER 132

Rapamycin treatment for a 4 year old boy with PTEN-Hamartoma-Tumor-Syndrome

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PHTS is a rare genetic disease with a wide range of symptoms and no standard therapy. This study describes the results of an experimental rapamycin treatment of a four-year-old boy with PHTS, massive lipomatosis, lymphatic hyperplasia and cachexia. Cell cultures from a resected lipoma of the patient were investigated *in vitro*.
Aims: Can the rapamycin therapy improve symptoms? Are proliferation and adipocyte differentiation in lipoma cells disturbed by the *PTEN* mutation? Can these disturbances be overcome by rapamycin treatment?
Results: Four months of rapamycin therapy improved the patient's quality of life, increased his physical activity, and resulted in a catch-up growth of 5cm, as well as a regression of the hyperplasia of the thymus (~30%) and the enteral mucosa. There was no reduction of lipomatous masses and no weight gain. With respect to the *in vitro* tests, the lipoma cells preserved a high capacity for adipocyte differentiation for more than 40 population doublings. Western blot tests revealed a decreased PTEN protein level and a constitutive phosphorylation of the enzyme AKT. Rapamycin decreased proliferation by ~30% and adipocyte differentiation by ~60% at a concentration of 100nmol/l. The insulin-like growth factor binding protein 2 (IGF-BP2) has been proposed as a diagnostic marker for the success of the rapamycin therapy. However, measurements of the patient's serum samples revealed only a slight decrease from 1269ng/ml to 860ng/ml.
Conclusion: Both the clinical observations and the *in vitro* data demonstrated that rapamycin might be used for patients with severe PHTS and no other therapy option.

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POSTER 133

Association analysis between a single nucleotide polymorphism (SNP) in the GPBAR1 gene and cholesterol gallstone susceptibility in a population of Sorbs

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Cholesterol gallstones develop in gallbladders with impaired motility and bile supersaturated with cholesterol. *GPBAR1* encodes a G-protein coupled receptor at the membrane of various enteric cell-types. Recently, studies indicated that GPBAR1 mediates bile salt induced dysfunction of gallbladder smooth muscle cells leading to stasis of bile. Furthermore, GPBAR1 deficient mice overexpressed *Cyp7a1*, the rate limiting enzyme of cholesterol degradation into bile salts and were confirmed to be gallstone resistant. In the current study, we analyzed *GPBAR1* as a gallstone susceptibility (*LITH*) candidate gene in a self-contained population of Sorbs. We employed a HapMap-based approach and identified rs11554825 as a single tagging SNP that represented the common genetic variation of *GPBAR1*. 184 gallstone carries and 833 controls were genotyped employing the TaqMan method. Data was analyzed in the additive model using logistic regression including age, gender and body mass index as covariates. This was the first genetic analysis for a putative contribution of *GPBAR1* variants to gallstone susceptibility. Our analyses do not show any effect of *GPBAR1* on gallstone risk ($P > 0.05$). However, the power of our study is limited and rare variants were not included in our analyses. Therefore, a role of genetic variation of *GPBAR1* for human gallstone susceptibility cannot be excluded.

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POSTER 134

C57BL/6JRj mice are protected against diet induced obesity (DIO)

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Aim: Due to genetic heterogeneity and various environmental factors influencing obesity, identifying susceptibility genes remains a big challenge. Experimental animal models offer a great opportunity to overcome these issues. However, potential genetic and phenotypic differences among C57BL/6 mice substrains need to be considered in the context of diabetes research. Here we investigated the influence of different diets on epigonadal fat mass in two C57BL/6 substrains. Furthermore we testet the hypothesis of genetic differences between both substrains. Methods: 16 healthy lean male mice of two different substrains C57BL/6NTac (Taconic) and C57BL/6JRj (Janvier) were fed with a high fat diet (HFD, N=4) or standard diet (SD, N=4) for 10 weeks. Phenotypical characterization included measurements of bodyweight, physical activity and food intake. Relative epigonadal fat mass was analyzed at the end. Genetic differences between both substrains were analyzed using a panel of 1449 SNP markers. Results: Phenotypic characteristics of the C57BL/6 inbred strains suggest that C57BL/6JRj are protected against diet induced obesity even under HFD. No significant difference in physical activity nor in daily food intake were observed between both strains. Moreover, we identified 11 chromosomal regions in which they differ from each other. Conclusion: C57BL/6JRj mice are protected against DIO and diverge genetically from the C57BL/6NTac substrain. To confirm these findings, backcross-studies are currently being performed to identify genetic loci which protect against DIO.

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POSTER 135

Childhood obesity: Fast and reliable magnetic resonance based quantification of

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Purpose:
To establish and validate a magnetic resonance (MR)-based fat quantification package that allows fast and reliable assessment of abdominal adipose tissue and liver fat in children.
Materials and Methods:
Ex vivo experiments with a torso model and water-oil-mixtures are conducted. Ten children are investigated. Abdominal Adipose Tissue (AAT) is covered by magnetic resonance imaging using a fat selective sequence and analyzed by a plug-in based on the open source software ImageJ. Liver fat (LF) is measured with localized 1H Magnetic Resonance Spectroscopy (1H MRS) and the jMRUI (java-based Magnetic Resonance User Interface) software package.
Results:
Ex vivo trials with the torso model showed that adipose tissue was measured appropriately with a systemic underestimation by 9.3±0.2% (0.32 ± 0.064 kg). In children, total time for scanning and analyzing took around 15 minutes for 43 slices per patient. Coefficients of variation for both intra- and inter-observer measurements ranged between 0 – 2.7% and repeated analyses showed significantly equivalent results ($p=0.00098$). Lipid content obtained by 1H MRS *ex vivo* revealed significant equivalence with the predefined fat content in water-oil-mixtures ($p=0.0034$), considering the minimal relevant difference $\delta=1/10$. *In vivo*, positive correlations were found between VATand LF results ($r = 0.711$). Equivalence is proven for multiple calculations of each 1H MRS measurement.
Conclusion:
A MR-based fat quantification package is established, enabling the reliable quantification of both AAT and LF in children within less than 30 minutes on a freeware-based platform.

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POSTER 136

Adipositas und Depression: Die pathogenetische Rolle von Schlaf-Wach-Regulation, motorischer Aktivität und neurochemischen Aspekten

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Im Gegensatz zu den typisch depressiven Symptomen der Appetit- und Schlaflosigkeit ist die atypische Depression durch erhöhte Nahrungsaufnahme und Hypersomnie charakterisiert. Allerdings ist der Zusammenhang zwischen Adipositas, Depression und Schlaf-Wach-Regulation noch nicht ausreichend verstanden. Folgende Mechanismen bieten einen Ansatzpunkt um diese Beziehung zu untersuchen: Die Schlaf-Wach-Regulation ist eng mit der Regulation der Nahrungsaufnahme, Energiehomöostase und Stimmung verknüpft. Verschiedene für die Schlaf-Wach-Regulation wichtige Hormone, Zytokine und Neuropeptide modulieren den Affekt. Motorische Aktivität greift in den Stoffwechsel ein und kann antidepressive Wirkungen haben.

Methodische Vorstudie
Da Störungen des Schlaf- Wach-Rhythmus als Fehlfunktion der Vigilanzregulation betrachtet werden können, soll ein „Wakefulness-Assessment-Test (WAT) zur Klassifikation verschiedener Vigilanzstadien in EEG-Aufnahmen entwickelt werden.

Hauptstudie
In der zweiten Phase werden Vigilanz-Regulation, motorische Aktivität sowie neurochemische Faktoren bei adipösen und normalgewichtigen Probanden mit und ohne Depression (N = 300) im Quer- und Längsschnitt erhoben. Folgende Fragen sollen beantwortet werden: Welche Vigilanzstadien treten in den vier Studienpopulationen jeweils am häufigsten auf? Inwiefern hängt Vigilanz-Regulation mit metabolischen Faktoren, Schlaf-Wach-Regulation und motorischer Aktivität zusammen? Ändert sich die Vigilanz-Regulation mit einer Veränderung des klinischen Status? Hat motorische Aktivität einen Einfluss auf Schlafqualität, Vigilanz-Regulation und Metabolismus bei adipösen Patienten?

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POSTER 137

Chemerin serum levels are associated with parameters of vascular inflammation in obese children

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Background: The adipokine chemerin plays an essential role in adipocyte differentiation and is associated with parameters of obesity and metabolic syndrome in adults. Here, we present the first study analyzing chemerin serum levels and their association to measures of obesity and parameters of cardiovascular risk in obese compared to lean children.
Methods: Serum levels of chemerin were quantified by ELISA in 69 lean and 105 obese children of the Leipzig Atherobesity childhood cohort and correlations with anthropometric, metabolic, cardiovascular, endothelial and inflammatory parameters were assessed.
Results: Chemerin serum concentrations are significantly higher in obese compared to lean children (117.82 ng/mL in obese and 89.75 ng/mL in lean; $p < 0.001$), and correlate with obesity-related parameters, such as BMI SDS ($r = 0.57$, $p < 0.001$), leptin ($r = 0.39$, $p < 0.001$), and skinfold thickness ($r = 0.54$, $p < 0.001$). Furthermore, chemerin is significantly correlated with measures of inflammation, as hsCrP (0.50, $p < 0.001$) and white blood cell count ($r = 0.30$, $p < 0.001$), as well as parameters of endothelial activation, as ICAM-1 ($r = 0.33$, $p < 0.001$) and E-selectin ($r = 0.30$, $p < 0.001$). Finally, in multiple regression analyses, chemerin is a predictor of hsCrP, white blood cell count, ICAM-1 and E-Selectin serum concentration independent of BMI SDS, age, sex and pubertal stage.
Conclusions: Similarly to adults, chemerin serum levels are associated with obesity and metabolic syndrome in children. Moreover, in children chemerin serum concentration is a predictor for endothelial activation as an early stage of atherogenesis.

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POSTER 138

Molecular Mechanism of the Insulin Sensitizing Adipokine Vaspin

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Vaspin (visceral adipose tissue-derived serpin) was identified as an adipokine with insulin-sensitizing effects, which is predominantly secreted from visceral adipose tissue in a rat model of type 2 diabetes (T2D). The molecular target of vaspin and its mode of action are completely unknown up to now.
Here, we show that the crystal structure of vaspin confirms the typical serpin structure and suggests a protease target. We find that vaspin is expressed in pancreatic b-cells and inhibits a member of the kallikrein family with a high specificity via typical serpin mechanism *in vitro*. This is the first identified target of vaspin. Consistent with a potential insulin protective role of vaspin, plasma insulin concentrations in response to glucose are higher in mouse models treated with recombinant vaspin compared to controls explaining the glucose lowering effect of vaspin. Significantly lower kallikrein serum concentrations in patients with type 2 diabetes together with increased vaspin expression in obesity / T2D corroborate the vaspin-kallikrein system as a physiological compensation mechanism in the metabolically challenged state of insulin resistance and suggest the vaspin-kallikrein system as a potent novel target for anti-diabetic treatment strategies.

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POSTER 139

PCSK1 as an obesity gene? – Clinical and functional characterization of known and newly identified variants.

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PCSK1 is a physiologic candidate gene for obesity with support from rare monogenic cases and association studies. We aimed to screen the gene for novel variants, to assess their effects on obesity and to evaluate their functional relevance *in vitro*. We sequenced all exons, intron/exon boundaries and 5´UTR in 52 obese children selected for high proinsulin and early impaired glucose tolerance. We identified 8 known SNPs and 2 novel heterozygous variants: a splice site mutation and a missense mutation – S24C. To evaluate the clinical relevance we genotyped all these SNPs in 704 obese and 974 lean children. Variant rs6232 (P=0.015) and rs6234 (P=0.013) were significantly associated with BMI SDS.
Functionally, promoter activity was significantly increased by rs725522 but was not affected by rs35753085 and rs6230 in Hek293 and ßTC3 cells. Analysis of the splice site variant confirmed exon skipping and a 71-amino acid in frame deletion. The mutated protein was not secreted as confirmed by western blotting, but was retained within the ER shown by immunofluorescence. The enzymatic activity was completely abolished. The clinical phenotype was characterized by extreme obesity, insulin resistance and impaired glucose tolerance at the age of 15.Despite causing a missense mutation in the signal peptide, the S24C variant did not affect cell trafficking, nor did it alter the release from the cells or enzymatic activity.

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POSTER 140

Metabolic and genetic predictors of AFABP serum concentrations in the Sorbs

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Background: Adipocyte fatty acid binding protein (AFABP) was recently introduced as a novel adipokine playing an important role in glucose homeostasis. In the current study, we investigated the relationship between serum AFABP levels and metabolic, as well as cardiovascular parameters, in the self-contained population of Sorbs. Furthermore, we analyzed the effects of common variants in the *FABP4* gene on AFABP serum concentration.
Methods: Serum AFABP concentrations were determined by ELISA and correlated with metabolic parameters such as insulin resistance and -secretion, serum lipids, inflammatory markers, and renal function in 868 non-diabetic subjects.
Results: Waist-to-height-ratio and glomerular filtration rate were independently associated with AFABP concentrations in multiple regression analysis in both females and males. Median AFABP serum concentrations were 1.5-fold higher in female subjects (23.03 (17.57) μg/l) as compared to males (15.86 (10.14) μg/l). In females, the number of children born was an independent positive predictor of circulating AFABP independent of overall body fat mass. Two single nucleotide polymorphisms in *FABP4* rs16909187 and rs10808846 did not show any effects on serum AFABP concentrations in our population.
Conclusion: AFABP serum concentrations are determined by parameters of fat distribution, renal function, gender, and potentially number of pregnancies.

Keywords: AFABP, Cardiovascular Diseases, Insulin Resistance, Metabolic Syndrome, Obesity, Renal Function

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POSTER 141

Erste Ergebnisse des T.A.F.F.-Projekts (Telefonberatung zur Adipositasprävention Für Familien): Response-Raten und soziodemografische Beschreibung der Teilnehmer

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Die Prävalenz von Adipositas im Kindes- und Jugendalter hat sich auf einem hohen Niveau stabilisiert. T.A.F.F. bietet Hilfestellung zur Integration eines nachhaltig gesünderen Lebensstils in den Familienalltag.
Fragen: 1) Wie effektiv war die Rekrutierung über Kinderärzte? 2) Gibt es soziodemographische Merkmale, welche die Teilnehmer auszeichnen?
Methodik: Rekrutiert wurde über ein bundesweites Screening im Kinderärztenetzwerk CrescNet. Einschlusskriterien waren: Alter 3-17 Jahre und BMI>90. Perzentile. Die Ärzte kommunizierten den Familien die Möglichkeit, am Projekt teilzunehmen. Familien, welche schriftlich ihr Interesse bekundeten *und* einen ausgefüllten Fragebogen zurücksandten, bildeten die T.A.F.F.-Kohorte. Diese wird bezüglich ihrer soziodemografischen Eigenschaften beschrieben. Da ca. 60% der Teilnehmer in Sachsen leben, stellt die sächsische Bevölkerung (Mikrozensus 2009) die Vergleichspopulation dar.
Ergebnisse: 4005 Kinder und Jugendliche wurden durch das CrescNet-Screening identifiziert. 16,2% der Familien bekundeten eine Teilnahmebereitschaft. Letztendlich konnten 7,7% der Familien in die Intervention einbezogen werden. Bezüglich der Soziodemografie wurden folgende Ergebnisse ermittelt:
– signifikante Unterschiede bezogen auf Altersverteilung, Familienstatus, Bildung der Väter, Haushalts-Nettoeinkommen und Personen im Haushalt.
– keine signifikanten Unterschiede bezogen auf Geschlecht, Bildung der Mütter und Erwerbsstatus der Eltern.
Die Ergebnisse sollen für zukünftige Präventionsprogramme genutzt werden, um mehr Familien zur Teilnahme zu motivieren und die Nachhaltigkeit von Interventionen zu optimieren.

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POSTER 142

Internet-basierte Psychotherapie für Binge-Eating Störung

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In den vergangenen Jahren konnte die Behandlungswirksamkeit der kognitiv-verhaltenstherapeutischen Psychotherapie bei der Binge Eating Störung in einer Reihe von Studien nachgewiesen werden. Im Rahmen einer randomisierten Kontrollgruppenstudie soll die evidenz-basierte Behandlung im Rahmen einer internet-basierten Psychotherapie evaluiert werden. Internet-basierte Psychotherapie bietet als niedrigschwellige Behandlungsalternative zur herkömmlichen Sprechzimmertherapie eine Reihe von Vorteilen für die Patienten: z. B. geografische Unabhängigkeit, durch Anonymität geringeres Erleben von Stigmatisierung. Für dieses Vorgehen wird zunächst ein Behandlungsmanual entwickelt, welches auf den Prinzipien der kognitiven Verhaltenstherapie für Binge Eating beruht. Patient und Therapeut kommunizieren hierbei ausschliesslich in Schriftform und asynchron, basierend auf dem Therapiemanual. Die Randomisierung findet zwischen der Behandlungsgruppe und einer Wartelistengruppe statt. Die Behandlung dauert insgesamt 4 Monate und Messzeitpunkte sind Prämessung, Therapiemitte, Postmessung und 3-, 6-, 12-Monats-Follow-up. Gemessen wird die Wirksamkeit der internet-basierten Therapie im Vergleich zur Wartelistengruppe zum einen an der Veränderung der Anzahl der Tage, an denen Essanfälle auftreten, zum anderen an der Verbesserung von Symptomen der Essstörung sowie der psychischen Komorbidität und die therapeutische Beziehung. Zusammenfassend soll durch diese Studie die Wirksamkeit einer internet-basierten therapeuten-gestützten Therapie einer Binge Eating Störung untersucht werden.

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POSTER 143

Automatische Fettquantifizierung im Abdomen mittels Magnetresonanztomographie

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Ziel: Abdominelles Fett ist mit einem erhöhten Risiko für metabolische und kardiovaskuläre Erkrankungen assoziiert und kann mit der Magnetresonanztomographie selektiv dargestellt werden. Eine manuelle Fettquantifizierung ist oft zeitaufwändig während eine automatische Analyse anatomisch bedingt nicht immer genau ist. Daher wird eine selbstentwickelte Software zur automatischen Quantifizierung mit einer manuellen Korrekturoption vorgestellt.
Material: An 10 Patienten (Ø 19 Jahre, Ø BMI 35) wurde das Abdomen fettselektiv im MRT abgebildet. Die Software berechnet mittels aktiver Konturen die Grenzen zwischen Hintergrund, subkutanem und viszeralem Fett. Zwei Untersucher bestimmten manuell die Volumina des Subkutan- (SAT) und des Viszeralfetts (VAT), wobei letzteres über eine Histogrammanalyse erfolgte. Die absolute Genauigkeit wurde an einem Gewebephantom mit Fettanteil V_{REF} abgeschätzt.
Ergebnis: Das manuell bestimmte Fettvolumen des Phantoms lag 1,2% höher als V_{REF}. Die Interobservervariabilität der manuellen Patientendatenanalyse betrug 3,7% / 0,8% (VAT / SAT). Die automatisch bestimmten Werte lagen im Mittel ca. 18±8% / 1±3% (VAT / SAT) darüber. Die Berechnung dauert rund 6 min pro Patient.
Folgerung: Die manuelle Analyse der Referenz war sehr genau. Die Interobservervariabilität für die Patientendaten war gering, insbesondere für SAT. Während SAT bereits automatisch sehr genau bestimmt werden konnte, wurde VAT gegenüber den manuell korrigierten Werten systematisch ($p<0,05$) aber mit geringen relativen Abweichungen überschätzt. Das Verfahren scheint für eine schnelle und klinisch genaue Fettquantifizierung vielversprechend.

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POSTER 144

Attitudes towards and Perception of Overweight and Obesity in the Public Opinion: a systematic review

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Up to this date, the obesity pandemic has yet to be confined. While weight reduction programmes based on individual behavior only yield a long term achievable weight loss of 10%, still leaving individuals obese, the role of interventions aiding to avoid negative consequences of overweight has grown. One major cause of negative consequences regarding individual (eating behavior, psychiatric comorbidity) and public health (prevention efforts etc.) dimensions is the perceived stigmatization and discrimination by their social surroundings. This review summarizes population-based studies reporting on weight stigma in the general public. While extensive research to determine prevalence of weight stigma in special populations, such as health care professionals, data on the frequency of negative attitudes and stigma in the general public is lacking. Only six studies (USA and Germany) presented results of population-based analyses. Obesity is regarded a major health problem as a result of all studies; however, there are still vast misconceptions of the etiology of obesity. Obesity is still regarded to be highly under internal control of the individual while genetic and environmental factors are seen subordinate. Ajzen's theory of planned behavior can serve as a theoretical background explaining negative consequences of perceived stigma and self-stigmatization (e.g. internalizing stigma). Intervention approaches can therefore encompass methods to reduce weight stigma in the general public as well as in specific populations but also interventions to inoculate obese individuals to minimize negative consequences of stigmatization.

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POSTER 145

First In-Human Data of a New Fluorine-18 Labelled Radiotracer for In-Vivo imaging of Brain Serotonin Transporters (SERT) with PET

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Current carbon-11 labeled highly selective radiotracer for visualisation and quantification of central SERT are hampered by the short half-life of ^{11}C, the moderate cortical test-retest reliability, and the lack for quantifying endogenous serotonin. The aim of our study was to first apply in human the new highly SERT-selective marker labelled with fluorine-18, which has a longer half-life compared with ^{11}C (108 min vs 20 min). We investigated five healthy volunteers (2 female, age 39±10 years) with PET after the intravenous injection of ~300 MBq [^{18}F]FMe-McN5652 (FMcN). Parametric PET data were analyzed after coregistration with individual MRI and compared with a reference data set of PET with the gold-standard SERT radiotracer [^{11}C]DASB in 21 healthy subjects (11 female, 38±8 years). The SERT values for the new radiotracer were slightly lower compared with the standard-tracer, e.g., in the frontal cortex (1.02±0.04 vs 1.10±0.07; p=0.05) or in the raphé region (2.04±0.11 vs 2.23±0.39, 0.04), but the lower standard deviation of FMcN SERT values can be advantageous with regard to test-retest estimations in larger study cohorts. Visually, image quality of FMcN is superior to DASB. Kinetic data of the new radiotracer are also presented. In summary, its cerebral uptake fits well with the known SERT distribution also in humans. Hence, FMcN might be suitable for in vivo quantification of SERT. Also, labeling with ^{18}F allows (1) later data acquisition times, which is useful for the investigation of the tracer kinetics in brain tissue (modeling) and (2) a widespread application within a satellite concept e.g. in multicenter trials.

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POSTER 146

Globale und cerebelläre Intensitätsnormalisierung in der Untersuchung des Glucosestoffwechsels von Patienten mit Alzheimer-Krankheit und Leichter Kognitiver Beeinträchtigung mittels [18F]FDG-PET

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Alzheimer-Krankheit (AD) und Leichte Kognitive Beeinträchtigung (LKB) sind neurodegenerative Erkrankungen, die mit Beeinträchtigungen der Gedächtnisleistungen einhergehen. Parallel zum klinischen Bild sind aus Untersuchungen mittels [18F]Fluorodesoxyglucose-Positronenemissionstomographie ([18F]FDG-PET) AD-typische Verringerungen des Glucosestoffwechsels in temporalen und parietalen cerebralen Regionen bekannt. Bei der Bewertung von PET-Bildern kommt der Referenzregion für die Intensitätsnormalisierung eine besondere Bedeutung zu.

Erstmals sollen globale und cerebelläre Intensitätsnormalisierung von [18F]FDG-PET-Aufnahmen hinsichtlich der Entdeckung eines verringerten Glucosestoffwechsels bei Patienten mit AD und LKB verglichen werden.

Patienten mit AD (n=15, 69,3±8,4) und LKB (n=28, 66,9±9,2) sowie gesunde Kontrollen (K, n=10, 58,4±6,0) wurden mittels [18F]FDG-PET unter Ruhebedingungen mit geschlossenen Augen untersucht. Die Intensität der PET-Bilder wurde (a) auf die Aktivität im Gesamthirn (globale Normalisierung) beziehungsweise (b) auf die Aktivität im cerebellären Cortex (cerebelläre Normalisierung) normalisiert. Die Gruppen wurden mittels Statistical Parametric Mapping hinsichtlich konventioneller (K>AD, K>LKB, LKB>AD) und paradoxer (AD>K, LKB>K, AD>LKB) Kontraste verglichen.

Bei der globalen Normalisierung fanden sich Clustergrößen von 1650 (K>AD), 37 (K>LKB) und 877 (LKB>AD) signifikanten Voxeln in den konventionellen Kontrasten sowie 1304 (AD>K), 393 (LKB>K) und 493 (AD>LKB) in den paradoxen Kontrasten. Im Vergleich dazu waren die Clustergrößen bei der cerebellären Normalisierung in den konventionellen Kontrasten 1,95mal (K>AD) und 6,03mal (K>LKB) größer beziehungsweise 6,22mal kleiner (LKB>AD). Die paradoxen Kontraste wurden bei der cerebellären Normalisierung nicht signifikant.

Im Vergleich von Patienten mit Kontrollen ist die cerebelläre Normalisierung der globalen Normalisierung in der Entdeckung eines veränderten Glucosestoffwechsels klar überlegen. Dem gegenüber ist die globale Normalisierung bei der Unterscheidung zwischen AD und LKB sensitiver als die cerebelläre Normalisierung für die Entdeckung eines verringerten Glucosestoffwechsels in AD-typischen Regionen. Gleichzeitig wird mittels globaler Normalisierung bei Patienten ein normaler Glucosestoffwechsel deutlich überschätzt und erscheint im Kontrast in AD-unbeeinträchtigten Regionen als Hypermetabolismus.

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POSTER 147

CT-BASED QUANTIFICATION OF PULMONARY CHANGES AFTER ALPHA-2-AGONIST ADMINISTRATION IN SHEEP

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Background: Alpha$_2$-agonists such as xylazine are potent sedatives and have been used in experimental studies involving sheep. Pulmonary edema and severe hypoxemia have been observed after xylazine administration (XA) in sheep. We used quantitative computed tomography (qCT) to measure the lung weight (M_{Lung}) and volume (V_{Lung}) after XA to monitor the possible development of pulmonary edema.
Methods: Sixteen anesthetized sheep received XA in three separate experiments: low dose XA in two experiments (LoD1 and LoD2, 0.15mg/kg) and high dose XA in the third experiment (HD, 0.3mg/kg). The arterial partial pressure of oxygen (PaO_2), M_{Lung}, V_{Lung} and the percentage of non-aerated lung (%M_{non}, relative to M_{Lung}) were measured at 5, 15 and 30 minutes after XA. Maximum changes (after 15 minutes) were statistically compared to baseline. Results are given as median (interquartile range).
Results: After XA, M_{Lung} (in g) increased significantly ($p<0.0001$) by 43 (25-65) for LoD1, 34 (18-43) for LoD2, and 48 (38-75) for HD. %M_{non} (in %) increased significantly ($p=0.001$) by 17 (7-29) for LoD1, 13 (5-21) for LoD2, and 22 (3-26) for HD. V_{Lung} (in ml) decreased significantly ($p<0.001$) by 358 (635-230) for LoD1, 408 (691-319) for LoD2, and 516 (765-278) for HD. PaO_2 (in mmHg) decreased significantly ($p=0.002$) by 360 (417-226) for LoD1, 367 (418-167) for LoD2, and 362 (419-173) for HD.
Conclusions: In our study, XA was followed by severe hypoxemia resulting from increased M_{Lung}, decreased V_{Lung}, and increased %M_{non}. We suggest avoiding the use of xylazine IV for experimental studies involving sheep, especially for pulmonary research.

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POSTER 148

Impact of gel-image software on quantitative 1-D electrophoresis gel analysis

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Objective: 1-D gel electrophoresis is a well established method. However, computerized analysis includes risk of artifacts and false-positive results. To investigate useability we analysed and compared data of two gel image analysis softwares. Methods: Automated serum protein electrophoresis was performed. After naphthol blue black staining gels were analysed by software solutions: TotalLab 120 (TL120) and LabImage340 (L340). Statistical methods (Bland-Altman, Passing Bablok, reliability) were used to compare data to reference data (obtained by accredited reference-laboratory). Results: Passing Bablok analysis: in both methods linearity of data vs. reference were passed ($p<0.01$; L340: $y=0.00+1.00x$ vs. TL120: $y= -0.01+1.02x$). Bland-Altman analysis of L340: low deviation to reference and lower standard deviation (mean: -1.5%; SD: 23.0% to -25.9%) vs. TL120 (mean: – 8.2%; SD: 32.6% to -48.6%). Reliability: L340 ($k=0.404$; 95% CI=0.315 – 0.493) vs. TL120 ($k=0.105$; 95% CI = 0.105 – 0.245). Detailled serum proteins analysis revealed that most data (except α1-globulin) obtained by L340 were within 5% tolerance range, in contrast to data of TL120 (mean%±SEM%: albumin: 0.68±0.49 vs. 6.26±1.44; α1-globulin: -10.80±3.02 vs. -33.72±4.78; α2-globulin: -2.19±1.75 vs. -16.51±2.13; β-globulin: 0.99±1.67 vs. -9.84±2.78; γ-globulin: -1.44±1.73 vs. 5.00±5.67). Conclusion: Data obtained by L340 offered an extraordinary high precision of measurements (similar to data of accredited-reference laboratory) in contrast to TL120. Therefore, we considered L340 as an appropriate tool for minimizing false-positive results in 1-D gel electrophoresis.

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POSTER 149

Isotropic High Resolution Diffusion Imaging of Human Habenula in vivo at 7T

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Introduction: The habenula has an important controlling role within the reward system. Overactivation is associated with depression. The habenula is positioned next to the third ventricle and is 5-9 mm in diameter. The combination of zoomed imaging with parallel imaging – ZOOPPA enables DWI acquisitions with 1 mm isotropic resolution at 7T. The data show distinct nuclei of the human habenula in vivo. Methods: MRI experiments were performed on a 7T whole-body MR scanner (MAGNETOM 7T) with a 24-element phased array head coil (Nova Medical). DW images were acquired with a unipolar Stejskal-Tanner sequence: TR = 10400 ms, TE = 82 ms, FOV =144x150 mm2, partial Fourier = 6/8, isotropic resolution 1.0 mm3, 71 slices with 10% overlap, DW with b = 1000 s/mm2, 60 directions and 4 averages. Multiple fibre orientations were computed in each voxel using the ball-and-2-sticks model. Results and Discussion: The data show distinct nuclei of the human habenula in vivo. We identified lateral and medial nuclei with their connecting fibre bundles to the forebrain and the brainstem. The nuclei are clearly visible on the quantitative T1 map with a high myelinisation of the lateral habenula and its commissure. Whereas fibres from lateral habenula seem to run mainly to the forebrain, tracts from the medial part go down to the brainstem and to its commissure as illustrated by streamline tractography using spherical deconvolution. Conclusion: Further study of the habenula and its role in brain function is likely to improve understanding of the pathophysiology of a wide range of neurologic and psychiatric disorders.

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POSTER 150

Flexibles Konzept zur MR-kontrollierten Navigation mit Echtzeit-Instrumentverfolgung aus beliebigen Kamerapositionen

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Ziel: Vorstellung eines Navigationskonzepts für MR-gesteuerte Interventionen auf der Basis einer optischen Instrumentenverfolgung.
Material und Methodik: Ein Tracker mit drei optischen Markern wurde an einer Koaxialnadel befestigt. Die Markerpositionen wurden von einer stereoskopischen Kamera erfasst und auf einem Navigations-PC in eine Scanebene entlang der Instrumentenachse umgerechnet. Diese Parameter wurden an den MR-Host gesendet, auf dem eine Echtzeit-Sequenz lief, die eine externe Anpassung der Scangeometrie erlaubt. Die MR-Bilder wurden auf dem In-room-Monitor angezeigt. Das Konzept wurde in einem geschlossenen 1.5T MRT evaluiert. Im Experiment versuchte der Untersucher von der Rückseite des Scanners, Erbsen in einem undurchsichtigen Phantom anzusteuern.
Ergebnisse: Die Manipulation des Instruments von der Rückseite des Scanners beeinflusste weder die Bildgebung noch das optische Tracking von der Vorderseite her. Eine freie Sichtlinie konnte leicht durch Veränderung der Kameraposition hergestellt werden. Nadelpositionierung und Annäherung an das Ziel erfolgten mit Hilfe der nachgeführten MR-Bilder mit einer zeitlichen Verzögerung von 600 ms. Der Nadelartefakt war deutlich auf jeder Aufnahme sichtbar.
Schlussfolgerungen: Im Gegensatz zu anderen Verfahren, erlaubt das vorgestellte Konzept eine äußerst flexible Platzierung der Kamera, sogar während der Navigation. Hierdurch lässt sich z. B. bei individuell auftretenden Hindernissen wieder eine freie Sichtlinie herstellen. Die Technik ist prinzipiell für jede Magnetkonfiguration und insbesondere für Geräte mit einer weiten Öffnung bzw. offene Scanner einsetzbar.

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POSTER 151

A novel approach to automated in-situ biomarker validation in rheumatoid athritis by laser scanning cytometry

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Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease of unknown origin that primarily affects joints and leads to their destruction. However, in contrast to our incomplete understanding of the etiology of RA, a large number of studies have identified a variety of different cells involved in the pathogenesis of RA. Especially synovial fibroblasts (SF), macrophages and dendritic cells (DC) constitute unique cell types that might be specific for RA and could be suitable to distinguish RA from other inflammatory conditions in the joint. Hence, surface markers of those cell types could be appropriate diagnostic biomarkers.
Methods: We investigated the occurrence and distribution of cells in synovial tissues of RA patients in comparison to controls. To obtain information about the overall marker expression, quantitative fluorescence analysis of complete cryosections was performed on a Laser Scanning Cytometer (LSC). Evaluation of results was obtained using receiver operator characteristic (ROC) curves to calculate sensitivity at given specificity.
Results and Conclusion: A significantly higher expression could be detected in synovial tissue of RA patients for the markers CD11b, CD90, CD64 and HLA-DR. Markers as described above could be used either alone or in combination as diagnostic biomarkers and hence, for differentiation between RA and control. Surprisingly CD64 and HLA-DR turned out to bring the best results for the ratio between sensitivity and specificity. In conclusion quantitative fluorescence analysis by LSC might be a pivotal tool for differential diagnosis in arthritic disease.

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POSTER 152

Protein Kinase CK2 activity uncouples Bid cleavage from Caspase-8 activation

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In the present study, we quantitatively analysed the interface between apoptosis initiation and execution by determining caspase-8 activation, Bid cleavage and mitochondrial engagement in individual HeLa cervical cancer cells following exposure to tumour necrosis factor-related apoptosis inducing ligand (TRAIL). Employing resonance energy transfer probes containing either the caspase-8 recognition site IETD or full-length Bid we observed a significant delay between the times of caspase-8 activation and Bid cleavage, suggesting the existence of control steps separating these two processes. Subsequent analyses suggested that the divergence of caspase-8 activation and Bid cleavage are critically controlled by kinase signalling: Inhibiting protein kinase CK2 using 5,6-Dichloro-l-(b-D-ribofuranosy-1)-benzimidazole (DRB) or by over-expression of a dominant negative CK2a catalytic subunit largely eliminated the lag time between caspase-8 activation and Bid cleavage. We conclude that caspase-8 activation and Bid cleavage are temporally uncoupled events, providing transient tolerance to caspase-8 activities.

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POSTER 153

Erste Erfahrungen mit der navigierten Radiofrequenzablation der Leber in einem geschlossenen 1,5T-MRT

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1 Radiologie

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Purpose: Sind Lebertumoren im CT schwer oder nicht sichtbar, lassen sich aber mittels Magnetresonanztomographie (MRT) zuverlässig darstellen, empfiehlt sich eine MR-gestützte Therapie. Ein potentielles Verfahren ist die Radiofrequenzablation (RFA), bei der ein Tumor durch Erhitzung lokal destruiert wird. Aufgrund der eingeschränkten Platzverhältnisse im Scanner wurde ein Verfahren erprobt bei dem die Platzierung der RFA-Sonde außerhalb des Scanners erfolgt aber auf einem virtuell reformatierten Bilddatensatz in Echtzeit navigiert werden kann.
Methods: Nach Aufnahme von Planungsbildern erfolgte die Platzierung der RFA-Sonde mithilfe eines flexiblen, optischen Navigationssystems außerhalb des Magneten. Eine kontinuierliche Registrierung der MR-Tischposition wird über drei fest am Tisch montierte MR-sichtbare Marker erreicht. Die Position des Instrumentes wird in Bezug auf die Patientenanatomie auf einem großen Bildschirm in Echtzeit angezeigt, und so bildnavigiert vorgeschoben. Die RFA erfolgte unter Verwendung standardisierter Ablationsprotokolle.
Results: Bisher wurden 7 Leberläsionen in 6 Patienten behandelt. Die reinen Interventionszeiten, Nadelplatzierung und RFA, waren vergleichbar mit denen der CT-gestützten RFA. Die Visualisierung der einzelnen Elektroden und des Ablationsvolumens konnte zuverlässig im MRT erfolgen.
Conclusion: Mit Hilfe des vorgestellten Verfahrens ist die RFA von CT-morphologisch schwer visualisierbaren Leberläsionen möglich. Unsere ersten Erfahrungen zeigen dass die navigierte Punktion der Leber im MRT und die darauffolgende RFA einen ähnlichen Zeitaufwand erfordern wie die Intervention im CT.

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POSTER 154

Mate- Tee als negatives orales Kontrastmittel in der MR Cholangiopancreaticogrphie

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Ziel:
Die MRCP ist als nicht invasive diagnostische Methode zur Darstellung der Gallenwege und Pankreasganges gut etabliert
Unsere Studie evaluiert ob die Verwendung von Mate-Tee die diagnostische Qualität der MRCP verbessern kann.
Material und Methoden:
Bei 40 Patienten mit Verdacht auf pathologische Veränderungen der Gallenwege wurde eine auf T2-HASTE Sequenzen beruhende MRCP (TE:137,TR: 997, slice thickness: 4mm, gap: 4,4, flip angle: 150) durchgeführt, 20 Patienten wurden ohne und 20 mit oraler Applikation einer Infusion von 100 mg Ilex paragueyensis pro 1L Wasser (Mate Tee) 20 Minuten vor der Untersuchung untersucht. Die Sichtbarkeit des Ductus hepaticus communis (DHC) und des Ductus pancreaticus (DP) wurde von 3 Radiologen verblindet evaluiert. Die ermittelten Daten wurden statistisch mit dem Mann-Whitney-U-Test ausgewertet.
Ergebnisse:
Bei 38, 3% der „ohne Mate" – Gruppe wurde eine gute Bildqualität des DHC erreicht, bei 25% mittelmäßig, bei 36, 7% suboptimal.
Die Sichtbarkeit des DP war als gut bei 30% beschrieben, bei 30% als mittelmäßig und bei 40% als suboptimal. Bei 73,3% der „Mate"-Gruppe wurde eine gute Bildqualität des DHC erreicht, bei 16, 7% mittelmäßig, bei 10% suboptimal. Die Sichtbarkeit des DP war als gut bei 43, 3% beschrieben, als mittelmäßig bei 20% und suboptimal bei 36, 7%. Die Beurteilbarkeit des DHC war in der „Mate"-Gruppe signifikant besser als in der in der „ohne Mate"-Gruppe ($p<=0,01$). Die Beurteilbarkeit des DP zeigte keinen signifikanten Unterschied zwischen den beiden Gruppen.
Konklusion:
Mate-Tee kann als negatives orales Kontrastmittel die überlagerungsfreie Darstellung der Gallenwege in der MRCP signifikant verbessern.

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POSTER 155

Acoustic Radiation Force Impulse (ARFI) Elastography for the Detection of Cystic Fibrosis Related Liver Disease in Adult Patients

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Background: Patients with cystic fibrosis (CF) can develop cholestatic liver disease. Acoustic radiation force impulse (ARFI) elastography is a new technology for non-invasive measurement of tissue stiffness in liver diseases. We aimed to evaluate the accuracy of ARFI for the detection of CF-related liver disease (CFLD).
Methods: CFLD was defined by at least two of the following criteria: hepatomegaly, abnormal findings in conventional liver sonography and elevated liver enzymes. 50 healthy volunteers and 40 patients with liver cirrhosis of different etiologies served as controls. ARFI results were expressed as shear-wave velocity (m/s). Diagnostic performance was evaluated using ROC curves.
Results: 40 adult patients with cystic fibrosis were recruited. 28 cases had no CFLD, seven had CFLD and five showed clinical signs of CF-related liver cirrhosis.
Individuals with CFLD (mean 1.06 m/s) had a shear-wave velocity similar to CF-patients without liver involvement (mean 1.09 m/s). Both subgroups did not significantly differ from healthy controls (mean 1.15 m/s).
CF-patients with liver cirrhosis (mean 1.47 m/s) had only a slight but significant elevation of liver stiffness compared to CF-individuals without CFLD ($p=0.003$; sens. 80.0%, spec. 92.9%, cut-off 1.34 m/s, AUC 0,91) and differed significantly from cases with cirrhosis of other etiologies (mean 3.06 m/s) ($p<0.001$).
Conclusion: ARFI has a lower diagnostic accuracy for liver cirrhosis in cystic fibrosis than for liver cirrhosis of other etiologies. The clinical value of ARFI measurements depends on the etiology of liver disease.

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POSTER 156

CT-gestützte Drahtmarkierung vor videoassistierter thorakoskopischer OP von pulmonalen Rundherden – eine Auswertung von 184 Fällen

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Zielsetzung: Minimal-invasive Techniken, wie zum Beispiel die videoassistierte Thoraxchirurgie (VATS- video-assisted thoracoscopic surgery), sind heut zu Tage zur Resektion suspekter und vor allem peripher gelegener Lungenherde Methode der Wahl. Um eine schnelle und sichere intraoperative Lokalisation der Herde zu gewährleisten, ist eine präoperative Markierung der Herde sinnvoll. Wir berichten über die Erfahrungen bei 184 Markierungen mittels eines speziellen Lungenmarkierungsdrahtes, der CT-gestützt präoperativ an den Herd gebracht wird.
Material und Methodik: Bei 184 Patienten (97m, 87w, mittleres Alter: 58,1 +/- 13,7 Jahre) mit unklaren Lungenherden (Größe: 7,0 +/- 3,9mm x 9,7 +/- 5,4 mm, Entfernung von der Pleura: 9,8 +/- 9,1 mm) wurde unmittelbar vor der VATS eine CT-gesteuerte Markierung des Herdes mit Hilfe eines Spiraldrahtes vorgenommen.
Ergebnisse: Der Markierungsdraht konnte in 181 Fällen (98,37%) erfolgreich platziert und transthorakal fixiert werden. Schwerwiegende Komplikationen traten nicht auf, geringgradige Komplikationen wie Pneumothorax (99 Fälle = 53,28%, Breite: 10,6 +/- 10,9 mm) oder eine perifokale Blutung (56 Fälle = 30,43%) bedurften keiner präoperativen Therapie. Eine vollständige Entfernung der markierten Herde gelang bei 98,4% der Patienten. Aufgrund von intraoperativen Komplikationen wie Blutungen, Adhäsionen oder Drahtdislokationen war in 29 Fällen die Konversion zu einer Thorakotomie erforderlich. Die histologische Untersuchung ergab in 52,5% einen benignen Befund, in 87 Fällen (47,5%) einen malignen, wobei insgesamt lediglich 21 Herde (11,5%) einem primären Lungenkarzinom entsprachen.
Schlußfolgerungen: Die Kombination aus CT-gesteuerter Herdfixierung mittels eines Spiraldrahtes und die anschließende thorakoskopische Entfernung (VATS) ist eine effiziente und sichere Methode zur Diagnostik von unklaren intrapulmonalen Rundherden, insbesondere für periphere, subpleural gelegene Herde.

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POSTER 157

Grundlagen einer endorektalen Elastographie der Prostata im Magnetresonanztomographen

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Ziel: Die MR-Elastographie (MRE) erlaubt die Bestimmung viskoelastischer Gewebeeigenschaften und stellt somit einen neuen Parameter zur Tumordiagnostik in Aussicht. Bei anatomisch ungünstig gelegenen Regionen wie der Prostata ist die für die Untersuchung notwendige Einkopplung niederfrequenter Vibrationen schwierig. Ein Verfahren zur potentiellen Anwendung in der Prostata wird vorgestellt, bei dem die Anregung direkt über die bildgebende Endorektalspule erfolgt.
Methodik: Ein Zugmechanismus mit elektromechanischer Anregung ermöglicht periodische Bewegungen des Ballons einer kommerziellen Endorektalspule. Dadurch werden Scherwellen auf ein Prostataphantom übertragen und mit einer bewegungssensitiven Sequenz im MRT abgebildet. Elastizitäts- und Viskositätskarten wurden berechnet.
Ergebnis: Der experimentelle Aufbau zur Einkopplung der Scherwellen führte zu keinen Beeinträchtigungen der Bildgebung. Eine gleichmäßige Ausbreitung der Scherwellen im Prostataphantom wurde für Anregungsfrequenzen ab 60 Hz erreicht. Objekte mit einem Mindestdurchmesser von 5 mm waren anhand ihrer Gewebehärte im Phantom abgrenzbar.
Folgerung: Endorektalspulen bieten sich aufgrund ihrer Nähe zum Organ und der guten Patientenakzeptanz als Anregungsquelle für die Prostata-MRE an. Aufgrund der direkten Einkopplung über den anliegenden Ballon können hohe Anregungsfrequenzen verwendet werden, die mit einer guten räumlichen Auflösung einhergehen. Die flexible Positionierbarkeit und insbesondere die Nutzung weitgehend vorhandener, MR-kompatibler Komponenten empfehlen das Verfahren für weitere, klinisch ausgerichtete Untersuchungen zur MRE der Prostata.

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POSTER 158

Stress for stress tolerance during cryopreservation

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Introduction:
Mesenchymal stem cells (MSCs) are adult stem cells found in the bone marrow and various tissues. They can be differentiated into bone, cartilage, fat and muscle cells. MSC are immune-modulatory and rejection of allergenic MSC is less likely. Because of their potentials for different therapeutic applications, they are very attractive to the medical and scientific community. However, they are very rare, and aging as well as expansion do change the properties of the cells. The standard to cryopreserved these cells is to freeze them in dimethyl sulfoxide (DMSO) and often bovine serum. In the process of producing and storing MSC for therapies it is necessary to adopt new and improved protocols for cryopreservation.
Material and methods:
Rat MSC was cold shock at 4°C for 2-3 hours, then recover for 2 hours in 37°C incubator. All samples were freezing down with 5% DMSO in Ringer acetate solution, then thawed and viability was measured using MTT, and differentiation was asset by measuring alkaline phosphatase activity.
Results:
Viability and differentiation of cold-shocked MSCs were similar to the control.
Discussion:
Perhaps the use cold-shock stress (2-3h at 4°C) is not enough to improve cryopreservation. Further experiment with chemicals that induce heat-shock proteins are under investigation.

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POSTER 159

Hydroxyethylstarch in cryopreservation of mesenchymal stem cells

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Mesenchymal stem cells (MSCs) can produce various functional cell types of mesodermal lineage which can be used in different therapeutic applications. Improvements of technologies which allow storing and banking of these cells without loss of cell viability, differentiation capacity and function is required for clinical applications. Cryopreservation is the most effective way to preserve cells and usually involves cytotoxic and xenogenous compounds as DMSO and serum. The perfect cryoprotectors should be nontoxic for cells and for patients, nonantigenic, chemically inert, provide high survival rate after thawing and allow transplantation without washing step. Hydroxylethylstarch (HES) is proved to possess many of these properties. In our study HES in combination with other substances were used as alternative cryoprotectors in attempt to replace DMSO and serum. Viability, expression of CD-markers and maintenance of differentiating capacity of MSCs after thawing were used to analyse the efficacy of cryopreservation. HES mixtures is as effective as DMSO to maintain rat MSCs viability and differentiation capacity during cryopreservation. Rat MSCs after cryopreservation with HES mixtures retain their typical CD phenotype and high potential to differentiate toward the osteogenic, adipogenic and chondrogenic lineages.

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POSTER 160

Modelling microadenoma in intestinal crypts

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The epithelium of the small intestine is the most rapidly regenerating tissue of adult mammals. Stem cell organisation in the intestinal crypt has been studied intensively. Recently, we have introduced a three-dimensional, pedigree-free model of stem cell and tissue organisation in murine crypts. Integrating the molecular, cellular and tissue level of description this model links a broad spectrum of experimental observation. The model is capable of quantitatively describing and predicting the dynamic behavior of the tissue during steady state and after selective gain or loss of gene function manipulations affecting Wnt- and Notch-signaling. Here we present simulation results on clonal conversion in normal crypts and in crypts with transformed cells. Transformed cells induce transient or stable microadenoma with a probability that strongly depends on the position at which the transformation occurred. Moreover, the conversion characteristics depend sensitively on biomechanical properties like active migration and cell-cell-interaction. Our results resemble those obtained in vivo suggesting that the behavior of both normal and transformed intestinal crypts can be explained without assuming an explicit stem cell hierarchy.

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POSTER 161

A Novel Branched Cell-penetrating Peptide for the Delivery of Oligonucleotides

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The therapeutic application of oligonucleotides (ON) is hampered due to their size and negative charge. In order to eradicate this drawback, cell-penetrating peptides (CPP) have emerged as a promising tool for efficacious ON delivery owing to their capacity to autonomously translocate into the cell with high efficiency. We designed a new branched cell-penetrating peptide, $(sC18)_2$, based upon two units of $CAP18_{106-121}$, which is derived from the 18-kDa Cationic Antimicrobial Peptide and was shown to effectively internalize into various cell lines without being cytotoxic to them.
The peptide was obtained highly pure (> 99 %) after preparative RP-HPLC. CD spectroscopy indicated formation of an α-helix in a membrane-mimicking environment, which is also the case for the parent peptide sC18 and is thought to be a key structural motif for translocation. Fluorescence microscopy and flow cytometry after introduction of a fluorescence label showed that the novel CPP highly effectively internalizes into various cell lines even at low concentrations, which constitutes a remarkable improvement compared to sC18. Most importantly, the peptide did not show any cytotoxic effects in this concentration range as verified by a resazurin-based cell viability test. Since the high content of basic amino acids and thus a net charge of +17 renders $(sC18)_2$ a candidate for non-covalent oligonucleotide delivery, we assessed its potential to form stable electrostatic complexes with nucleic acids by electromobility shift assays. We observed full retention of plasmid DNA in an agarose gel after complexation with $(sC18)_2$ even at very low charge ratios.

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POSTER 162

Effect of aging on adipose derived mesenchymal stem cells – risk and benefits for therapy

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Adipose tissue has been shown to contain high numbers of adipose-derived mesenchymal stem cells (ADSC), which can be applied for therapeutic application in regenerative medicine. ADSC showed similar characteristic to bone marrow-derived MSC which makes ADSC an advantage for research and clinical purpose since minimal invasion procedure is required for tissue withdrawal and a large number of ADSC can be obtained. There is evidence that the ADSC functions changes with age and might affect therapeutic outcomes. Defining the changes in ADSC function will speed up the development of cell-based therapies.
We compared human ADSC from subcutaneous adipose tissue from donors raging from 18-90 years. We observed that aged ADSC have higher expression of telomerase activity and reduced ability to response to stress such as DNA damage. In addition, aged ADSC showed a reduction in migration and differ genes expression compared to young ADSC. No difference in telomere length was observed between aged and young ADSC.
These results point out age related changes in function of the ADSC. This indicates that ADSCs from old age patients are not a good source for therapeutic purposes and finding a way to rejuvenated aged ADSC will provide with the advantage of using ADSC in autologous transplantations

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POSTER 163

Thymocyte precursor cells and thymic Th cell output in rheumatoid arthritis

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In RA patients, the homeostatic proliferation of naïve CD4+ T lymphocytes is dysregulated and the peripheral T cell pool has repertoire defects and shows signs of replicative exhaustion. The underlying cause could either be a defect in the thymus or a primary stem cell defect . If the latter was true, a deficiency in thymocyte precursor cells could lead to a disturbed proliferation of the peripheral T lymphocytes, thereby causing the observed T cell pathology in RA. In the present project, the number of thymocyte precursor stem cells in the peripheral blood of RA patients was investigated and compared to healthy controls. In parallel, the frequency of CD45RA+ T lymphocytes expressing CD31 was analyzed.
The results show, that the absolute number of the thymocyte precursor cells as well as the percentage of those cells within the overall CD34 positive stem cell population are not significantly lower in RA patients compared to age-matched healthy controls. In contrast, the analysis of recent thymic emigrants, defined by CD31 expression, in the blood of RA patients and healthy controls shows, that these cells are diminished in RA patients compared to healthy controls.
The results suggest, that the observed T cell pathology in RA is not due to a primary stem cell defect. Instead, defects in the thymic output are likely to be responsible for the T cell pathology in RA, which will be the major focus in the ongoing project.

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POSTER 164

On the way to online steered cartilage production in bioreactors

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Tissue engineering is an effectiv strategy of regenerative medicine. One important example is cartilage production in 3D production systems. In a perfused bioreactor tissues are engineered by setting cells, e.g. mesenchymal stem cells (MSCs) or chondrocytes (Cs) on a porous scaffold and let circulate a fluid inside the bioreactor with nutrient supply. The aim is the production of functional tissues for in vivo transplantation. One essential nutrient is oxygen, which has the power to impact on MSC fates. Oxygen influences proliferation and differentiation as well as migration and metabolism of cells. It is one important aim in cartilage production to optimise the oxygen supply inside the bioreactor.Here we show a mathematical model that simulates fluid flow of the nutrient in a perfused bioreactor with oxygen support. The model also includes proliferation and migration of MSCs inside the porous scaffold.In our simulation studies we tested different parameter settings on the impact of local oxygen tension on cell fate decisions, including MSC proliferation and migration activity, and the oxygen metabolism of these cells itself. We demonstrate that different settings lead to clearly different transplant organisations. Based on our simulation results we provide some general rules for effective MSC expansion in porous scaffolds. This rules are capable to support the future bioreactor design.

Assoziation: PbF III

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POSTER 165

Positivity for CD34 is a feature of α-cells, but not β-cells, in early bovine pancreata

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Motivated by the tantalising idea of replenishing lost β-cells by *in vivo* reprogramming of α-cells, or *in vitro* differentiation of CD34$^+$ cells derived from human embryonic stem cells, we analyzed the contribution of CD133$^+$ and CD34$^+$ cells to the development of the bovine pancreas. In embryos and foetuses with crown to rump lengths (CRL) ranging from 1 to 47 cm (i.e 30 to 180 gestational days), CD34$^+$ α/or CD133$^+$ cells were consistently more numerous in pancreatic parts arising form the dorsal anlage, compared to the part originating from the ventral anlage. In embryonic and early fetal pancreata (CRL< 5 cm), CD34$^+$ α/or CD133$^+$ cells were present along the border of the epithelial cell cords. In later developmental stages (CRL> 5 cm), individual, or groups of CD34$^+$ α/or CD133$^+$ cells were present in newly formed acini, which bulged out from the duct system that had originated from the cords. With increasing gestational age, the positively-stained intra-acinar cells accumulated within foci of hyperplastic epithelium. These acinoinsular complexes appeared to enlarge and to develop into intralobular islets of Langerhans. The described CD34$^+$ α/or CD133$^+$ cells displayed co-localization with glucagon and were devoid of pancreatic and duodenal homeobox protein 1 at later developmental stages. A negligible number of cells showed co-localization of CD34/CD133 with insulin. Glucagon$^+$ cells were usually distinct from insulin$^+$ cells, and were more abundant. Whether CD133 α/or CD34 expression is representative of a particular stage in α-cell development, or reflects functional heterogeneity among equally mature α-cells remains elusive.

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POSTER 166

Rational Development of Peptides with High Affinity to Inorganic Surfaces

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Immobilization of specified chemokines is of great interest in the field of "intelligent" biomaterials. It has been shown previously, that peptides can be discovered that bind to different metal surfaces in non-covalent manner . Interestingly, those peptides can be obtained by solid-phase peptide synthesis, which provides high flexibility and sufficient amount to perform structure-activitiy studies.
Here we present an ELISA-like assay for a straightforward quantification of peptide-surface interactions. Peptides were synthesized by solid-phase peptide synthesis and N-terminally extended by biotin. This allows a rapid detection of the peptides bound to different surfaces by using a streptavidin-POD-conjugate. The subsequent oxidation of $TMBH_2$ catalyzed by the enzyme is measured photometrically at 450 nm and is dependent on the amount of surface-bound peptides. We could apply the system to determine the binding of peptides on a multitude of surfaces ranging from TiO_2, ZnO to SiO_2. Furthermore the tested peptides showed sigmoidal dose-response-curves indicating specific binding. Thus we were able to determine EC_{50}-values ranging from the low μM-range for good binders to values above 1 mM for weak binders.
Considering the advantages of an ELISA-based assay with respect to parallel testing of different peptides on various surfaces we are now able to improve the understanding of peptide-surface interaction. This is necessary to bridge the gap from the common combinatorial procedure to a more rational approach to obtain peptide sequences that show a high affinity and an improved selectivity towars inorganic surfacces

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POSTER 167

Qualitative and quantitative toxicological methods in organotypic brain slice co-cultures

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Here we present an organotypic brain slice co-culture model consisting of the ventral tegmental area/substantia nigra (VTA/SN) and the prefrontal cortex (PFC) or the striatum (STR). This co-culture model allows us to reconstruct the dopaminergic projection system *ex vivo* and to investigate the fibre growth promoting effect as well as the toxicological properties of investigated compounds.
The immunohistochemical characterisation of the co-cultures has already been presented. The quantification and analysis of fibre outgrowth into the target region of the projection system has been well established. The aim of the present study is to supplement the model with qualitative and quantitative toxicological methods as well as with additional characterisations (expression/modification of certain proteins).
In detail, the following methods had been established:
(1) Lactate dehydrogenase activity measurement in the culture medium; (2) Propidium iodide staining followed by image processing and subsequent densitometric quantification; (3) Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-assay allowing the visualisation of apoptotic cell nuclei; (4) Active caspase 3 staining; (5) Celestine Blue for the labelling of damaged cells; (6) Hoechst staining to show nuclear shrinkage in apoptotic cells and (7) Immunoblotting (e.g. neuronal and glial markers, members of signalling pathways).
The data presented on the poster show the feasibility of the above mentioned techniques to investigate the properties of unknown compounds in comparison to well known controls under *ex vivo* conditions.

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POSTER 168

Genipin cross-linking inhibits macrophage infiltration in decellularized esophagus scaffolds

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In this study, decellularized pig esophagus scaffold tissues were transplanted into rats. The rate of infiltrating immune cells was investigated, depending on scaffold cross-linking with genipin, glutaraldehyde and carbodiimide. After decellularization and immunohistological matrix characterization, circular cross-linked scaffold pieces (n=60) were implanted subcutaneously into Sprague-Dawley rats (untreated scaffolds=positive control; bovine pericard (RP)=gold standard). The rate of infiltrating fibroblasts, lymphocytes (CD3), macrophages (CD68, CD163), giant cells, and capillaries was determined (immunohistologically and histologically) to quantify inflammation after 1, 9 and 30 days. Statistical analysis was performed with Kruskal-Wallis, Mann-U-Whitney and ±95% CI. Complete decellularized esophagus scaffolds were shown to maintain native matrix morphology and extracellular matrix composition. Typical inflammatory reactions were observed in all implants, however the infiltration by immune cells (day 30) was reduced in the genipin group (partially reduced also in the glutaraldehyde group) compared to untreated scaffolds. Signs of chronic rejection were not detected. We conclude that genipin (GP) is the most efficient and best tolerated cross-linking agent to attenuate an inflammation in decellularized esophagus surrogates.

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POSTER 169

BIOCOMPATIBILITY TESTING OF A WEAR-RESISTANT COBALT CHROMIUM ALLOY

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Cobalt chromium (CoCr) alloys have been used as implant material for decades but aseptic loosening caused by metallic wear particles remains still a problem. The modification of the material with nitrogen plasma immersion ion implantation (PIII) increases the surface hardness and abrasion resistance. Here, we used a combination of methods for testing the cytocompatibility of surface modified CoCr (mCoCr) alloys.
Immunological compatibility was evaluated by measuring T cell specific cytokines following culture of mononuclear cells on mCoCr. The proliferation and viability of Saos-2 cells was determined after culture on mCoCr. Furthermore, thrombogenic activity and haemolysis were analysed by determination of the activation dependent thrombocyte surface marker CD62P and free haemoglobin in the supernatant, respectively. Results were compared to base CoCr (CoCr) alloy and polystyrene (PS).
Determination of spontaneous released cytokines revealed reduced concentrations of IFN-g and IL-10 while TNF-a was increased in mCoCr samples compared to CoCr and PS. Compared to CoCr and PS Saos-2 cells showed a decrease in proliferation and viability when cultured on mCoCr. The activation of thrombocytes and lysis of erythrocytes in mCoCr samples was comparable to CoCr and PS.
The applied cytocompatibility tests indicate that PIII surface treatment causes reduced cytocompatibility of CoCr devices, possibly by an increase in free Co ions while wear resistance improved. Nevertheless, compared with the commonly used medical CoCr alloys, the highly increased resistance of mCoCr possibly overtrumps the weak decrease in cytocompatibilty.

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POSTER 170

Blue light collagen cross linking to treat progressive myopia

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The aim of this study is to develop an effective and applicable method to treat progressive myopia. Myopia is the most common eye disorder of the world and up to 30% of myopic patients suffer from progressive (axial) myopia. That is characterized by a pathological excessive eye growth caused by a biomechanical weakness of the sclera and is associated with severe pathological changes, such as retinal tears, chorioretinal atrophy and macula degeneration. The idea is to use Riboflavin/blue light collagen cross linking to increase the scleral stiffness and thereby, to stop eye growth.
Biomechanical measurements of isolated scleras from adult rabbits revealed an increased stiffness/rigidity after collagen cross linking. The safety standard determinations of treated rabbit eyes indicate a critical light intensity of about 400mW/cm^2. Higher irradiation intensities induced collagen fiber damage, neurodegeneration and glial cell reactivity in affected retinal areas. Young rabbits treated with an effective and safe laser energy of about 10mW/cm^2 showed a significant reduction (up to 5%) of their eye growth compared to fellow control eyes. Histological and immunohistochemical examinations revealed a damage threshold of radiation intensities lower than 200mW/cm^2. First results confirm the idea that increasing scleral stiffness by Riboflavin/blue light collagen cross linking might be an effective and safe method to treat progressive myopia.

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POSTER 171

Engineered heart tissue-a new approach for the treatment of dilative cardiomyopathy in a in vivo rat model

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Purpose: We investigated the effect of EHT and its histological and electrical integration in rat hearts with dilative cardiomyopathy (DCM).
Methods: EHT was created from isolated neonatal cardiomyocytes, collagen, matrigel and media. After consolidation time, EHT was electrically stimulated (1mA, 1mV, 1Hz). After 14 days EHT beats spontaneously and generated force (0.3mN). EHT was implanted around the beating heart of rats with DCM (n=10). 1 month later the heart was explanted and prepared for epicardial mapping analysis on the Langendorff system. 256 electrodes were placed around the heart surface and measured the cardiac activation time and the peak to peak amplitude (PTP) under control conditions (pH 7.4) and under conditions for partial uncoupling of gap junctions (pH 6.5). Additionally, histological investigations of the EHT in vivo vs. EHT in vitro were performed.
Results: Echocardiographical investigations showed a significantly improve of fractional shortening (FS) in rats with DCM after EHT implantation (38.32±5.85%), in comparison to rats with a sham surgery (28.36±8.44; $p<0.05$). Furthermore, uncoupling experiments exhibited the electrical integration of EHT with the donor heart. Histological investigation indicated that EHT was grown with the recipient heart, well vascularised (55vessels/mm²; in vitro: 6vessels/mm²) and emerged organised collagen structure, elastic fibres and consists of Troponin I positive cardiomyocytes.
Conclusion: EHT integrated electrically and histologically with the recipient heart. Surprisingly, implantation of EHT improved the cardiac function in DCM.

supported by BMBF

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POSTER 172

RNA Interference-mediated Experimental Modulation of the Expression Patterns of Measles Virus Genes in Glial and Neuronal Cells

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Chronic, persistent and slow virus infections can result in neurodegenerative disease processes e.g. subacute sclerosing panencephalitis (SSPE). The disease results from infection of brain cells with measles virus (MV), a negative strand RNA virus. MV can persist *in vivo* in neurones and oligodendrocytes due to altered viral gene expression, and it infects neuronal and glioma cell lines persistently *in vitro*. In order to better understand underlying molecular mechanisms, modulation of MV infection by RNA interference (RNAi) was addressed in infection of permanent permissive cell cultures. siRNA as well as miRNA based systems were used. Target sequences were a conserved 5'-region of the MV nucleocapsid (N) gene or several conserved regions dispersed within the haemagglutinin (H) gene. The siRNA was expressed as single siRNA expression cassette (SEC). Alternatively, the miRNA expression cassette (miR) provided the opportunity to express several miRNAs simultaneously. Both systems have been used by transient transfection to reduce the amount of viral target mRNAs efficiently up to 90% while control housekeeping gene mRNAs remained largely unaltered. In addition to DNA transfection, lentiviral vector systems based on HIV or SIV were established for transduction of end-differentiated cells with SECs. The siRNA effect on the MV N gene was measured by quantitative rtRT-PCR. A reduction of 84% +/- 4% was detected two weeks after transduction of a rat glioma cell line persistently infected with MV (C6/SSPE). To further increase the RNAi effect, a lentiviral system to introduce miRs instead of SECs into cells will be tested.

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POSTER 173

Low levels of hepatitis C virus specific B cell immune responses in infected individuals

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Background: Hepatitis C virus (HCV) is one of the leading causes of chronic liver disease worldwide. Viral clearance is associated with vigorous HCV-specific T-cell responses, whereas T-cell responses are of lower frequency in individuals that develop chronic infection. Few data are available on the B-cell memory responses.
Method: We quantified the HCV-specific memory B cell responses against different HCV proteins including the structure protein HCV core, the glycoprotein E2 and non-structure proteins NS3A, NS4 and NS5A in subjects with persistent and cured HCV infection using B-cell ELISpot.
Results: HCV core-specific memory B-cells were detectable in 7 of 15 persistently infected subjects and in 4 of 6 individuals with resolved disease. Memory B-cells to other HCV proteins were below the detection level. In contrast, memory B-cells against influenza virus nucleoprotein and tetanus toxoid were observed in all individuals.
Conclusions: HCV infection induces low levels of circulating virus-specific memory B-cells. These were detected in both persistently infected and cured patients and indicate that HCV-specific memory B-cells do not correlate with of either chronic or resolved HCV infection.

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POSTER 174

microglia: part of the glia limitans?!

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Alexander Surikow,
The glia limitans provides the decisive barrier for immune cells infiltrating the brain's parenchyma. It is known that incoming T cells must be re-stimulated/recognize their cognate antigen in perivascular spaces before they can migrate across the glia limitans. Text books state that this barrier consists of astrocytic endfeet exclusively. Using triple fluorescence for astrocytes, basement membranes and nuclei, we found that microglial processes regularly terminate at the outer vascular membrane. Electron microscopy revealed that the processes in fact extent into the glia limitans. Thus, intraparenchymal brain antigens can be presented at the interface between perivascular spaces and the parenchyma. Chronic activation of these cells may trigger autoimmune neuroinflammatory diseases such as multiple sclerosis.

Funded by the DFG (Forschergruppe Brain Macrophages)

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POSTER 175

Monitoring of mitochondrial membrane potential changes in live cells

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Mitochondrial membrane potential is an important indicator of cellular health and respiration. The mitochondrial membrane potential-dependent dyes JC-1, a lipophilic cationic dye, and TMRE are well-established tools to monitor changes within mitochondrial membrane potential. JC-1 enters into mitochondria selectively and changes reversibly its colour from green to orange as membrane potentials increase. This study compares both dyes for their potential use in image- and fluorescence microplate reader-based analysis of the mitochondrial membrane potential in cells with antimycin A-blocked respiration, rubella virus-infected and apoptotic cells. In comparison to slow growing cells, staining intensity of JC-1 is better in fast growing cells. While TMRE is well suited for fluorescence microplate reader-based measurements, JC-1 is hardly suitable for these purposes. This is due to its poor solubility in water. However, substantial changes within mitochondrial membrane potential after induction of apoptosis can best be visualized in image-based applications with JC-1.

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POSTER 176

Deficient apoptosis of rheumatoid arthritis monocytes in response to TRAIL is promoted by autocrine IL-8 and decreased TRAIL-R2 expression but not by IL-1ß

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Purpose: The autoimmune disease rheumatoid arthritis (RA) is driven by the production of monocytic cytokines like TNFa and IL-1ß. We previously reported a defect in spontaneous apoptosis of monocytes from RA patients due to pathological IL-1ß production. Goal of the present study was to analyse the TRAIL induced apoptosis in RA monocytes.
Methods: Monocytes were isolated from peripheral blood of RA patients and healthy donors (HD). After incubation with recombinant TRAIL for 16 hours, monocyte apoptosis was measured by annexinV-PI staining. Cytokine production and TRAIL receptor expression were analysed.
Results: Analysis of TRAIL induced apoptosis of monocytes from HD and RA patients revealed that only HD monocytes are subject of TRAIL induced cell death while RA monocytes were not. Analysis of TRAIL receptor expression revealed a decreased TRAIL-R2 expression on RA monocytes compared to HD. TRAILR1, R3 and R4 were equally expressed on monocytes of both cohorts. We also analysed the participation of IL-1β in the resistance of RA monocytes to TRAIL induced apoptosis. TRAIL did not induce IL-1β production, but increased IL-8 levels in RA monocytes but not in HD monocytes. Neutralization of IL-1β did not sensitize RA monocytes to TRAIL induced apoptosis. But addition of soluble IL-8 to HD monocytes inhibits TRAIL induced apoptosis.
Conclusion: Monocytes of RA patients display an inability to respond to TRAIL with apoptosis, possibly due to an intrinsic defect. This resistance to TRAIL is caused by decreased TRAIL-R2 expression. But also autocrine IL-8 seems to be an important factor promoting the resistance to TRAIL.

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POSTER 177

CD56+ Monocyte Subpopulation expands with Age and Waist Circumference

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Peripheral blood monocytes can be divided into different subpopulations. Besides the rather classical differentiation by using CD14/16 markers, the recently found CD56 positive subset came into our focus of interest.
The physiological function of this subset remains widely unclear, a regulatory one interfering in cytotoxity has been suggested and it is also found to be increased in Crohn's disease.
Aim of the study was to measure the frequency of the CD56+ monocyte subset in blood samples from healthy subjects and to analyze their relationship to age, body mass index (BMI) and waist circumference (WC).
Using flow cytometry, we counted and analyzed peripheral blood mononuclear cells stained for CD56 and CD14 surface markers from 33 healthy individuals.
The frequency of $CD56^+$ monocytes increases with the subject's age ($r=0.5647$, $p=0.0006$). Our data also suggests a link to the measured waist circumference (WC), showing a higher incidence of the monocyte's subpopulation in subjects with a WC going along with a raised cardiovascular risks (WC $\geq$ 80 cm in women, $\geq$ 94 cm in men, $p=0.0063$).
Taking these findings into consideration, the amount of $CD56^+$ monocytes could play a role in immunosenescence on the one hand and body constitution dependent alterations of the innate immune system on the other hand.

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POSTER 178

Characterization of mitochondria isolated from rubella virus-infected Vero cells

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Mitochondria represent the cellular powerhouses and play important roles in providing ATP and by induction of mitochondrial apoptosis as a cellular defence strategy. Their role in viral infections is not well understood. As a model for virus-cell-interaction, rubella virus (RV) was investigated. During RV infection substantial changes occur within the cell, including redistribution of mitochondria in proximity to viral replication factories. In an attempt to further characterize the interaction of RV with mitochondria, intact mitochondria were isolated from RV-infected Vero cells. In comparison to the mock-infected control, an increase in the activity of respiratory chain complex III and an altered distribution of mitochondrial proteins were detected. The work presented significantly extends the understanding of virus-induced alterations of mitochondrial functions.

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POSTER 179

Zytokinfreisetzung aus stimulierten Zellen des peripheren Blutes unter Einwirkung ausgewählter Psychopharmaka

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Es gibt es zunehmend Hinweise darauf, dass eine Aktivierung von TH1-Zytokinen eine wichtige Rolle in der Pathophysiologie der Depression spielt. Bei der Schizophrenie scheint jedoch vor allen eine Aktivierung der TH2-Zytokine zu bestehen. Psychopharmaka entfalten ihre Wirkungen möglicherweise nicht ausschließlich über ihre Wirkung an Neurotransmitterrezeptoren sondern auch über eine Modulation des Zytokinsystems. Auch Nebenwirkungen verschiedener Psychopharmaka, beispielsweise allergische Reaktionen, Gewichtszunahme und Sedierung gehören, sind über das Immunsystem vermittelt. Eine systematische immunologische Charakterisierung der Psychopharmaka gab es bisher jedoch nicht. Möglicherweise ist die immunologische Reaktion eines Patienten prädiktiv für das Ansprechen auf ein Medikament und das Risiko für Nebenwirkungen.
Wir untersuchten fünf Neuroleptika, vier Antidepressiva, sowie das Phasenprohylaktikum Lithium in jeweils vier verschiedenen Konzentrationen bezüglich ihrer Wirkung auf die Zytokinproduktion. Dafür stimulierten wir das Vollblut von zehn gesunden Probandinnen mit jeweils den Immunmodulatoren PHA, OKT3/CD40 und TSST-1. Dabei untersuchen wir die Zytokine IL-1beta, IL-2 IL -4, IL-6, IL-17, IFN-gamma und TNF-alpha in einem Multiplex-Bead-Array Verfahren, in welchem, mit Hilfe fluoreszenz-markierter Antikörper, Zytokine quantitativ bestimmt werden.
Die Ergebnisse zeigen an, wie bestimmte Psychopharmaka das Zytokinsystem beeinflussen können. Daraus soll perspektivisch ein Test entwickelt werden, mit dem man individuell die Wirkungen oder Nebenwirkungen eines Psychopharmakons in der klinischen Praxis abschätzen kann.

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POSTER 180

Human fibroblasts support the expansion of IL-17 producing T-cells via up-regulation of IL-23 production by dendritic cells

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The initiation of immune responses is associated with the maturation of dendritic cells (DC) and their migration to draining lymph nodes. En route activated DC encounter cells of the tissue microenvironment such as fibroblasts. Since we have shown that DC interact with fibroblasts during immune responses we studied the impact of skin fibroblasts on human monocyte-derived DC function and subsequent human T cell (TC) differentiation.
We show that fibroblasts support IL-23 secretion from DC preactivated by lipopolysaccharide (DCact) compared to LPS-activated DC alone. The underlying complex feedback-loop mechanism involves IL-1β/TNFα (from DCact) which stimulate fibroblasts Prostaglandin E2 production. Prostaglandin E2, in turn, acts on DCact and increases their IL-23 release. Furthermore, fibroblast-stimulated DCact are far superior to DCact alone, in promoting the expansion of Th17 cells in a cox-2-, IL-23-dependent manner. Using CD4+CD45RO+ memory TC and CD4+CD45RA+ naïve TC we showed that fibroblasts induce a phenotype of DCact that promote the expansion of Th17 cells. In conclusion, skin fibroblasts are involved in regulation of IL-23 production in DC and – as a result- of Th17 expansion.

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POSTER 181

Immunphänotypisierung von p8-knock-out Mäusen

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Hintergrund: Das Protein p8 wird während der akuten Pankreatitis (AP) u.a. in Milz, Leber und Pankreas exprimiert. Es ist bekannt, dass p8-knock-out Mäuse ($p8^{-/-}$) im Vergleich mit dem Wildtyp ($p8^{+/+}$) einen schwereren Verlauf der AP aufweisen. Es wird eine Beteiligung am Abwehrprogramm vermutet, das im Rahmen der inflammatorischen Prozesse während der AP abläuft. Der Einfluß von p8 auf das Immunsystem ist nicht bekannt.
Zielsetzung: Immunphänotypisierung von $p8^{-/-}$-Mäusen.
Methode: Histologische (Pankreas, Leber, Milz, Lymphknoten (LK), Thymus, Lunge) und durchflußzytometrische Untersuchungen zur Bestimmung der Lymphozytensubpopulationen (CD3, CD4, CD8, CD45R) und Makrophagen (CD11b) vergleichend an $p8^{-/-}$- und $p8^{+/+}$-Mäusen.
Ergebnisse: $p8^{-/-}$-Mäuse zeigten signifikant größere Milzvolumina und –gewichte bei gleichem Körpergewicht im Vergleich zu $p8^{+/+}$. HE-Schnitte der Milzen ergaben Unterschiede in der Architektur mit Reduktion von Lymphfollikeln und Binnenstruktur. Pankreas, Leber, LK, Thymus und Lunge waren nicht verschieden. FACS-Analysen ergaben bisher nicht signifikante Unterschiede in der Verteilung von Lymphozyten sowie Makrophagen aus Milz und Lymphknoten zwischen $p8^{-/-}$ und $p8^{+/+}$.
Diskussion: $p8^{-/-}$-Mäuse zeigen keinen offensichtlichen Phänotyp, haben allerdings eine veränderte Zusammensetzung des Immunsystems und des Aufbaus der Milz. Wir vermuten, dass die beobachteten schweren Verläufe der AP bei $p8^{-/-}$ auf eine Modulation des Immunsystems zurückzuführen sind. Im weiteren Verlauf soll die Immunphänotypisierung von $p8^{-/-}$ in der AP erfolgen, um funktionell-immunologische Unterschiede in der Immunantwort aufzudecken.

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POSTER 182

The Neuroanatomists' dirty little secret

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In 1900, summarizing his experiments with toxins and Ehrlich's earlier observations with intravital dyes, the Berlin physician Lewandowski concluded that "brain capillaries must hold back certain molecules". The term "Bluthirnschranke" (blood-brain barrier, BBB) describes this phenomenon with persuasive beauty, but itsextension of meaning into the context of leukocyte recruitment is misleading. Endothelial expression of BBB-typical "belts" of tight junctions requires their direct interaction with astrocytes provided inthe capillary segment of the vascular tree, but not in postcapillary venules, where infiltration takes place (Bechmann et al., Trends in Immunology 2007). We injected classical markers of BBB integrityand found that the brain parenchyma indeed was not labeled. However, dyes accumulated in the vascular wall and perivascular macrophages of pre- and postcapillary vessels and the choroid plexus. Thus, Ehrlich's observation that the brain remains "white as snow" after tracer injected refers to the neuropil proper, while the site of entry of leukocytes in neuroinflammation is permissive for BBB markersunder normal conditions.

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POSTER 183

Isolation, Identification and Transformation of Human Influenza Nucleoprotein-specific Memory B-Cells

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Memory lymphocytes and serum antibody reflect the individual history of infection or vaccination. When activated, antigen-specific memory B-cells differentiate into antibody-secreting plasma cells. We have developed a method to isolate influenza nucleoprotein (NP)-specific memory B-cells and activate the cells in the presence of feeder cells. Activated cells were screened for NP specificity by EliSpot. We have also started to produce human NP-specific antibodies by transforming these cells with Epstein-Barr virus.

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POSTER 184

Function of CD11c (dendritic) cells within the CNS

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The existence of dendritic cells (DC) within the brain has been denied until we and others recently demonstrated presence of axonal and myelin-related antigens in cervical lymph nodes after brain injuries and emigration of leukocytes out of the skull into the nasal mucosa using the cribriform plate as exit route. In mice, expressing the green-fluorescent protein (gfp) together with the DC-marker CD11c, we localized a population of ramified cells at the interface between brain parenchyma and the perivascular space, a decisive checkpoint in neuroinflammation. These cells are randomly scattered throughout the brain with preferential accumulation in predilection areas of autoimmune neuroinflammation (e.g. spinal cord white matter, optic nerve, periventricular fiber tracts). Following induction of autoimmune encephalomyelitis, an animal model of multiple sclerosis (MS), performed in chimeric mice bearing GFP-CD11c+ cells exclusively within the brain under normal conditions, genomic GFP could be amplified from cervical lymph nodes strongly suggestion emigration of DC from brain to lymphoid organs. Chronic activation of these cells, e.g. as a consequence of controlled infection, may be a crucial step in the pathogenesis of MS.

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POSTER 185

Analysis of microRNA expression profile in CD4+ T cells in a murine asthma model

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MicroRNAs are small non-coding RNAs that regulate gene expression by translational repression as well as by messenger RNA degradation. Over the past years there has been increasing interest in microRNAs, since the possibility for new promising therapeutic strategies. Previous studies demonstrated a potential role of specific microRNAs in allergic diseases like asthma, but did not localize microRNA expression in specific cells. For the pathogenesis of allergic asthma CD4+ T helper (Th) type 2 cells are crucial. Therefore, we focused our investigation on microRNA expression profile in CD4+ T cells from antigen-sensitized mice.
METHOD: To identify specific microRNAs regulated in CD4+ T cells we used an established ovalbumin-induced Th-2 dominated asthma model. For this purpose CD4+ splenocytes from sensitized versus control mice were separated and microRNA expression profile was measured by miRXplore™ Microarray. MicroRNA expression profile was analysed by calculation of re-ratios comparing immunized versus control mice. Additionally data were verified by real-time PCR for the specific microRNAs from CD4+ T cells of spleen and mediastinal lymph nodes.
RESULT: Using microarray analysis we found microRNA223 was upregulated in immunized versus control mice; whereas miR26B was downregulated. The asthma specific microRNA expression or downregulation could be partially confirmed by real-time PCR.
CONCLUSION: Our results may suggest an involvement of microRNAs, expressed in CD4+ Th cells, in the development of allergic asthma. Identified microRNAs could be interesting targets for new therapeutic interventions.

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POSTER 186

Analytical validation of the hevylite tm-iga assay for the diagnosis of monoclonal gammopathies

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BACKGROUND: The analysis of monoclonal proteins in serum is an integral part in the diagnosis of monoclonal gammopathies. Currently used detection methods are mainly based on electrophoretic techniques, characterized by limited sensitivity and lack of quantification.
AIMS: The aim of our study was to analytically validate the Binding Site Hevylite™-IgA (HLC) assay, a newly developed immunoassay for the detection of monoclonal heavy chains type IgA κ and λ.
METHODS: Intra- and interassay precision were determined using patient sera (n=8) containing IgA monoclonal protein in a range between 0.1-31.0 g/L. Accuracy was estimated by testing linearity after dilution of patient sera with high monoclonal protein levels (n=4) and by spiking of assay calibrators into sera of healthy subjects (n=3). A potential interference with rheumatoid factors (RF) was investigated by dilution of sera containing monoclonal protein (n=2) with sera containing low or high amounts of RF IgM (37 to 974 U/ml). A method comparison has been performed with sera from patients with monoclonal gammopathies (IIMM, n=35; MGUS, n=6; LCMM. n=4)
RESULTS: Intra- and interassay precision ranged between 1.5 to 20.0% for the coefficient of variation. Testing accuracy of the analytical method resulted in a linear recovery from 0.9 to 13.0 g/L. RFs did not affect test results until a concentration of 974 U/ml. All 33 IFE positive samples could be confirmed by the HLC assay.
SUMMARY/CONCLUSION: Our test validation revealed high precision and accuracy of the analytical method and a high concordance between test results of IFE and the HLC assay. We are currently investigating the diagnostic value of the Heavylite™-IgA assay in estimation of prognosis and disease activity.

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POSTER 187

Thy-1 (CD90) regulates the extravasation of leukocytes during inflammation

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Human Thy-1 (CD90) has been shown to mediate adhesion of inflammatory cells to activated microvascular endothelial cells via interaction with Mac-1 in vitro. Since there are no data showing the physiological relevance of Thy-1 for the recruitment of inflammatory cells in vivo different inflammation models were investigated in Thy-1-deficient mice and wild type mice.
In thioglycollate-induced peritonitis the number of neutrophils and monocytes was significantly diminished in Thy-1-deficient mice. During acute lung inflammation the extravasation of eosinophils and monocytes into the lung was significantly reduced in Thy-1-deficient mice. Moreover, during chronic lung inflammation the influx of eosinophils and monocytes was strongly decreased in Thy-1-deficient mice. These effects were independent on Thy-1 expression on T cells shown by reconstitution of bone marrow of Thy-1-deficient mice with wild type bone marrow. In spite of the strong Thy-1 expression on T cells in chimeric mice the extravasation of inflammatory cells was significantly diminished compared to control mice. Finally, the altered number and composition of infiltrating leukocytes in Thy-1 deficient mice modified the chemokine/cytokine and protease expression at the site of inflammation. In conclusion, Thy-1 is involved to the control of the recruitment of inflammatory cells and thus is involved in conditioning the inflammatory microenvironment.

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POSTER 188

Phorbol ester-induced apoptosis of polymorphonuclear leukocytes.

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The apoptosis of polymophonuclear leukocytes (PMNs) is a crucial step during the cellular events leading to the termination of inflammation. Thereby the formation of reactive oxygen species (ROS) and subsequent changes in the intracellular redox status seem to be important to induce cell death. This holds for the spontaneous apoptosis PMNs as well as for cells activated at inflammatory sites.
During this study we investigated the apoptosis of both resting PMNs and cells stimulated with phorbol 12-myristate-13-acetate (PMA) by means of flow cytometry. Thereby we determined 1 nM PMA and an incubation time of 1 h to be optimal conditions for moderate cell stimulation and an increased apoptosis rate.
We also investigated the formation of ROS by both flow cytometry and chemiluminescence measurements. Intracellular ROS formation was measured by using dihydrorhodamine 123 as a fluorescent probe. The extracellular ROS formation was followed by using Pholasin, the photoprotein of *Pholas dactylus*.
The impact of NADPH-oxidase, MPO, and 5-lipoxygenase activity on ROS formation was investigated using both stimulated and non-stimulated cells. For this purpose the inhibitors diphenyliodonium (DPI), 4-aminobenzoic acid hydrazid (ABAH), and zileuton were used.
This study provides a suitable model for the *in-vitro* investigation of the apoptosis of PMNs under both physiological and moderate pro-inflammatory conditions. This study also addresses the question, which pathways for ROS formation are important for apoptosis induction in PMNs.

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POSTER 189

Effects of extracellular NAD+ on biological responses of human monocytes

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Background: Nicotinamide adenine dinucleotide (NAD^+) has emerged as a molecule with various functions besides redox capacity. Considering that at sites of inflammation intracellular metabolites are released from damaged cells, it was of interest whether elevated serum levels of NAD^+ would have an impact on surrounding immune cells. Human monocytes, potent cells of innate immunity which are abundant at sites of inflammation, can influence inflammatory processes by several effector functions. Here we asked, whether extracellular NAD^+ displays calcium signaling properties or can modify biological responses of human monocytes.
Results: Extracellular NAD^+ triggers a rapid and transient increase in $[Ca^{2+}]_i$, which is generated by nucleotide receptors of the P2 family, consisting of ligand gated ion channels (P2X) and G-protein-coupled receptors (P2Y). We showed that in freshly isolated monocytes the Ca^{2+} signal is produced by the activation of P2X receptors ($P2X_1$, $P2X_4$, $P2X_7$), while in 16h LPS-activated cells P2Y receptors ($P2Y_1$, $P2Y_{11}$) are mediating the response by the release of Ca^{2+} from intracellular stores [1;2]. When incubating monocytes with NAD^+ the LPS-induced oxidative burst was enhanced, and we found a change in the secreted amounts of cytokines and chemokines.
Conclusion: The modulation of monocyte activity by elevated amounts of extracellular NAD^+ could regulate inflammation to improve the immune response and to avoid excessive cell damage.

1. Grahnert A, Klein C, Hauschildt S. *Purinergic Signalling* 2009; 5: 309-319.
2. Klein C, Grahnert A, Abdelrahman A, Muller CE, Hauschildt S. *Cell Calcium* 2009; 46: 263-272.

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POSTER 190

Influence of LPS on NAMPT expression, secretion, and enzyme activity in human monocytes

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Nicotinamide phosphoribosyltransferase (NAMPT) is an enzyme that plays an important role to meet the requirement of nicotinamide adenine dinucleotide (NAD) in cells. Catalyzing the conversion of nicotinamide (NAM) and phosphoribosyl pyrophosphate to nicotinamide mononucleotide (NMN) and pyrophosphate, NAMPT is crucial for the recycling pathway generating NAD from NAM. Beside the intracellular enzymatic function, extracellular NAMPT was discussed to possess cytokine properties.
The aim of this work was to determine in how far activation of human monocytes with lipopolysaccharide (LPS) affects the intracellular expression of NAMPT protein and enzyme activity. Furthermore, we asked whether monocytes secrete NAMPT upon stimulation with LPS and whether recombinant NAMPT displays cytokine properties. NAMPT protein was quantified in lysates and supernatants of stimulated cells using a NAMPT-ELISA. NAMPT enzyme activity was determined in cell lysates by measuring the production of [14C] labeled NMN from [14C] NAM using a precipitation-filter assay as described by Rongvaux et al.[1].
Recombinant NAMPT was generated in HEK-cells carrying a plasmide containing an N-terminal Flag-tagged NAMPT. Here we show that exposure of human monocytes to LPS results in an increase in intracellular NAMPT protein and activity as well as NAMPT secretion. Inhibiting the enzyme activity in monocytes results in a decrease in LPS induced TNFa production, suggesting a functional link between NAD metabolism and inflammation. Addition of recombinant NAMPT to monocytes shows no influence on cytokine production.

[1] Rongvaux *et al.* 2002. *Eur. J. Immunol.* 32

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POSTER 191

TRPM2 is required for TNF-α production in human monocytes

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Transient receptor potential melastatin 2 (TRPM2) is a Ca^{2+}-permeable non-selective cation channel that is stimulated by oxidative stress and specifically activated by intracellular ADP-ribose. In former studies we found TRPM2 in human primary monocytes to be significantly up-regulated in the presence of LPS or other monocytic activators [1]. The aim of the present study was to determine a possible role of TRPM2 in the LPS-induced cytokine production of human monocytic cells. For this purpose we created a stable TRPM2-knockdown THP-1 cell line using shRNA.
We exposed the TRPM2-knockdown cells and the appropriate control cell line to LPS and found a significant reduction of TNF-α, IL-6, IL-8 and IL-10 at the mRNA and protein level in shRNA-treated cells.
To assess the role of Ca^{2+} influx in TNF-α production, THP-1 cells were incubated in culture medium containing the chelating agent EGTA. The omission of extracellular Ca^{2+} strongly decreased TNF-α production in TRPM2 expressing cells.
The effect of TRPM2 channel activation on $[Ca^{2+}]_i$ in activated TRPM2-knockdown cells and control cells was measured by calcium imaging at different time points after the addition of LPS. The application of LPS led to a time-dependent increase in intracellular Ca^{2+} concentrations in THP-1 cells that was clearly reduced by down-regulation of TRPM2 [1].
Thus, we assume that TRPM2-mediated Ca^{2+} entry is a central mechanism for LPS-induced TNF-α production in monocytic cells. The identification of TRPM2 as a major player in this LPS-dependent process makes it a promising tool in modulating monocyte functions.

[1] Wehrhahn *et al.* J.Immunol. 2010;184

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POSTER 192

The impact of membrane lipid composition on the oxidative metabolism of macrophages

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Polyunsaturated fatty acids (PUFAs) exhibit various immunmodulating properties. In phagocytes PUFAs may modulate the intracellular production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during oxidative burst. The aim of the present study is to investigate the effects of the n-3 PUFAs alpha-linolenic acid (LA), eicosapentaenoic acid (EPA), docosahexanoic acid (DHA) and the n-6 PUFAs linoleic acid (LNA), arachidonic acid (AA) on the oxidative metabolism of murine macrophage cell line RAW 264.7.
Cells were supplemented with LNA, EPA, DHA, LA and AA respectively in a concentration of 15μM for 72h and than stimulated with PMA (1μM) or LPS (1μg/ml) for 15/30/45min and 6/24h. ROS production was detected by the fluorogenic probe Dihydrorhodamine 123. RNS formation was determined using Griess reagent.
Exposure of unstimulated cells to PUFAs resulted in a significant increase of ROS production. Furthermore, when stimulated with PMA or LPS macrophages supplemented with LNA, DHA and AA showed a less intense increase of ROS production compared to unsupplemented cells. This effect was most pronounced with AA and DHA for PMA treatment and with LNA and DHA for LPS treatment. No effect on RNS production could be observed after stimulation with PMA and LPS for all PUFAs tested.
The modulation of the oxidative metabolism of macrophages by PUFAs depends on the Methylene Bridge Index (MBI) of the fatty acids as well as the activation status of the cells. Thus, PUFAs may be of use in the supportive therapy of various disorders of the oxidative metabolism.

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POSTER 193

The role of T helper cells and macrophages in IL-4R-dependent pathology in a pulmonary fungal infection

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Cryptococcus neoformans is an opportunistic fungal pathogen that causes meningoencephalitis in immunocompromised patients. In this infection the interleukin 4 receptor (IL-4R) is an important pathogenicity factor. In the lung, this receptor supports the induction of alternative activation of macrophages, goblet cell hyperplasia, airway hyperreactivity, recruitment of eosinophils, and dissemination of cryptococcal cells from the lung into the periphery. Cryptococcal infection might be also a risk factor for immunocompetent patients by favoring the development of allergic inflammation or asthma. We recently found a gene-dosage effect of this receptor for cryptococcosis in a murine infection model, i.e. the expression level is proportional to the severity of pathogenesis. In the present study we were interested in the role of IL-4R on T helper cells and macrophages in pathogenesis during a cryptococcal pulmonary infection. Therefore, we used cell-specific knockout mice that are deficient in the IL-4R on $CD4^+$ T cells (Lck) and macrophages (LysM). These mice are significantly more resistant than normal littermates (Flox). Mice that lack the IL-4R on T helper cells or macrophages, show diminished eosinophil recruitment, reduced goblet cell hyperplasia of the lung, absence of alternative activation of macrophages, prolonged survival time and enhanced survival rate. This study highlights the importance of T helper cells and macrophages in the pathogenesis of pulmonary cryptococcosis and reveals new targets for anticryptococcal and antiasthmatic therapy.

Assoziation: PbF III

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POSTER 194

Mapping of Infection and Characterisation of infected cortical cells in experimental measles encephalitis in Lewis rats

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In the experimental rat model for measles encephalitis, neurones are the major infected cell-type in the CNS. One purpose of this work was the mapping of measles virus infected cortical cells in Lewis rats. The proliferation of intracerebral injected virus in different brain areas, as well as in the different cell types: neurons, endothelial cells, astrocytes, oligodendrocytes and microglia, was analysed. In order to further characterise the infected cells Lewis rats were infected with the neurotropic measles virus CAM/RB (MV). Infected cells were visualised by indirect immunofluorescence labelling with monoclonal antibody directed against MV nucleocapsid proteins. Severel celltypes were distinguished by specific marker molecules. Infected cells were found in the motor cortex, somatosensoric cortex, visual cortex, auditory cortex and in the prefrontal cortex. Endothelial cells, oligodendrocytes, astrocytes and microglia were free of virus. At and around MV-infected infected neurons activated microglia and astrocytes were ascertained. The spread of the CAM/RB measles virus was confined therefore exclusively in neurons. In order to further characterise infected neurons, antibodies were used that are directed against the marker enzymes for GABAergic, glutamatergic, cholinergic and catecholaminergic neurones. Confocal laser-scanning microscopy revealed that cholinergic and catecholaminergic subclasses displayed no signs of infection and were assumed to be not infectable. Further experiments are in progress to elucidate GABAergic and glutamatergic neurons as apparently predominant infected neuronal subpopulations.

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POSTER 195

Fatal Th2 development is accompanied by eosinophils during pulmonary allergic inflammation induced by Cryptococcus neoformans infection

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Cryptococcosis is a common infection in immunocompromised humans in developing countries, often resulting in death of affected patients. In our mouse model susceptibility against C. *neoformans* is associated with T helper (Th) 2 responses. There is a surprisingly late onset of Th-cell derived Interleukin-4 production in contrast to early Th1 and Th17 responses. Th2 responses are accompanied by influx of eosinophils into the lung. Currently we assess whether eosinophils modulate the Th2 response. Our results provide insights in the mechanisms of Th2 induction against a fungal pathogen and help to identify a cellular target for therapeutic intervention in bronchopulmonary mycosis.
Funding: Doktorandenförderprogramm Universität Leipzig

Assoziation: PbF III

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POSTER 196

Differential arachidonic acid metabolism in healthy subjects after LPS whole blood activation

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Eicosanoids as metabolites of arachidonic acid are known to play key roles in promotion and inhibition of central inflammatory processes. An imbalance of the arachidonic acid metabolism is therefore implicated in the pathophysiology of inflammatory diseases. The aim of our study was to investigate the individual eicosanoid response of healthy subjects on mediator and gene expression level as a potential marker of susceptibility for inflammatory diseases.
In preliminary experiments, human whole blood (lithium-heparin) from 3 healthy subjects was incubated with lipopolysaccharide (LPS; 100ng) for 1, 4 and 24 hours. RNA was isolated and 6 target genes (COX-1, COX-2, TBXS, PGFS, 12-LOX, 5-LOX) of arachidonic acid metabolism were analyzed by quantitative fluorogenic RT-PCR. Eicosanoids (11-HETE, TXB_2, PGE_2, PGF2α, 12-HETE, 5-HETE) were analyzed in supernatants by LC-MS/MS (API 5500 QTrap, AB SCIEX).
We found a time-dependent eicosanoid response on mediator and gene expression levels for all investigated pathways. Induction of gene expression was up to 35fold (COX-2). For COX-1, COX-2 and 12-LOX pathways, we observed a parallel increase in gene expression levels and mediator release. In contrast, eicosanoid response and gene expression of the TX and 5-LOX pathways were not coordinated suggesting regulatory mechanisms independent of regulation of gene expression. Further work is necessary to investigate potential relations of gene expression, eicosanoid response and predisposition to inflammatory diseases such as coronary artery disease.

Funding: life

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POSTER 197

Characterization of a novel locus of coronary artery disease susceptibility on human Chromosome 7

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In previous work a novel locus of coronary artery disease (CAD) susceptibility was identified on human Chromosome (Chr) 7. However, the underlying pathomechanism at this locus has not been investigated, yet.
To this end, we replicated the locus in the Leipzig Heart study, a cohort of patients with varying severity of CAD (n=1134; $P = 4.78x10^{-3}$). Within the identified block, a novel candidate gene of CAD was identified. Next, we determined mRNA expression levels of the gene in various tissues using quantitative RT-PCR and found that it was also expressed in plaque tissue as well as in peripheral blood derived mononuclear cells (PBMC). Expression analysis in PBMC from participants of the Leipzig Heart study (n=1098) revealed significantly increased expression in patients carrying the CAD risk allele ($P = 0.01$). Immunohistochemical analyses of the gene further revealed co-localization with smooth-muscle cells and CD68-positive macrophages. To investigate the functional role of the candidate gene, we performed siRNA knockdown experiments and found that down-regulation of the gene was associated with significant expression changes of genes involved in cell cycle regulation and apoptosis ($P < 0.05$; $0.7 <$ fold change > 1.4)
In conclusion we provide evidence that the previously identified locus on Chr7 is associated with CAD and that expression of a novel candidate gene is associated with the genotype at Chr7 and atherosclerosis severity. Our data suggest a potential role of the candidate gene in the regulation of cell cycle and apoptosis but further work is necessary to understand the underlying molecular mechanism.

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POSTER 198

Genome-wide eQTL Mapping Reveals Candidate Genes of Atherosclerosis in F2 Mice

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Quantitative trait locus (QTL) mapping in atherosclerosis-susceptible C57BL/6 and atherosclerosis-resistant BALB/cByJ female mice on the LDL-receptor deficient background ($LDLR^{-/-}$) revealed a novel locus of atherosclerosis susceptibility on mouse chromosome (Chr) 2. The confidence interval of this locus spans from 0 to 71.7 Mb and harbors 754 genes. To identify potential candidate genes at this locus, we have performed genome-wide expression analyses (Illumina Mouse ref-8 V2) in livers of 176 female F2 mice. Expression QTL (eQTL) of 25697 transcripts with 127 genomic markers was performed. To correct for multiple testing, we only followed up candidate genes mapping to Chr2 with LOD scores > 8. In total, we identified 4 genes that were regulated *in cis* co-localizing with the top atherosclerosis LOD score at marker rs27192030. Of these genes, Tbc1d13, Surf4 and Fam73b were validated in livers of female C57BL/6 and BALB/cByJ F0 mice (n=6/6, $P < 0.05$). Furthermore, Tbc1d13 and Surf4 were differentially expressed in spleens of C57BL/6 and BALB/cByJ F0 mice (n=6/6, $P < 0.02$). Proteins encoded by Tbc1d13 contain a RabGAP/TBC domain thought to regulate GTPase activator activity. The Surf4 gene encodes an integral membrane protein interacting with endoplasmic reticulum-Golgi intermediate compartment proteins.
In conclusion, we have identified Tbc1d13 and Surf4 as two novel candidate genes of atherosclerosis susceptibility on mouse Chr2. Further work will be necessary to understand how these genes might influence atherosclerosis susceptibility at this locus.

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POSTER 199

Genetische Varianten der Cholesterinveresterung

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Cholesterin ist ein entscheidender Risikofaktor für kardiovaskuläre Erkrankungen und kommt im Körper vorrangig in veresterter Form vor. Eine strikte Regulation der Cholesterinveresterung ist von wesentlicher Bedeutung für die Cholesterinhomöostase. Die individuellen genetischen Faktoren der Cholesterinveresterung sind bislang nicht aufgeklärt.
Es wurde eine genomweite Assoziationsstudie (GWA) zur Sterolveresterung basierend auf den gemessenen Konzentrationen freier und veresterter Sterole (n = 4222) in der populationsbasierten, epidemiologischen KORA S3/F3-Studie sowie eine genomweite Genotypisierung (n = 1644) mittels Affymetrix 500k SNP Array durchgeführt. Zur Identifizierung weiterer möglicher Genvarianten wurde zusätzlich ein Kandidatengen-Ansatz verfolgt.
Die Auswertung der GWA ergab 40 Loci für die Cholesterin- sowie 62 Loci für die Phytosterolveresterung (-log p ≥ 4.0), dabei lag der Großteil der identifizierten SNPs in intergenischen Regionen. Die Analyse der Haplotypen-Struktur zeigte 16 potentielle Kandidatengene für die Cholesterol- sowie 49 Gene für die Phytosterolveresterung – u.a. *OSBPL10* und *STARD3*. Der Kandidatengen-Ansatz lieferte 148 weitere Loci der Cholesterinveresterung, die jedoch noch zu validieren sind.
Die GWA zeigt distinkte Loci der Cholesterin- und Phytosterolveresterung auf. Die Analyse der Haplotypen-Struktur an diesen Loci liefert mehrere potentielle Kandidatengene der Sterolveresterung. Zur statistischen Evaluierung sollen die identifizierten Loci zunächst in der CARLA-Studie repliziert und zur Beurteilung der klinischen Relevanz in der LE-Heart-Studie weiter untersucht werden.

Funding: life

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POSTER 200

The role of genetic variation in the sodium-glucose cotransporter 2 gene (SGLT2) in the pathophysiology of type 2 diabetes

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Treatment with SGLT2-inhibitors results in decreased fasting glucose levels, reduction of HbA1c and lower BMI. Mutations in the *SGLT2* gene, which codes for a gut and renal sodium-glucose cotransporter, cause renal glucosuria. We therefore investigated the effects of common genetic variation in *SGLT2* on glucose traits and BMI in non-diabetic subjects as well as the association with type 2 diabetes (T2D). Four HapMap tagging single nucleotide polymorphisms (SNPs) (www.hapmap.org) were genotyped (TaqMan, Applied Biosystems, Inc.) for subsequent association studies on BMI, T2D and related metabolic traits in 1046 Sorbs from Germany who had undergone a detailed phenotyping. The SNPs were representative of their linkage disequilibrium groups and were selected according to $r^2>0.8$ and minor allele frequency>0.01. An independent cohort from Berlin, Germany (N=2046) was taken for replication. In a case control study including 106 patients with T2D and 786 controls with normal glucose tolerance, none of the SNPs showed association with T2D. However, rs9934336 was nominally associated with 30 min plasma glucose, 2 hr insulin concentrations and incremental $AUC120_{glucose}$ during oral glucose tolerance test in 892 non-diabetic subjects ($P<0.05$ in additive model adjusted for age, sex and BMI). In the Berlin cohort the SNP was nominally associated with 60 min plasma glucose (adjusted $P<0.05$) in a subgroup of subjects with impaired fasting glucose and impaired glucose tolerance (N=485). In conclusion, our data suggest a role of *SGLT2* genetic variation in the regulation of insulin and glucose levels in non-diabetic individuals.

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POSTER 201

Genetic Risk Variants for Rheumatoid Arthritis in 100 French Families

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Rheumatoid Arthritis (RA) is a multifactorial, systemic, autoimmune disease with it´s main manifestation in multiple erosively inflamed joints. About sixty percent of disease risk are attributed to genetic factors. However, markers accounting for most of the suspected genetic risk still remain to be identified. The best-replicated and strongest genetic risk markers lie within the genes HLA-DRB1 and PTPN22. For a number of other potential genetic risk factors, evidence is sketchier and effect sizes are low. So far, evidence for interaction of genetic risk factors is scarce, it is unclear to what degree different risk factors accumulate in patients, and it remains to be determined to what degree genetic risk factors can differentiate patients from controls.
The goal of the work presented here was to determine and analyze a number of known and suspected genetic risk factors for RA within one hundred French family trios with children affected by RA. Data were available for eleven SNPs in nine candidate genes. Analyses included tests for single marker association, graphic representation of the distribution of risk alleles, a sum score, a sum score weighted by effect size, and assessment of pair wise interaction of single markers.
SNPs in HLA, PTPN22, IL18, and CTLA4 were associated with RA at single marker level. ITGAV and a second SNP in CTLA4 showed trends towards association. There was evidence for interaction of risk alleles. Risk scores based on genetic variants clearly differentiated between patients and controls. However, risk factors beyond HLA-DRB1 and PTPN22 did not seem to contribute visibly to this observation.

Funding: life

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POSTER 202

Hierarchical statistical model for analysis of multiple genomic and phenotypic data

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In the classical analyses, molecular-genetic modifiers are tested for association with traits one by one. We aim to develop and apply new statistical meta-regression approaches for the combined analysis of multiple traits and markers utilizing biological knowledge about underlying pathways. The presented model based analysis is motivated by a recently published genome-wide association study (GWAS) regarding phytosterol phenotypes.
A number of candidate SNPs were selected from a GWAS dataset regarding different sterol phenotypes. Two of the SNPs showed genome-wide significance with phytosterols while the others showed less pronounced effects. A physiological model of cholesterol regulation including phytosterols, lanosterol, covariables and effects of the combination of all candidate SNPs was developed and translated into a Bayesian hierarchical model. Markov Chain Monte Carlo methods were used to fit the model. Corresponding parameter estimates allow the selection of plausible models. Genetic effects were re-estimated by Bayesian model averaging taking uncertainty of model structure into account.
Besides the two SNPs which already reached genome-wide significance, one additional SNP was up-weighted by our analysis. Interestingly, this SNP was the only one which could later be confirmed in several replication studies.
We conclude that the presented modeling approach is a powerful method in order to combine several genotypic and phenotypic information leading to new perspectives on the data. It can incorporate biological knowledge and is well suited to deal with missing data or hidden intermediate phenotypes.

Funding: life

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POSTER 203

Ontology-based Registration of Entities for Data Integration in large biomedical Research Projects

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Large biomedical projects often include workflows running across institutional borders. In these workflows, data describing biomedical entities, such as patients, bio-materials but also processes itself, is typically produced, modified and analyzed at different locations and by several systems. Therefore, both tracking entities within inter-organizational workflows and data integration are often crucial steps.

To address these problems, we centrally register entities and their relationships by using a multi-layered model. The model utilizes the developed LIFE Investigation Ontology (LIO) and a typed system graph. LIO uniformly defines all types of physical entities, such as special specimen types, but also data and material generating processes (e.g., medical checkups and interviews). Using these definitions LIO allows to semantically describe and classify entities and their relationships. The modeled typed system graph combines both, concepts of LIO and physical systems, and, thus, describes which kinds of entities are managed by which system. Finally, the entities are associated to the typed system graph.

Our registration approach allows to centrally track entities along the project workflows and can be used in explorative data analyses as well as by other data integration approaches using the registered entity relationships. The approach makes it possible to access entity data on demand in their original source. We describe the model, the LIFE investigation ontology, and a system implementing this approach. This system is the central infrastructure component in LIFE, a large biomedical research project in Leipzig.

Funding: life

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POSTER 204

Identification of Elovl6 as Novel Candidate Gene of Atherosclerosis Susceptibility in Mice

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In previous work, we have identified an atherosclerosis susceptibility locus on mouse chromosome (Chr) 3 by quantitative trait locus (QTL) mapping in atherosclerosis-susceptible C57BL/6 (B6) and atherosclerosis-resistant FVB female mice on the LDL-receptor deficient background ($LDLR^{-/-}$). Thus, it was the aim of the current study to identify potential modulators of atherosclerosis susceptibility at this locus.

To this end, we performed whole genome expression analyses (Illumina Ref-8 arrays) in FVB and congenic FVB.$Chr3^{B6/B6}$ (80-160 Mb) mice (n=4/4). Out of 181 genes in the confidence interval of cross A (F0:mB6xfFVB), 8 were differentially expressed with a FVB.$Chr3^{B6/B6}$/FVB ratio greater than 1.4. In cross B (F0:mFVBxfB6), out of 451 genes 10 were differentially expressed. Of these, 6 genes were verified by quantitative RT-PCRs in livers of FVB.$Chr3^{B6/B6}$ and FVB mice ($P<0.05$) and also validated in livers and aortas of F0 B6 and FVB mice ($P<0.05$). Expression QTL studies in 459 F2 mice revealed *cis*-regulation of two genes: *Elovl6* in cross A and *Vcam1* in cross B. Whereas *Vcam1* is a known candidate gene of atherogenesis, *Elovl6* has not been associated with atherosclerosis, yet. In cross A, the B6-Allel was associated with higher atherosclerosis, VLDL Plasma levels and higher *Elovl6* expression. *Elovl6*-expression was also directly correlated with atherosclerosis severity and VLDL plasma levels.

In conclusion, we have identified *Elovl6* as a novel candidate gene of atherosclerosis susceptibility. Further work will be necessary to understand the functional mechanism by which *Elovl6* influences atherosclerosis development.

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POSTER 205

Kopplung von Mikro-Freiflusselektrophorese mit hochauflösender Massenspektrometrie

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Die Mikro-Freiflusselektrophorese (μFFE) ist aufgrund ihres geringen Probenbedarfs und hoher Kompatibilität zu Biopolymeren eine attraktive Hochgeschwindigkeits-Trennmethode für die Proteom- und Metabolomanalytik bei der Substanzgemische innerhalb weniger Sekunden aufgetrennt werden. In Verbindung mit hochauflösender Massenspektrometrie (MS) ist es möglich auch komplexe biochemische Proben zu charakterisieren und unbekannte Verbindungen zu identifizieren.

Obwohl die μFFE im Hinblick auf die Trennung von Zellen bis zu niedermolekularen Analyten sich als außerordentlich vielfältig erwiesen hat, ist die Onlinekopplung mit der ESI-MS kaum untersucht[1]. Die erstmalige Realisierung einer echten Online-Kopplung von μFFE und Elektrospray-Massenspektrometrie und deren Einsatz in der Metabolomic ist das Ziel des vorgestellten Projektes.

Im bisherigen Projektverlauf wurden fluoreszente, aber auch aminbasierte Testsysteme für drei Varianten der Freiflusselektrophorese entwickelt und diese hinsichtlich ihrer Trenneffizienzen in MS-kompatiblen Puffersystemen untersucht. Diese werden zur Validierung von Mikrochips auf Polymerbasis mit assemblierten Nanosprayna-deln und von Glasmikrochips mit monolithischen Emittern, welche eine totvolumenfreie Kopplung zum Massenspektrometer ermöglichen[2], eingesetzt.

[1] A. Chartogne, U. R. Tjaden, J. van der Greef, *RAPID COMMUNICATIONS IN MASS SPECTROMETRY* 2000, *14*, 1269–1274.
[2] P. Hoffmann, U. Hausig, P. Schulze, D. Belder, *ANGEWANDTE CHEMIE-INTERNATIONAL EDITION* 2007, *46*, 4913–4916.

Funding: life

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POSTER 206

Detection of Rare Variants in Disease associated Genes – Experiences of the GAW17 Workshop

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Rare causal variants are believed to significantly contribute to the genetic basis of common diseases or quantitative traits. Appropriate high-throughput sequencing methods for the measurement of rare variants exist. However, appropriate statistical methods to identify the disease relevance of these variants are required.
The publically available GAW17 dataset is based on a dataset of 697 individuals and 24487 genetic variants combined with a simulated complex disease model comprising intermediate quantitative phenotypes. By calculating top-gene lists, we tested and compared different collapsing and scoring methods aiming to detect causal genes. In a detailed analysis of our results we identified conditions under which single methods perform best. Findings were validated in own simulation studies.
In contrast to collapsing methods, scoring methods of markers performed clearly different. The minimum statistic was superior when there are major single causal marker in the gene and when a liberal cut-off of the gene-list is used, while the Hotelling test was superior when there are several independent causal markers of the gene and when a stringent cut-off is used. This pattern was rather consistent for all phenotypes and was confirmed by single gene analyses and simulation studies. Analysis of rare variants was only useful for quantitative phenotypes.
We conclude that the search for causal rare variants can best be accompanied by improved scoring techniques. However, no general recommendation can be given as performance of methods depends on the structure of the genetic effect and the number of selected genes.

Funding: life

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POSTER 207

Genotype Imputation in Genome Wide Association Study

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Genotype imputation is now an essential tool in the analysis of genome-wide association studies. Imputation methods are used either to estimate the partially missing genotypes in a given sample data or to predict the genotypes at a large number of SNPs that are not directly genotyped in the study sample. In order to perform a GWAS study, an important issue is the control of genotype quality. In our study we aim to address the question whether filtering low quality SNPs has an influence on the performance of imputation algorithms (such as MACH an IMPUTE2) and which quality criteria are most informative regarding their performance. For this purpose we analyse an available dataset of 100 genotyped individuals. At first the dataset was filtered with different quality criteria to obtain different data-subsets having different SNP numbers. Afterwards imputation is simulated in these different subsets by masking a randomly selected specified percentage of genotypes of high quality SNPs which make us confident that the measured genotypes on these SNPs are accurate. At the end, the results obtained from imputing those different data-subsets were compared. Analyses are still ongoing but preliminary results suggest that rigorous filtering of low quality SNPs afflicts the power of imputation algorithms.
In our poster we will present:
the background and Motivation of why genotype imputation is necessary, the basic ideas for widely used Hidden Markov Model imputation algorithms,our research results regarding ''Imputation before or after genotype quality control.''

Funding: life

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POSTER 208

Vaspin and Psoriasis

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Vaspin is a member of the serine protease inhibitor family related to obesity and glucose metabolism with expression in adipose tissue, liver, pancreas and skin. The dysregulation of skin proteases and their inhibitors can contribute to the onset of inflammatory skin diseases. In the present study we investigated the role of vaspin in the pathogenesis of psoriasis, an obesity associated, chronic inflammatory skin disease. The effect of vaspin on the function of dendritic cells involved in the inflammatory process was analyzed by FACS and ELISA. Vaspin did not influence the differentiation and maturation of monocyte-derived dendritic cells (MoDC) so far. Furthermore we analyzed the expression pattern of vaspin in skin by immune histological staining. We detected vaspin expression by keratinocytes in the epidermal layers of the skin in both healthy subjects and psoriasis patients. To investigate a potential link between vaspin, obesity and psoriasis we measured the vaspin serum level of psoriasis patients and healthy subjects. Vaspin level in serum was elevated in patients with psoriasis and normal BMI. In healthy subjects the vaspin serum level correlated with BMI. In obese subjects the vaspin levels were elevated in both healthy subjects and psoriasis patients. These results indicate that vaspin is expressed in the epidermis and that the serum level of vaspin is triggered by two different factors, an increased BMI and psoriasis. Further investigations are needed to asses the relation of vaspin serum level and PASI and to analyze the regulation of vaspin expression in skin specific cell types.

Funding: life

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POSTER 209

Metadata Repository für die klinische und epidemiologische Forschung in LIFE

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Die Spezifikation der Datenerhebung und Dokumentation in klinischen und epidemiologischen Studien stellt einen wichtigen Teil in der Projektplanung dar. Dabei hat die Festlegung der Erfassungsmerkmale, Messprozesse und Merkmalsabhängigkeiten erheblichen Einfluss auf die Aussagekraft und Qualität der Kohortenstudien. Der Einsatz international-etablierter Merkmale durch die Referenzierung bereits existierender Standards und die Bezugnahme auf Erhebungsinstrumente anderer Projekte hat sich dabei bewährt. Dies ermöglicht einerseits die Harmonisierung der Vorgehensweisen und andererseits später die Zusammenführung von Daten im Rahmen von Metaanalysen oder genomweiten Assoziationsstudien.
Auf Basis der im LIFE-Projekt durchgeführten epidemiologischen, diagnostischen und prognostischen Studien wird im Promotionsprojekt ein Repositorium von ca. 5000 Studienitems (d.h. annotierten Dokumentationsmerkmalen) als sog. Metadata Repository spezifiziert, welches die epidemiologische Forschung in der Wiederverwendung solcher Merkmale unterstützen soll.
Die Analyse der Strukturen einer Vielzahl von bereitgestellten Dokumentationsmerkmalen (Basisdatensätze, Befragungsinstrumente) aus verschiedenen klinischen und epidemiologischen Studien zeigte, dass diese sehr komplexe Datenstrukturen haben. Um eine Wiederverwendung zu gewährleisten, müssen die Merkmale und ihre Komponenten semantisch korrekt erfasst, strukturiert sowie repräsentiert werden. Aufbauend auf der Top-Level-Ontologie General Formal Ontology und dem ISO/IEC 11179-Standard machen wir einen Schritt zu einer ontologisch begründeten Semantik für komplexe standardisierten Systeme.

Funding: life

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POSTER 210

Methodischer Vergleich zweier Messverfahren zur objektiven Erfassung des Schlaf-Wach-Rhythmus (SenseWear Pro 3 vs. Actiwatch A7)

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Einleitung: Mittels Aktometrie können Schlafparameter (z.B. Schlafdauer und –effizienz) objektiv erfasst werden. Problematisch ist, dass es zu Fehlinterpretationen von immobilen Wachphasen kommen kann. Im LIFE-Projekt soll deshalb mit dem SenseWear Pro3™ ein Gerät zum Einsatz kommen, welches neben reiner Aktometrie auch weitere Parameter (z.B. Hautleitfähigkeit, Körpertemperatur) erfasst. Da die SenseWear hauptsächlich für den Bereich der Sport- und Ernährungsmedizin konzipiert wurde, liegen nur unveröffentlichte Daten des Herstellers zur Schlaferfassung vor. Im Rahmen einer Feasibility-Studie des LIFE-Projekts sollte deshalb ein methodischer Vergleich mit einem in der Schlafforschung gut etablierten und mehrfach validierten klassischen Aktometer (Actiwatch A7) durchgeführt werden.

Methodik: In einer einwöchigen Untersuchung trugen 26 gesunde Probanden simultan beide Aktometer und führten ein Schlafprotokoll. Die durch beide Geräte ermittelten Angaben zur durchschnittlichen Schlafdauer, -effizienz und –latenz wurden mittels Wilcoxon-Test verglichen.

Ergebnisse: Es ergaben sich signifikante Unterschiede in Bezug auf alle Schlafparameter (z.B. Schlafdauer: SenseWear = 06h 31min, Actiwatch = 05h 56min, $p = 0{,}001$).

Diskussion: Es ist zu vermuten, dass sich die gefundenen Unterschiede dadurch begründen lassen, dass die SenseWear durch ihre multimodale Messmethodik Schlaf-Wach-Phasen besser differenzieren kann, als die Actiwatch als reines Akzelerometer.

Funding: life

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POSTER 211

Is the pathophysiology of type 2 diabetes swayed by vaspin and its genetic variants?

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Aims: Vaspin is suggested to link obesity, insulin resistance (IR) and type 2 diabetes (T2D). We investigated the effects of recombinant vaspin treatment on insulin sensitivity in *db/db* mice and analyzed the role of genetic variation in the human *vaspin* in the pathogenesis of T2D.
Material and methods: Animal studies: After administration of recombinant vaspin glucose tolerance (GT) tests and hyperinsulinemic-euglycemic clamps were performed in *db/db* mice (N=10).
Human genetic studies: *Vaspin* was sequenced in 48 DNA samples. 27 tagging single nucleotide polymorphisms (SNPs) were genotyped in 1046 Sorbs from Germany for subsequent association studies on metabolic traits.
Full-length and short-length *vaspin* were cloned into p3xFLAG-myc-CMV™-expression vector and transfected into HEK-cells. Proteins were detected by western blot.
Results: Animal studies: Vaspin administration in *db/db* mice resulted in improved GT. Glucose infusion rate during the steady state of the clamp significantly increased after vaspin treatment.
Human genetic studies: Sequencing the vaspin gene revealed one SNP resulting in a stop codon. Western blot showed a prominent ~25-kDa band for short-length vaspin. Both, the full- and the short-length vaspin were expressed in eukaryotic cells.
Furthermore several SNPs were nominally associated with waist-to-hip-ratio, 30min glucose levels or 2-hr-insulin levels, $AUC_{Glucose}$, insulin sensitivity and resistance indices.
Conclusion: Our data demonstrate the substantial insulin sensitizing effect of vaspin and suggest a role of *vaspin* genetic variants in the pathophysiology of insulin resistance and T2D.

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POSTER 212

Is there a specific binding of (phospho)lipids to silica gel? A thin layer chromatographic, MALDI-TOF mass spectrometric and 31P NMR spectroscopic study

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Objectives: In the field of lipid and particularly phospholipid (PL) research thin-layer chromatography (TLC) is a highly established separation method, which is used to identify certain lipids in a mixture and isolate them. Unfortunately, it is not yet known if there is a specific binding of certain lipids to the silica gel or whether all PLs are eluted to the same extent. It is also unknown if differences in the fatty acyl compositions of individual PL classes affect the affinities to the stationary phase.

Results: It is known that individual lipid classes are not located in the same depth of the silica gel. With an increased migration distance, the sample penetrates deeper into the stationary phase. In order to investigate this aspect, the hen egg yolk extract was separated by TLC and the complete lane afterwards eluted with different amounts of a defined solvent mixture. The organic extract of hen egg yolk was used as control. A strong dependence of the lipid yield from the used volume of extraction solvent could be monitored. It was not possible to elute the whole amount of lipid from the silica gel.
The most important result of this study is that the composition of lipid mixtures is not changed by TLC: all lipid classes, independent of their fatty acyl compositions or headgroups, are released from the silica gel. There is a considerable loss of the absolute amount of lipids, which can partially be overcome by the use of a larger excess of the extraction solvents. It is our conclusion that a specific binding of lipids to the silica gel surface can be excluded but all relevant lipids are bound to the same extent.

Funding: life

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POSTER 213

Intrauterine Stresshormone beeinflussen den Fettstoffwechsel weiblicher Nachkommen des Weißbüschelaffen (Callithrix jacchus)

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Viele sogenannte Zivilisationskrankheiten des Menschen, wie Adipositas oder Atherosklerose, werden durch variable Faktoren hervorgerufen. Jüngster Forschung zufolge kann bereits intrauterin eine Prädisposition für spätere Erkrankungen erworben werden, z.B. durch den Einfluss maternaler Stresshormone auf den sich entwickelnden Fetus. In dieser Studie wurden die Auswirkungen pränataler Glukokortikoidgaben auf den Fettstoffwechsel der weiblichen Nachkommen in der F1- bis F3-Generation beim Weißbüschelaffen (*Callithrix jacchus*) untersucht.
Zu diesem Zweck wurden Blutparameter weiblicher Nachkommen von Affen, die während der Trächtigkeit mit Dexamethason behandelt wurden (F1: n=5, F2: n=6, F3: n=3), bestimmt und mit denen gesunder, ihrem Alter entsprechender Kontrolltiere (n=12) verglichen. Sowohl die F2- als auch die F3-Generation wies höhere Cholesterol- und niedrigere Triglyceridspiegel auf, während die F1 ähnliche Ergebnisse lieferte wie die Kontrollgruppe. Des Weiteren zeigte die F2-Generation signifikant mehr LDL-Cholesterol (Median 1,8mmol/l gegenüber 1,0mmol/l, p=0,01) und signifikant weniger HDL-Triglyceride (Median 21,0mg/dl im Gegensatz zu 34,7mg/dl, p=0,01) als die Kontrollen. Die F3-Generation hatte ebenfalls signifikant höhere Anteile an LDL-Cholesterol (Median 2,2mmol/l versus 1,0mmol/l, p=0,03) sowie signifikant niedrigere HDL-Triglyceridspiegel (Median 25,3mg/dl im Kontrast zu 34,7mg/dl, p=0,03). Zusammenfassend lässt sich die Aussage treffen, dass eine pränatale Applikation plazentagängiger Glukokortikoide negative Effekte auf Fettstoffwechselparameter der 2. und 3. weiblichen Folgegeneration hatte.

Funding: life

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POSTER 214

MS2 affinity purification and visualization of ncRNA-protein-complexes

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Recent studies have uncovered an enormous diversity of non-coding RNAs (ncRNAs), although most of them are not yet functionally described. To study both the function and localization of selected ncRNAs, we use an affinity purification system that is based on the RNA of interest. Most common methods for analyzing RNA-protein interactions, like RNA-immunoprecipitation, are protein-based, thereby particular target proteins are used to identify unknown RNA binding partners. In contrast, we apply ncRNAs that we previously discovered in genome wide tiling and custom array analyzes to detect novel interacting protein-complexes. To this purpose, we use the MS2 affinity tag system, which involves a short RNA hairpin tag sequence that binds specifically to the MS2 coat protein. To adopt this system, the bait ncRNAs are tagged by the MS2 hairpin RNA, and the MS2 coat protein is expressed fused either to a capture molecule (maltose-binding protein) for affinity purification *in vitro* or fluorescent proteins (eGFP, eCFP, dsRed) for *in vivo* visualization. This approach is adaptive to large numbers of ncRNAs, allowing the identification of undiscovered ncRNP-complexes together with their cellular localization.

Funding: life

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POSTER 215

Targeted Proteomics for Metabolic Diseases

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The incidence of lifestyle-based metabolic diseases is growing to epidemic proportions, and current trends suggest further increase worldwide. However, the complex multifactorial disease processes involve multiple pathways that can be influenced by both genetic and environmental factors. Recent GWA studies pointed at several loci associated with metabolic diseases and their phenotypes. In-depth knowledge of the proteomic link between both is necessary to pin down the statistical associations onto the underlying pathways.

We identified proteomic targets for metabolic diseases by comparative meta-analysis of published GWAs, known marker proteins, and candidates from our Leipzig Heart Study.

To quantify the target peptides we applied fast liquid chromatography and quadrupole/linear ion trap mass spectrometry (QTRAP LC/MS/MS system) using proteotypic peptides and isotope-labeled standards after tryptic digestion.

Preliminary results show the great potential of the approach. Without depletion we could quantify CRP, ApoA1, ApoB100 and ApoE in only 100μL of serum, further candidate peptides as e.g. Sortilin1, NT-proBNP &c. are currently targeted.

Targeting proteomics on the candidate peptides of metabolic diseases emerging from GWAs, epidemiological studies and clinical evidence is a promising approach to fortify the associations between transcriptome and metabolome with functional knowledge and may elucidate the pathways whereon disease-related loci affect the metabolic phenotype.

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POSTER 216

Identification of novel biomarkers in cerebrospinal fluid of patients with Multiple Sclerosis using Magnetic Bead Separation and Matrix-assisted Laser Desorption/ Ionization Time-of-flight Mass Spectrometry

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Introduction: Peptidome profiling is a promising tool to identify disease associated biomarkers in human cerebrospinal fluid (CSF). Our aim was to develop a pretreatment protocol for reproducible profiling of CSF using magnetic bead (MB) separation and MALDI-TOF MS followed by standardized CSF analysis in patients with multiple sclerosis (MS) and healthy controls.

Methods: A standardized pretreatment protocol was generated, investigating effects of exogenous variables and endogenous interferences on peptidome analysis of pooled CSF samples. Using our standardized protocol, the peptidome in CSF samples from patients with MRI trusted MS (n=22) and healthy controls (n=20) was analyzed.

Results: For standardization of CSF peptidome analysis, a storage time <6 hours at room temperature and a blood contamination <0.075 μmol/L have to be particularly taken into account. Comparing the peptidome of CSF from MS patients and healthy controls, we were able to show 16 differentiating mass peaks. After literature search, one of those (m/z 1739 Da) could be identified as a complement C4 fragment.

Conclusion: Our published pretreatment protocol allows preanalytical standardization and facilitates reproducible peptidome profiling of human CSF using MB MALDI-TOF MS. The differentiating mass peaks between MS patients and healthy controls are currently confirmed in a further study collective.

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POSTER 217

Stimulation of Sodium Transport by Insulin

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In the course of postnatal conversion and alveolar fluid clearance in newborns the epithelial sodium channel (ENaC) plays a decisive role, because clearance is mainly driven by unidirectional sodium transport. To enable effective clearance functional of ENaCs and Na-K-ATPases are necessary. Previous investigations suggested a stimulatory influence of insulin on ENaC function in tissues like bladder, renal cells or frog skin. To analyze the effect of insulin on alveolar sodium transport, fetal distal lung cells of rat fetuses (E19-20) were isolated and cultured for 48 hours. Ussing Chamber measurements showed the presence of amiloride-sensitive short circuit currents (Isc) representing the ENaC as well as Ouabain-sensitive-Isc related to the Na-K-ATPase. Insulin-stimulation (20 nM, 200 nM and 2 μM) showed a dose-dependent increase of the sodium transport attributed to an elevated activity of the participating ion transporters. We also tested the influence of insulin on their mRNA-expression revealing no alteration. Therefore insulin must exert posttranscriptional effects on sodium transport. Further experiments analyzing the involvement of the serum and glycocorticoid-dependent kinase 1 (SGK1) in the insulin-induced increase of sodium transport are planned. Thus we hope to elucidate the mechanism by which insulin improves alveolar sodium transport and thereby alveolar fluid clearance.

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POSTER 218

Glucocorticoids differentially modulate the CFTR-channel

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Cystic Fibrosis (CF) is the most common recessive, lethal genetic disease in Caucasians. The hallmark ion transport defects in CF are a diminished or absent Cl^--secretion and Na^+-hyperabsorption. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) are pathognomic and agents improving the transcription, rescue or channel activity supposedly lessen the pathologic features. Glucocorticoids are known to increase the function of epithelial sodium channels (ENaC), but little information exists about the impact on CFTR. However experimental evidence also suggests a stimulatory role. Here we report a controversial influence of glucocorticoids on CFTR mRNA-expression and channel activity depending on the analysed cell type. We used RT-PCR and Ussing-Chamber measurements to analyze the CFTR. In subbronchial gland cell-derived Calu-3 cells dexamethason (D: 100 nM) has little influence on CFTR mRNA-expression, but increases the channel activity significantly. However, in fetal distal lung epithelial (FDLE) cells from rat fetuses, the mRNA-expression is dramatically reduced by D and the electrophysiological activity diminished accordingly. A difference between the two cell types is the expression of ENaC in FDLE-cells. It is known that CFTR is a regulator of ENaC activity, but our experiments suggest that ENaC also regulates CFTR and reduces its activity upon D treatment. Further analysis will approach this assumption in more detail. However caution is necessary for using glucocorticoids in inflammatory CF-associated complications, because channel reduction might worsen the clinical outcome.

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POSTER 219

Quantitative in-vivo, ex-vivo, and in-vitro cell analyses

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Cells from different sources are used for cell therapy. But how pure are they or do they need to be respectively? What cell types at which differentiation status are they actually and what functions do they exhibit? This information is important to have and might be inevitable with upcoming regulations in cell therapy. Beside viability tests, cells' identity has to be checked in order to meet criteria for medicinal products. Detailed cell characterization can be done with different technologies. Flow cytometry (FCM) is well known, can be highly multiplexed and is able to analyze thousands to millions of cells in a short period of time. However, it is restricted to cells in suspension. For the analysis of cells in culture or tissue sections Image cytometry is more appropriate. It generates the same quantitative data as FCM and is capable of multiplexing as well. With both methods, cells can be investigated on a single cell level. Subsequent in-vivo imaging allows for identification of cell clusters in live animals. Administered cells can be monitored over time enabling investigation of biodistribution, retention time, and biological effects. While most cell analysis techniques rely on fluorescence detection, impedance flow cytometry do not need any label at all. Dielectric properties such as membrane capacitance and cytoplasm conductivity are analyzed and reflect membrane properties and cell function, which in turn correlate with physiological differences between cells or pathological changes in cells over time. Irrespective of the used technology, detailed cell characterization is of particular importance for cell therapy.

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POSTER 220

Investigations on structure and functions of microbial communities via proteomic approaches

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The fast development of methods in the last decades created new fields of research which brought much knowledge for microbiology. Especially with emergence of the omics-techniques like genomics, transcriptomics, proteomics and metabolomics, deep insight into microbial life could be gained. But single microorganisms rarely occupy habitats alone and there is still a big lack of knowledge about microbial communities. Questions about the microbial composition and the key players for different metabolic pathways have to be solved. Modern proteomics has the means to answer these questions. The "simple" identification of proteins in environmental samples can show the phylogenetic pattern which is present in the ecosystem of interest. Further information can be gained by Protein-SIP experiments. The environmental samples or cultures are incubated with substrates labelled with stable isotopes. These would usually be 13C or 15N labelled substrates. After incubation the percentage of incorporation into the proteins can be calculated and thus key players for the degradation of e.g. pollutants can be identified. Also carbon or nitrogen fluxes can theoretically be visualized or verified by this approach. How proteomics in general and especially Protein-SIP experiments can or already did help, respectively, in answering questions regarding microbial communities will be illustrated in the following examples.

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POSTER 221

Conflicting Impact of Glucocorticoids and Female Sex Steroids on Alveolar Epithelial Sodium Transport

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Female sex steroids, as well as glucocorticoids exert stimulatory effects on epithelial sodium transport, including increases in mRNA-expression of the participating ion transporters (epithelial sodium channel – EnaC and Na,K-ATPases) and their electrophysiological activity. However, it is still unknown how the combination of female sex steroids and glucocorticoids influence the sodium transport responsible for alveolar fluid clearance. To address this issue we isolated alveolar epithelial cells from 18-19-day gestational age rat fetuses and seeded them on permeable supports. The cells were grown in serum-free media supplemented with dexamethasone (D: 100 nM) and different concentrations of estradiol (E2: 0 – 1 μM) and progesterone (P: 0 – 2.8 μM). Surprisingly RT-PCR analysis showed a decrease of the α- and γ-ENaC subunit in the P-rich media. The Na-K-ATPase β_1-subunits and the β-ENaC subunit expression were not altered. Also the short-circuit currents (I_{SC}) were not further increased through the combination of D with E2 and P. Therefore, we conclude that P antagonizes the stimulatory effects of glucocorticoids on gene expression, supposedly through binding to the same enhancer element as D. Hence we cannot find additive effects of glucocorticoids and sex steroids on sodium transport, but rather discovered a diminishing impact, as shown by RT-PCR.

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POSTER 222

Mutational Screening of LHX3 Regulatory Regions in Patients with Combined Pituitary Hormone Deficiency (CPHD)

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The transcription factor LHX3 plays an important role in cell specification of the pituitary gland and the nervous system. Mutations within coding regions of the *LHX3* gene were shown to cause autosomal recessive forms of CPHD. Recently, *cis*-acting elements have been identified that are involved in the spatio-temporal control of LHX3 expression.
In the present study the occurrence of genetic variations within regions regulating the expression of LHX3 isoforms was investigated in patients with CPHD.
100 CPHD patients with clinical manifestations comparable to individuals carrying homozygous *LHX3* mutations were selected. 5 regions supposed to be involved in the regulation of LHX3 expression were selected. Fragments were PCR amplified, pre-screened by denaturing HPLC followed by dideoxy-sequencing of conspicuous PCR products. Previously, mutations within the coding sequence were excluded.
3 novel heterozygous single nucleotide variations (SNVs) were identified in 4 different patients. One SNV found in 2 patients occurred combined with known SNPs. 2 SNVs map to the promoter or 5'-UTR of isoform LHX3A and one resides within a putative downstream enhancer element.
Our mutational screening revealed 3 novel SNVs. The functional and pathophysiological relevance remains to be elucidated. Failure to detect homozygous sequence aberrations might be due to i) the relatively small patient collective; ii) homozygous mutations within regulatory sequences might manifest distinct from classical *LHX3* mutations or iii) although least likely, homozygous *LHX3* mutations in regulatory regions might be incompatible with life.

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POSTER 223

Control Function – Towards Activatable SDF-1α Analogues

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SDF-1 (CXCL12) is a CXC chemokine, but its distinct chromosomal localization and low homology to other group members makes this protein unique along the CXC chemokines. It is constitutively expressed in many tissues, signals through CXCR4 and at least binds to CXCR7; however the role of this recently discovered receptor is not fully understood, yet.
SDF-1 attracts stem cells in a concentration dependent manner, in particular guides HPCs to the bone marrow and modulates neurons and their progenitors. Furthermore, it participates in embryonic heart, brain and intestine development as well as in metastasis of CXCR4/7 positive cancer cells toward SDF-1 expressing tissues. This broad range of biological functions makes this protein interesting as a drug candidate in regenerative medicine.
Herein we present a bacterial expression and refolding strategy, which allows the reliable preparation of native and mutated SDF-1 variants. We stabilised the N-Terminus by the point mutation S4V against MMP-2 as described recently. Further, we added an AAV motif at the N-Terminus and performed enzyme assays with subsequent SDS-PAGE and MS analysis, which revealed resistance against the MMP-9 but not the neutrophile elastase. In a Jurkat cell migration assay this variant is inactive, however in the presence of DPP-4, which cleaves off the alanine-alanine motif, the remaining V-SDF-1 shows activity as a partial agonist.
In conclusion, we developed a robust SDF-1 analogue, which responds to the presence of an inflammation-related enzyme by gain of function.

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POSTER 224

Molecular signatures of long non-coding RNAs (ncRNAs) in breast cancer patients

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Background: In several studies it has been shown that the expression of small ncRNAs, like miRNAs, is associated with diseases including cancer. However, the group of long ncRNAs has drawn less attention despite their genome-wide distribution. These long ncRNA genes contribute substantially to regulatory features ranging from epigenetic control and transcriptional regulation.
Material and methods: For this pilot study we selected 25 breast carcinomas representing the five clinically relevant tumor mRNA expression subclasses as well as normal breast tissue from breast reduction operations. Total RNA from these samples was analyzed utilizing the custom nONCOchip. The nONCOchip covers both, experimentally identified cancer related ncRNAs of oncogenes (STAT-3), tumor-suppressor genes (p53), and cell cycle controlled genes, as well as known or predicted non-coding RNAs from public databases.Results: The expression analyses of long non-coding RNAs showed that various ncRNAs are expressed in breast tumors. Long ncRNAs exhibit heterogeneous patterns of expression in breast tumors, whereupon the largest differential expression is observed between Luminal A (most common type of breast cancer that tends to have a good prognosis) and Basal-like (associated with poor prognosis) breast tumors.Acknowledgements: We thank Bjørn Naume for providing the breast patient tumor material as well as Ida Bukholm and Margit Hesla Riis for providing the normal breast material.
(*KR and LOB contributed equally to this study and should be regarded as joint first authors).

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POSTER 225

MicroRNA-31 is cell cycle-regulated

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Non-coding RNAs (ncRNA) represent a considerable portion of the mammalian transcriptome and are involved in a variety of fundamental cellular processes. MicroRNAs are small ncRNAs and pleiotropic regulators of gene expression. Some are known to be aberrantly expressed in cancer and other diseases. In lung cancer miR-31 functions as oncogene and in breast cancer miR-31 acts as a tumour suppressor by decreasing the rate of metastasis. We found that miR-31 is significantly over-expressed in colon cancer compared to normal colon tissue. Furthermore, using the UCSC-Genome Browser we could identify the ncRNA *LOC554202* locus as gene host for the *miRNA-31* gene. In order to understand the function of ncRNAs, one important line of investigation is to look at regulation of their expression. We observed that the *LOC554202* ncRNA is differentially expressed during cell cycle. Its RNA level increases dramatically in the G_1-phase. Importantly, miR-31 is also differently expressed during the cell cycle. The expression level of miR-31 is at a maximum in S-phase. Here we demonstrate for the first time a cell cycle-dependent expression of miR-31. Additionally, we identified the promoter region of the gene for ncRNA *LOC554202*. In chromatin immunoprecipitation (ChIP) experiments we demonstrated that this promoter is responsive to the E2F cell cycle-transcription factor. Taken together, our findings suggest that miR-31 and LOC554202 are co-regulated during cell cycle. These results provide new insights into the regulation of ncRNAs and could be of general importance to understand the mechanism by which miRNAs act in cancer or other diseases.

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POSTER 226

Development of Novel Artificial Metalloenzymes for Enantioselective Catalysis

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Over the years enantioselective catalysis gained more and more in importance especially in phamaceutical, chemical and food chemistry. Typical industrial catalysts comprising 4d or 5d elements have almost no natural counterparts. The superior enantioselectivity and substrate specifity of enzymatic catalysts can usually not be reached by conventional small molecule catalysts. A combination of the enantioselectivity of an enzyme with a 4d or 5d metal centre would lead to a new and unique type of catalysts which combine the superior properties of the enzyme with special catalytic properties of these transition metal ions.
Based on the structure of RNase S we intend to design an enantioselective catalyst. The RNase S system provides a framework to incorporate a nonnatural catalytic centre into a protein environment using peptide protein complementation (RNase S = S-protein + S-peptide). Reassembling the RNase S system with S-peptides containing artificial amino acids leads to novel unique metal binding sites e.g. for asymmetric reduction of olefins. A model system of RNase S with two cysteines was already created, in which the metal binding was confirmed using x-ray crystallography.

Assoziation: PbF III

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POSTER 227

Yeast hexokinase (KlHxk1) function is controlled by oligomerization and covalent modification

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The crystal structure of the unique hexokinase 1 (KlHxk1) from the yeast *Kluyveromyces lactis* has been determined from eight different crystal forms. A ring-shaped homodimer is found in five crystal forms, as also known from solution studies by small-angle X-ray scattering. The physiological dimer has a head-to-tail arrangment, while the small domain interacts with the opposite large domain and vice versa. Favourable contacts from the first 15 N-terminal amino acids as beeing part of the large domain are required for interaction with the small domain. The observed head-to-tail dimer explains the reduced activity of the homodimer in comparsion to the monomeric enzyme and the influence of substrate and product molecules on dimer formation and dissociation. In detail, the symmetrical dimer demonstrates that phosphorylation of conserved residue Ser-15 causes electrostatic repulsions by nearby negatively charged residues of neighboring subunit which gives rise to the dissociation of homologous dimeric hexokinases KlHxk1 and ScHxk2 (baker's yeast). Two different glucose-bound crystal forms allow to show substrate binding to the open conformation as followed by classical domain-closure motion of yeast hexokinases. The study expands the current perception of glucose signalling in yeast and adds to the induced-fit model by including aspects of N-terminal phosphorylation and dissociation of homodimeric yeast hexokinases.

Assoziation: PbF III

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POSTER 228

Molecular architecture and structural basis of allosteric regulation of eukaryotic phosphofructokinases

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

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[2] Sträter N. et al., Molecular architecture and structural basis of allosteric regulation of eukaryotic phosphofructokinases; *FASEB Journal* 2011; 25; in press

Assoziation: PbF III

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POSTER 229

Structural Studies on Eukaryotic Phosphofructokinases

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Type VII glycogen storage disease (e.g. Tauri disease) is caused by mutations in the gene for muscle phosphofructokinase (PFKM). In patients with Tauri diseases a complex systemic disorder is induced by intertwine of marked alterations in muscle bioenergetics and the erythrocyte metabolism. Phosphofructokinase (Pfk) catalyses the formation of fructose 1,6-bisphosphate from fructose 6-phosphate and MgATP in prokaryotic and eukaryotic cells. The catalytic activity is tightly regulated in a wide variety of organisms by diverse positive (e.g. AMP) and negative (e.g. ATP) effectors. The structural basis of the catalytic steps and allosteric changes of prokaryotic Pfks has been characterized early based on crystal structures of *Escherichia coli* Pfk. Bacterial Pfks have a homotetrameric structure of D_2 symmetry. Each monomer contains one active site with the ATP and fructose 6-phosphate binding sites and an effector binding site for PEP or ADP. The binding sites for F-6-P and the effectors are located at the interface between subunits. Eukaryotic Pfk evolved by a process of tandem gene duplication and fusion to yield a protein that has a multiple size of their bacterial counterparts, a much more complex structural organization and allosteric regulation. The Mammalian Pfks smallest active form is a tetramer of ~330 kDa. All mammalian enzymes show a tendency to form larger aggregates and they can form isoforms in a tissue-dependent manner. We plan to characterize the molecular basis of allosteric regulation of the human Pfk-isoforms (*M, L and P*) by Small Angle X-ray Scattering and X-ray crystallography.

Assoziation: PbF III

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POSTER 230

Structure-Activity Relationships of hNPFF2 Receptor

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The G protein-coupled $NPFF_{1/2}$ receptors were discovered in 2000/2001 [1]. They belong to an opioid-modulatory system, interact with the inhibitory G_a protein and are stimulated by neuropeptide FF (NPFF, FLFQPQRF-NH_2). Three additional peptides with related sequences are known in humans: NPAF, NPVF and NPSF. All peptides exhibit a conserved structure, the RFamide peptide motif and are $NPFF_{1/2}$ receptor ligands with different nanomolar affinities.
As all RFamide peptides contain the RFamide motif, which is known to be essential for ligand binding as well as signal transduction, we hypothesized a similar ionic interaction of the Arg^7 of the NPFF ligand. Furthermore the role of the Phe^8 within the RFamide motif should be elucidated.
To investigate the ligand-receptor interaction, the cDNA of human $NPFF_2$ receptor was cloned into an eukaryotic expression vector. Furthermore, NPFF and several analogues at positions of the Arg^7 and Phe^8 were synthesised by solid phase peptide synthesis. To investigate the ligand-receptor-interaction, an IP_3 signal transduction assay was performed, applying a chimeric $G\alpha_{qi4}$-protein [3]. We could confirm that Arg^7 and Phe^8 of the NPFF play a major role in ligand binding to the $hNPFF_2$ receptor and its signal transduction. Our results indicate on a molecular level, which ligand modifications have an impact on binding affinity.

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POSTER 231

Analysis of mice brains transplanted with adult stem cells using western blotting

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Alzheimer is one of the most common forms of dementia in the elderly. Alzheimer is a neurodegenerative disease and no therapy is currently available. The cause of the disease is not yet fully understood, but there are some hypotheses. One of the risk factor for Alzheimer is aging. Aging, oxidative stress and neuronal loss are closely linked and might play a role in Alzheimer. Stem cell therapies against Alzheimer are being investigated in the moment. Most studies investigate the effect of neuronal stem cell transplantations on Alzheimer.
We treated aged mice and Alzheimer mice with different adult stem cells. The stem cells were injected systemically and after 7 days the animals were killed and analysed. Proteins from several organs such as the hippocampus were isolated and analysed using western blott. We investigated the amyloid precursor protein, superperoxide dismutase 1 and 2, the receptor for advanced glycation end products and catalase.

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POSTER 232

Metabolic networks in soil microbial communities investigated by protein-based stable isotope probing

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It is generally known that bacteria and especially fungi greatly contribute to the degradation of plant-derived materials like cellulose and lignin by expressing numerous extracellular enzymes. However, the individual roles of fungi and bacteria and their interactions within these processes are not well understood to present day.
By applying Protein-SIP (protein-based stable isotope probing) to leaf litter degrading fungal and bacterial communities the project is highly expected to provide a closer insight towards the identification of metabolically active species, metabolic fluxes and even metabolic networks within soil-related degradation processes of plant material.
In preliminary experiments specific extracellular enzymes could be successfully extracted and identified out of the supernatant of fungal pure cultures incubated with leaf litter from corn plants. Further advanced experiments will be based on the Protein-SIP method involving the incubation of leaf litter from either ^{13}C or ^{15}N labeled tobacco and corn plants with microbial communities (fungal and bacterial) associated with soil.

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POSTER 233

Untersuchung der Eignung artifizieller extrazellulärer Matrizes zur Unterstützung von Wundheilungsprozessen – eine quantitative Proteomstudie

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Die Zielstellung des Sonderforschungsbereiches Transregio 67 ist die Erforschung und Weiterentwicklung von artifiziellen extrazellulären Matrizes (aECM) als Implantatmaterialien zur Unterstützung der Wundheilung bei Haut- und Knochenverletzungen. Im Rahmen dieser Studie wurden Mischmatrizes bestehend aus Kollagen und nicht sulfatierter bzw. sulfatierter Hyaluronsäure im Zellmodell getestet. Die zelluläre Antwort von Fibroblasten wurde auf Proteinebene mittels SILAC („*stable isotope labeling by amino acids in cell culture*“) quantitativ untersucht. Hierfür wurden alle Proteine in Zellkultur mittels isotopenmarkierten Arginin und Lysin markiert und anschließend 1 bzw. 5 Tage auf den neuen Matrixmaterialien bzw. auf einer Kontrollmatrix (Polystyrol) kultiviert. Nach der Zelllyse wurden die Proteine mit dem Kontrollansatz 1:1 gemischt. Mittels nano-HPLC/nano-ESI-MS/MS konnten potentielle matrix-induzierte Änderungen der Expressionlevel von mehr als 700 Proteinen quantifiziert werden. Auf der Grundlage einer Clusteranalyse der signifikant regulierten Proteine anhand deren zellulärer Funktionen wurde die Eignung der Matrizes bewertet.
Sowohl die sulfatierte als auch die nicht sulfatierte aECM fördern das Wachstum der Zellen. Auf Proteinebene kann eine signifikante Steigerung des Energiestoffwechsels der Fibroblasten festgestellt werden. Auch bei einer längeren Kultivierungszeit werden keine Proteine reguliert, welche als Marker für eine Stressantwort gelten. Somit liegt kein Indiz für verstärkte Abstoßungseffekte vor. Vielmehr deutet eine verminderte Expression von Apoptosemarkern auf eine verbesserte Verträglichkeit hin.

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POSTER 234

Comparative methods for the identification of protein-RNA-interactions

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In recent years, the involvement of long non-coding RNAs in epigenetic processes has been discovered. However, the function of the majority of these ncRNAs remains still elusive. There is evidence that some long ncRNAs participate in histone modification processes. Based on a genome-wide tiling array study, we found several long ncRNAs to be differentially expressed upon cytokine stimulation. In order to identify ncRNAs associated with chromatin remodeling machinery, we isolate relevant multi-protein complexes from cell lysates by RNA immunoprecipitation (RIP). Interacting RNAs are coprecipitated and identified using customized microarrays interrogating high numbers of regulated ncRNAs. Subsequently, molecular studies will be performed to reveal the function of those ncRNAs found to be associated with multi-protein complexes. In this work, different RIP methods are tested against each other in regard to distinct aspects.

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POSTER 235

Structural studies of DnaK in complex with proline rich antimicrobial peptides

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

Assoziation: PbF III

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POSTER 236

In vitro CCA-addition on pathology-associated mutated human mitochondrial tRNACys and tRNAGln

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Many point mutations in human mitochondrial tRNA genes are known to correlate with a variety of human mitochondrial diseases. One of these is the acquired idiopathic sideroblastic anemia (AISA). This syndrome is characterized by a defective heme synthesis in mitochondria, as the supply of ferrous iron (Fe^{2+}) for incorporation into protoporphyrin IX to form heme is disturbed. In 104 patients with acquired idiopathic sideroblastic anemia, 17 base substitutions in tRNA genes encoded in the mitochondrial genome were identified. As it is known for several other mitochondrial tRNA mutations, these base substitutions can lead to deficiencies in tRNA processing like 3' end cleavage, CCA-addition and aminoacylation; reduction of tRNA stability and, consequently, translational defects. As a result, these effects may contribute to an inhibition of protein synthesis in mitochondria, affecting the composition of respiratory chain subunits which are involved in mitochondrial iron supply for heme synthesis.
Using quantitative *in vitro* assays, we investigate the influence of such human mitochondrial tRNA mutations on the CCA-addition catalyzed by tRNA nucleotidyltransferase. In this study, two of the 17 AISA point mutations were analyzed by detailed kinetic analysis. Whereas the mutation C4339T in $tRNA^{Gln}$ does not affect CCA-addition, point mutation C5821T in $tRNA^{Cys}$ causes a 3-fold decrease in the CCA-addition efficiency. A similar reduction in CCA-addition was already described for other mitochondrial tRNA mutations with pathogenic potential. Hence, it is possible that the observed increase in K_m might contribute to the molecular pathogenesis of the acquired idiopathic sideroblastic anemia.

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POSTER 237

NTPDases of microbial pathogens

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Nucleoside triphosphate diphosphohydrolases (NTPDase) catalyze the hydrolysis of extracellular nucleotides. These enzymes are found in mammals as well as in microbial pathogens where they are thought to modulate the host-response to an infection by hydrolysis of host ATP. We aim to determine crystal structures of microbial NTPDases to use them for structure-guided drug design.
For the production of NTPDases from Legionella pneumophila, Schistosoma mansoni, Toxoplasma gondii, Trichomonas vaginalis and Trypanosoma cruzi we have established E. coli expression systems. NTPDases of Toxoplasma gondii and Trichomonas vaginalis were expressed as insoluble inclusion bodies. Using rapid dilution systems it was possible to refold the denatured protein to an active form. NTPDase from Legionella pneumophila was expressed in soluble form by secretion to the periplasm. Subsequently the proteins were purified by chromatographic methods and applied to crystallization screens. We were able to determine the crystal structures by different phasing methods, namely SAD and MIRAS. Furthermore, the proteins could be crystallized in complex with substrate analogs. These crystal structures provide insight into the domain motion of the enzyme and broaden our knowledge about the catalytic mechanism and substrate specificity (as well as promiscuity) already derived from the crystal structure of rat NTPDase2.

Assoziation: PbF III

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POSTER 238

A "One Pot" Combination of Expressed Protein Ligation and Cu(I)-Catalyzed Azide/Alkyne Cycloaddition to Immobilize Proteins

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The 1,3 dipolar cycloaddition between alkynes and azides was first developed by Huisgen and co-workers. In 2002 the groups of Meldal and Sharpless independently reported that Cu(I) catalyzes this reaction. The use of Cu(I) decreased the reaction time and allowed mild reaction conditions. Until now, the Cu(I)-catalyzed alkyne/azide cycloaddition (CuAAC) has been applied in many fields of organic synthesis, pharmaceutical chemistry and for the modification of biomolecules.
We recombinantly expressed two model proteins in *E. coli* by using the IMPACT® system (Intein mediated purification with an affinity chitin-binding tag). Furthermore, a short peptide with an N-terminal cysteine and an alkyne moiety was synthesized by standard Fmoc-solid phase peptide synthesis. After purification the target protein thioesters were ligated to the peptide via expressed protein ligation. The alkyne function was then used to couple the ligation product to an azided support by CuAAC. The combination of these two techniques in a "one pot approach" leads to active enzymes with excellent yields.
Recombinant proteins were characterized by MALDI-TOF analysis, kinetic assay and SDS-PAGE. The characterization of the peptide was realized by MALDI-TOF and RP-HPLC. Immobilized proteins were identified by ELISA and tryptic digestion and subsequent peptide mass fingerprint analysis.
We have achieved a successful immobilization of two model proteins on an azide modified support. Furthermore the immobilized proteins feature their native conformation and remain biologically active. Accordingly, CuAAC was established as a promising ligation method.

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POSTER 239

In vitro evolution of CCA-adding enzymes via in vivo selection

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CCA-adding enzymes are specific RNA polymerases that incorporate the nucleotide triplet CCA to the 3' end of tRNAs. Only a tRNA with such a 3' terminus represents a functional transcript that can be aminoacylated and participate in protein synthesis.
The mechanism of the RNA/DNA template-independent CCA-addition, including a specificity switch from CMP to AMP incorporation, is still a matter of debate. However, it is known that a small flexible loop in the catalytic core is necessary for the terminal A addition. This loop might work as a lever that interacts with residues of the NTP binding site and forces the binding pocket into an open conformation for ATP accommodation. Despite such an important function, this structural element shows no conservation at the sequence level between CCA-adding enzymes of different phylogenetic origin. However, within individual phylogenetic groups, the loop region shows consensus sequences typical for the individual genera, leading to the existence of incompatible loop families that interfere with CCA-addition when inserted into the context of a phylogenetically distinct CCA-adding enzyme.
To investigate the role of this region in more detail, an evolutionary approach is applied in which the amino acid composition of the loop is randomised. Loops leading to fully functional CCA-adding enzymes can be detected by an *in vivo* selection system.
The identification of alternative loop sequences that are compatible with the enzyme's activity will help us to identify and understand the contribution of this unusual catalytic core element to the polymerization reaction catalyzed by CCA-adding enzymes

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POSTER 240

Studies on the Structure and Dynamics of the Tubulin Binding Domain of Tau in Complex with Phospholipid Membranes

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The microtubule-associated protein tau is found aggregated into paired helical filaments (PHFs) in neurofibrillary deposits in patients of Alzheimer's disease. In solution tau is intrinsically unstructured. However, the tubulin binding domain consisting of three or four 31-32 amino acid repeat regions is known to have a significant β-structure propensity and to make up the proteolysis resistant core of PHFs. Here we studied the structure and dynamics of the three-repeat domain of tau (i.e. K19) when bound to phospholipid membranes consisting of phosphatidylcholin and phosphatidylserin. K19 binds with micromolar affinity to phospholipids as measured by fluorescence spectroscopy. The interaction is driven by electrostatic forces and induces the formation of a stable secondary structure as shown by CD spectroscopy and solid-state magic angle spinning NMR spectroscopy. Isotropic ^{13}C chemical shift values for all valine and leucine residues are consistent with a β-structure. In addition, motionally averaged ^{1}H-^{13}C dipolar couplings indicate a high rigidity of the protein backbone. The structure formation of tau K19 was shown to depend on the charge density of the membrane. Increasing the content of negatively charged phosphatidylserine leads to a gain in the α-helix structure propensity and redistribution of K19 along the membrane which was studied by fluorescence quenching and static ^{31}P and ^{2}H NMR spectroscopy. Our results provide the first structural insights into the membrane bound state of tau K19 and support a potential role of phospholipid membranes in mediating the physiological and pathological functions of tau.

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POSTER 241

Sequence specific analyses of a real-time PCR assay for the differentiation of Candida and Aspergillus species

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Fungal infections significantly increased over the past two decades and are a major cause of morbidity and mortality in immunocompromised patients. In Europe, the clinically most important opportunistic mycoses are caused by *Aspergillus* and *Candida* species. Conventional diagnostic tests such as blood cultures or galactomannan ELISA do not always show sufficient sensitivity for the early diagnosis of invasive fungal infections. A rapid diagnosis and species characterisation before therapeutic intervention would be beneficial. For this reason, a real-time PCR assay was developed for the detection and identification of *Candida species*. This test allows the differentiation between *Candida albicans*, *Candida parapsilosis, Candida glabrata, Candida tropicalis and Candida dubliniensis* by using the LightCycler PCR system. By subsequent melting curve analysis, conclusions are drawn on the *Candida species*. The real-time PCR is a useful tool for quick identification of different species, we also used the test to identify various *Aspergillus species*. We were able to show that the differences in melting temperatures ascribe to the sequence differences at the DNA level. The sequence analysis was performed and compared with in silico data. It was shown that with lower melting temperatures more base substitutions were found between the different species. In summary, we describe here a real-time PCR assay, which can simultaneously detect differences in melting temperatures of clinically relevant *Candida* and *Aspergillus* species. This assay allows a rapid analysis of critical patient samples in the future.

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POSTER 242

Luminescence sandwich ELISA for measurement of tissue transglutaminase

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Tissue transglutaminase (tTG) belongs to a family of calcium-dependent enzymes that catalyze cross links between protein(s) and / or primary amines. These isopeptide bonds stabilise intra- and extracellular proteins that executing a variety of physiological functions. The enzyme ubiquitously expressed and its synthesis is stimulated under a variety of pathological conditions. However, the role of tTG in the development of disease is poorly understood. Several studies showed that tTG is aberrantly expressed in the course of neurodegenerative disorders. Therefore, the detection of tTG protein in biological samples is important to evaluate more precisely the pathophysiological role of this enzyme.
In our sandwich ELISA, tTG is captured by the monoclonal antibody (mab) 3C10 and detected by biotinylated mab 10F3, followed by incubation with peroxidase conjugated streptavidin. Subsequently, bound tTG is visualized by peroxidase reaction applying a luminescence substrate.
To our knowledge, this is the first ELISA using a combination of two specific mabs directed against human tTG. The detection limit was 40 pg per mL. The enzyme could be detected in crude cellular lysates and tissue homogenates of man and mice suggesting cross reactivity of the mabs with murine tTG. Recovery of spiked recombinant tTG from biological samples was high. Furthermore, increased amounts of tTG could be observed after stimulation of cultured cells by retinoic acid and interferon gamma, known inducers of the tTG.
In conclusion, the new luminescence ELISA may be successfully applied for investigation of disorders associated with inadequate tTG expression.

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POSTER 243

ESR analyses of domain movements in tRNA nucleotidyltransferases during CCA addition

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The single-stranded 3'-end of tRNA molecules is a highly conserved structural element and consists of the invariable nucleotide sequence C-C-A which is necessary for a suitable charging of the tRNA with the corresponding amino acid. As this sequence is not encoded in many tRNA genes, it has to be added posttranscriptionally by tRNA nucleotidyltransferase (CCA-adding enzyme). This enzyme is a unique RNA polymerase that synthesizes a specific sequence without using a nucleic acid as a template.
Instead, the enzyme carries a set of amino acids in a single nucleotide binding pocket which forms a protein-based template selecting the individual nucleotides CTP and ATP in a sequence-specific way. During this reaction, the size of the binding pocket has to be adjusted after CC-incorporation in order to accommodate the larger ATP. We have experimental evidence, that a flexible loop might serve as a hinge during CCA-addition, that allows a movement of individual domains of the enzyme, which is necessary for the conformational rearrangements after CC-incorporation. However, the mechanism underlying this specificity switch in and the actual role of the loop region during CCA-addition is not understood.
In this study, we are focusing on several approaches to investigate the specificity switch of the binding pocket in CCA-adding enzymes using ESR analysis as well as computer simulations. Using a combination of mutated enzyme variants and ESR investigations, we hope to correlate defined domain movements with individual reaction and substrate interaction steps during the polymerization reaction of these fascinating enzymes.

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POSTER 244

The fidelity of the Archaeoglobus fulgidus CCA-adding enzyme is not dependent on the highly conserved arginine R224

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During protein biosynthesis tRNAs are charged with their respective amino acids at the tRNA's 3' terminus ending with the sequence CCA. In most organisms this CCA triplet is synthesized by CCA adding enzymes which fall into two structurally distinct classes. Yet, these enzymes share a common active site signature including a highly conserved arginine which functions as an amino acid template for CCA synthesis. However, replacing this arginine by alanine has a less dramatic impact on the accuracy of CCA synthesis than expected. 46 to 63 % of analyzed tRNA sequences from assays with *Escherichia coli* and *Homo sapiens* CCA-adding enzymes carried a correct complete or partial CCA terminus, while tRNA 3' ends with misincorporated nucleotides were not further elongated. Based on these observations, a back-up mechanism for CCA addition in class II CCA-adding enzymes had been proposed.
Here, we show that an R to A mutation of the corresponding conserved arginine residue (R224) in the class I CCA-adding enzyme of *Archaeoglobus fulgidus* has no detrimental effect on the fidelity of the reaction. *In vitro* nucleotide incorporation assays with $tRNA^{Phe}$ variants followed by sequencing revealed that not only the wild type enzyme but also the R224A mutant form of the enzyme synthesized correct complete or partial tRNA 3' termini. As it was shown that the tRNA primer contributes to the nucleotide selection and therefore to the enzyme's specificity, it seems that class I enzymes use their substrate as an external specificity module for the reaction.

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POSTER 245

Wnt/ß- catenin and hedgehog signalling – crosstalk and feedback loops between two morphogenetic pathways in one organ

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In signaling pathways, feedback loops can influence the dynamic behavior of the involved components. In case of morphogenetic signaling, the crosstalk between different pathways may lead to complex feedback loops of variable length.
Wnt/ß-catenin signaling has recently been shown to play an important role in balancing hepatic metabolism, acting as a master regulator of metabolic zonation in adult livers. When analyzing the transcriptional response of stimulated or interrupted Wnt/ß-catenin signaling in the liver, we found evidence for novel interactions with hedgehog signaling forcing both pathways to change their activity in parallel. This is highly relevant for understanding how morphogenetic this signaling controls the liver zonation. The poster we present here, shows different feedback loops within and among both pathways based on own results by using mice with conditional interruption of hedgehog signaling and RNA interference experiments in cultivated hepatocytes as well as on published data. The three Gli proteins Gli1, Gli2, and Gli3, as essential mediators of hedgehog signaling, form a special core module for crosstalk and other interactions. One novel finding is our discovery of feedback inhibitions by Gli1 on the expression of its inducing factors Gli2 and Gli3. Also is known that the Gli1 mRNA is stabilized by Wnt/ß-catenin signaling. Furthermore examples of feedback loops besides these two pathways are the nuclear receptors LXR and PPARγ which play an important role in metabolic regulation.
The Crosstalk between the Wnt/ß-catenin and hedgehog signaling seems to affect the zonation of the adult liver.

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POSTER 246

Activation and B(a)P exposure jointly regulate miRNA expression in Jurkat T cells as revealed by miRNA arrays and Proteomics

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In a time where environmental pollutants, like Benzo(a)pyrene (B(a)P), are a widely discussed topic, also the function of the immune system gains importance, since these pollutants have been shown to affect the immune system even at low concentrations. As B(a)P is a product of incomplete combustion it occurs ubiquitously in smoke resulting from the burning of organic material, hence it can be found in char-grilled food as well as in tobacco smoke. It has been shown that B(a)P induces gene mutations, DNA damage and other genotoxic effects in vitro and in vivo. The induced changes in gene expression result in altered protein expression.
MicroRNAs (miRNAs) belong to the group of non-coding RNAs that do not encode for proteins but function directly at the RNA level to regulate the expression of genes. There is emerging evidence that miRNAs play a major role in regulating the differentiation and also the function of immune cells.
To investigate the influence of miRNAs on the regulation of protein synthesis altered upon B(a)P incubation and cell activation, differentially expressed miRNAs were identified by microRNA microarrays and differentially expressed proteins were examined with DIGE and LC-MS (LTQ-Orbitrap). The potential interactions between the regulated miRNAs and the mRNAs of the differentially expressed proteins were analyzed by target prediction programs.

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POSTER 247

Stat3-regulated non-coding RNAs in tumor cells

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The roles of Stat3 are complex, because Stat3 can have opposing effects on different cells and there is still a lack of understanding how Stat3 can generate multiple outcomes at gene expression level. Aberrant Stat3 signaling plays an important role in pathogenesis of many neoplasms, by supporting cell cycle progression and survival of tumor cells. Our group has previously reported the obligatory role of Stat3 for the IL-6-mediated anti-apoptotic signal in the human multiple myeloma cell line INA-6. However, there is evidence that induction of protein-coding genes by Stat3 alone cannot account for its oncogenic properties. In order to identify IL-6/Stat3-regulated transcripts globally, a genome-wide transcriptome analysis in INA-6 cells was conducted. This study revealed the existence of approximately 20 rather long ncRNAs that are regulated by IL-6 in addition to the known protein-coding target genes. Six of these transcripts were chosen for further analysis. Their induction by IL-6 in INA-6 cells could be confirmed by real-time PCR. Furthermore, all analyzed IL-6-regulated transcripts are like many long ncRNAs located within the nucleus, which suggests that they might have an influence on gene expression. Further analyses revealed that expression of some of these transcripts appears to be almost exclusively restricted to cells of B-cell origin whereas the others are found in diverse tissues. All these findings support functional roles of the analyzed ncRNAs in cellular processes. Additionally there is evidence that these transcripts may play a role in tumorigenesis and could be potential markers of specific malignancies.

Funding: life

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POSTER 248

Functional characterization of a novel homozygous mutation in the Insulin-Like Growth Factor-I Receptor

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The IGF-1 receptor (IGF-1R) plays an essential role in intrauterine and postnatal growth regulation. To date, several heterozygous mutations in the IGF-1R leading to IGF-1 resistance have been described. In mice, homozygous Igf-1r knock out results in perinatal death due to respiratory failure. Aim of the study is to explore the impact of a novel homozygous IGF-1R mutation identified in a girl born small for gestational age (SGA), by genetic, comparative and experimental approaches. The girl was born with a length of -3.16 SDS and a weight of -0.95 SDS. Clinical examination revealed no additional phenotypic abnormalities. IGF-1 and IGFBP3 levels were elevated. Denaturing HPLC screening and direct DNA sequencing of the index patient's genomic DNA disclosed a homozygous *IGF-1R* mutation resulting in an amino acid exchange at position 56 from glutamic acid to aspartic acid (p.E56D). The highly conserved residue is located in the ligand binding domain (L1) of the receptor. *In vitro* analyses in R-cells transiently transfected with wild type or mutant receptor plasmids showed that the mutation results in a decreased autophosphorylation of the receptor in response to IGF-1 and a diminished protein kinase B/Akt activation compared to the wild type. In contrast, the mutation does not affect the expression of the receptor on transfected COS-7 cells, measured using flow cytometry. Assays to determine the IGF-1 binding properties of the receptor are in progress. Thus, the conservative amino acid substitution impairs IGF-1R function but does not result in a complete loss of receptor function and might therefore be compatible with life.

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POSTER 249

Analysis of the STAT3 interactome using SILAC

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Signal transducer and activator of transcription 3 (STAT3) is activated in response to a variety of cytokines and growth factors, among them IL-6. STAT3 activation is mediated by phosphorylation of tyrosine 705, leading to its translocation into the nucleus, binding to DNA and thereby activating genes that regulate cell proliferation, differentiation and apoptosis. In the context of IL-6 signal transduction, we are interested in the identification of novel STAT3-specific interacting proteins.
Therefore we combined Stable isotope labeling with amino acids in cell culture (SILAC) with stringent precipitation of biotinylated STAT3 and quantitative mass spectrometry analyses. SILAC is a simple and reliable method for comparative proteomic experiments based on metabolic labeling of proteins. Cells representing the two conditions of interest are grown in medium containing either 'light' (^{12}C) or 'heavy' (^{13}C) amino acids, respectively. The incorporation of labeled amino acids leads to a defined mass difference that can be found by mass spectrometry analyses. For high affinity precipitation, STAT3 is extended by a small tag derived from E.coli system that becomes biotinylated in vivo.
First, we showed that biotinylated STAT3 is transcriptionally active like the unmodified protein. Using the SILAC approach we found about 80 proteins which are putative interaction partners of STAT3. Preliminary results confirmed some interesting proteins and its influence in STAT3 transcriptional activity. The SILAC approach will also enable us to study how mutations, affecting STAT3 functions influence the STAT3 protein interaction network.

Funding: formel1

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POSTER 250

A rational approach to riboswitch design

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Riboswitches are RNA-modules able to regulate genes without the need for a protein. These short sequences are often found in the 5'-untranslated region of genes. They consist of an aptamer domain that is capable of binding even small ligands with high affinity and specificity and an expression platform, for example a transcriptional terminator. Once a ligand binds to the aptamer, this expression platform is structurally rearranged, usually resulting in gene activation.
Being remnants of the RNA world, riboswitches are still working in today´s organisms but do also offer various opportunities for current research. As aptamers can be selected for binding nearly every molecule of interest, there is great concern to establish new expression systems based on riboswitch function, e. g. for detection of contaminants in sea waters. However, most aptamers binding ligands *in vitro* are not capable of functioning as gene regulating riboswitches *in vivo* due to a lack of selection methods *in vivo*. This study therefore aims on the selection of RNA riboswitches in an *in silico* approach. In a secondary structure prediction we focus on transcriptional terminators that change their structure when a ligand is bound to an adjacent theophylline aptamer. Subsequently we screen for gene activation of a beta-galactosidase reporter gene by a set of *in silico* selected riboswitches *in vivo*. As some theophylline aptamers are known to be functional as a riboswitch *in vivo* this experiment is for evaluating if an *in silico* design of completely new riboswitches may be applicable for future research.

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POSTER 251

Modeling the Hinge Region of the TSH Receptor

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The thyroid stimulating hormone receptor (TSHR) belongs to the glycoprotein hormone receptors (GPHRs) a subfamily of the G protein-coupled receptors (GPCR). Due to its involvement in regulation of the thyroid gland, malfunctions of the TSHR are associated with several pathological conditions like hyperthyroidism due to constitutively activating mutations and Grave's disease caused by activating auto-antibodies. Thyrotropin (TSH), the natural ligand of the TSHR and Grave's disease antibodies mediate their action by binding to the large extracellular domain. This N-terminal part of the protein consists of 2 structural domains, the LRR domain and the hinge region, which connects the LRR domain with the seven-transmembrane-helix bundle. While the structure of the LRR domain was resolved by X-ray diffraction, no structural data of the hinge region is available. In order to gain insights into possible structures of this domain, which seems to play a major role in ligand binding and signal mediation, computational methods are applied. Here an approach utilizing different tools of molecular modeling, including de novo protein structure prediction, molecular dynamics, protein-protein docking and homology modeling, is presented. Resulting structure-proposals will be validated with experimental data and might be the source for further experiments. By understanding the structural basis of TSH binding and signal mediation the rational design of novel therapeutics might be feasible.

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POSTER 252

Gain of function in a tRNA nucleotidyltransferase deletion variant

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tRNA nucleotidyltransferases - CCA-adding enzymes - are ubiquitous enzymes catalyzing the template-independent incorporation of the invariant triplet C-C-A to the 3' end of tRNAs. Interestingly, some prokaryotes carry two enzymes sharing the CCA-adding function: One enzyme adds the first two C residues, while the second enzyme incorporates the terminal A residue.
Although these CC- and A-adding enzymes exhibit such restricted activities, they carry the same set of highly conserved motifs in the catalytic core that are required for a complete CCA-addition. In the case of CC-adding enzymes, it could be shown that a deletion of a small flexible loop region between two conserved motifs is responsible for the reduced activity, as this loop is a prerequisite for switching the enzymes specificity from CTP to ATP. For A-adding enzymes, however, the molecular basis of the restricted activity still remains unclear. To identify elements responsible for an exclusive A-incorporating activity, chimeras between A- and CC-adding enzymes of *D. radiodurans* were generated. Thereby, the non-conserved C-terminus of the A-adding enzyme was replaced by the corresponding CC-adding enzyme part. Activity tests revealed that in these chimeras, a full CCA-adding activity was restored. To analyze whether this gain of function is caused by the exchanged C-terminus, a variant of the A-adding enzyme lacking this part was tested. Surprisingly, this C-terminal deletion variant also showed a complete CCA-adding activity. Obviously, the C-terminus of the A-adding enzyme has an inhibitory function and restricts the enzyme's activity to A-incorporation.

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POSTER 253

Development of a Genetic System for Geobacter metallireducens

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Members of the metal oxide respiring genus *Geobacter* play an important role in the bioremediation of organic and uranium oxide contaminants. They are obligate anaerobes belonging to the *Deltaproteobacteria* and are able to completely oxidize organic compounds to carbon dioxide with Fe(III), Mn(IV), U(IV) or nitrate as the terminal electron acceptor (1). Growth substrates of *Geobacter* species are short chain fatty acids and also monoaromatic compounds like benzoate, phenol, *p*-cresol and toluene. To study the biochemical pathways of the degradation of aromatic compounds we aimed to develop a first genetic system for *G. metallireducens*. The antibiotic sensitivity of this organism was characterized and conditions for efficient cultivation on solid medium were established. A procedure for introducing foreign DNA by electrotransformation was developed. The broad-host range vector pCD342 (2) was used to express the benzoate-CoA ligase (encoded by *bamY*) from *G. metallireducens* homologously. This enzyme converts benzoate to benzoyl-CoA which is the central intermediate in the metabolism of aromatic compounds (3). The inactivation of *bamY* is therefore expected to disable growth on aromatic compounds. To study this effect the mutagenesis of *bamY* by homologous recombination is currently in progress.

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(3) Wischgoll et al. (2005), Mol Microbiol. 58(5):1238-1252

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POSTER 254

Replication Initiator 1 Gene (Repin1) is Involved in the Pathophysiology of Human Obesity

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Repin1 maps within a QTL for obesity (OB) and is related to dyslipidemia in subcongenic rat strains. Here, we investigated the role of *Repin1* in the pathophysiology of human OB.
Repin1 mRNA expression was measured in adipose tissue of 196 individuals with a wide range of metabolic phenotypes using RT-PCR. *Repin1* was sequenced in DNA samples from nonrelated Caucasian subjects to identify genetic variants. 18 variants were identified, including a 12bp deletion. The deletion and nine SNPs including six HapMap tagging SNPs representing their linkage disequilibrium groups were genotyped for subsequent association studies in two independent cohorts with detailed metabolic testing: German Caucasians from Leipzig and a self-contained population of Sorbs, totalling 3240 subjects.
We found significant correlations between *Repin1* mRNA expression in human adipose tissue and total body fat mass as well as adipocyte size, suggesting *Repin1* as novel candidate gene for OB and related traits. In a case control study including subjects with type 2 diabetes (T2D) vs. subjects with normal glucose tolerance (NGT), two SNPs were significantly associated with T2D in the Leipzig cohort. In subjects with NGT, three SNPs were significantly associated with cholesterol, triglycerides, with % bodyfat and 2 hr glucose. In the Sorbs, rs4725336 showed association with OB in a case control study obese vs. lean subjects .
Correlations of mRNA expression in adipose tissue with OB as well as the association of *Repin1* genetic variants with T2D, OB and relevant metabolic traits suggest a potential role of *Repin1* in the pathophysiology of human obesity.

Funding: formel1

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POSTER 255

Smoking? – You must be joking! The carinogenic toxin of cigarette smoke Benzo[a]pyrene causes cellular diseases

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Benzo(a)pyrene (B[a]P) is a carcinogenic polyaromatic contaminant occurring in cigarette smoke and automobile exhaust. Although the effects of high B[a]P-concentrations have been studied extensively, little is known about its effects at subacute toxic concentrations, that are typical for environmental pollutants. We exposed murine Hepa1c1c7 cells to a toxic (5 μM) and a subacute concentration (50 nM) of B[a]P over a period of 2 to 24 h to differentiate between acute and pseudo-chronic effects and performed B[a]P-influenced protein expression with 2D-DIGE. A set of 120 out of 1227 total protein species were found to be significantly altered of which 112 were identified by mass spectrometry. Our results indicate an immediate response to the contaminant at the protein level and demonstrate that B[a]P exposure alters the cellular response by disturbing proteins involved in oxidative stress, cell cycle regulation, apoptosis and cytoskeleton organisation. Furthermore, network analysis of protein-protein interactions revealed a complex network of interacting, B[a]P-regulated proteins mostly belonging to the cytoskeleton organisation and several signal transduction pathways. To valdiate the results obtained with the 2D-DIGE-analysis, SILAC (stable incooperation of labeled amino acids in cell culture) was established and applied to B[a]P-treated Hepa1c1c7 cells. Thus, reproducible quantitative protein expression data on cellular B[a]P-effects will be generated for the correlation with gene expression data within the network and the later model development predicting the effects of structurally related chemicals on cellular systems.

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POSTER 256

Characterization of a tRNA editing activity in Saccharomyces cerevisiae

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In mitochondrial genomes of metazoans, some tRNA genes overlap by one to six nucleotides with the neighboring downstream tRNA gene on the same strand. Examples are the human mitochondrial genes for $tRNA^{Tyr}$ and $tRNA^{Cys}$ which overlap by one nucleotide. In the processing pathway of the primary transcript, the downstream located $tRNA^{Cys}$ is released as complete molecule, while the upstream $tRNA^{Tyr}$ carries a corresponding truncation at the 3'-terminus, missing the overlapping nucleotide. Subsequently, an RNA editing reaction restores the missing position and completes this tRNA.
Surprisingly, although *S. cerevisiae* does not carry overlapping tRNA genes in its genome, it is able to restore such truncated tRNAs. Obviously, *S. cerevisiae* carries a promiscuous nucleotide incorporating activity that accepts these transcripts and adds the terminal nucleotide. These data support the hypothesis of the evolution of RNA editing by recruitment of a pre-existing and promiscuous nucleotide inserting activity.
In order to identify this editing activity, a two phase approach was designed.
The first aim is to determine the editing activity in *S. cerevisiae*. Many hints point to ribo-nucleotidyltransferases, such as CCA enzyme, poly(A)polymerase, Trf4 or Trf5, both belonging to a family of newly discovered poly(A) polymerases in yeast.
Once this activity is identified, a homology search like BLAST can be applied to find corresponding editing enzyme candidates in the human genome. Furthermore, complementation experiments with a human cDNA library in the *S. cerevisiae* editing knock out strain should also identify of the human enzyme.

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POSTER 257

Structure and function of an m-xylene degrading sulfate-reducing enrichment culture revealed by molecular and stable isotope tracer techniques

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Microbial communities are usually consisting of several species of microorganisms occupying different ecological niches, and they generally provide data for studying the flow of elements in the environment. To understand the role and function of microbial communities we need to understand the role of each individual species in the community.
The microbial community we investigated is an *m*-xylene degrading sulfate-reducing mixed culture originally enriched from ground water of a BTEX contaminated field site. Xylene belongs to the group of BTEX compounds (benzene, toluene, ethylbenzene, xylene) and as toxic and common substances they all represent a big threat to humans and the environment. The research interest that we are focused on is to learn more about the anoxic degradation of such compounds following the incorporation of heavy isotopes, like ^{13}C or ^{15}N, within the proteins of a microbial community (Protein-SIP).
For labeling, we grew the culture using *m*-xylene labeled with ^{13}C at both methyl groups. Control cultures were grown with unlabelled *m*-xylene, acetate and benzoate. Labeled and non-labeled *m*-xylene were degraded in similar rates with sulfate as electron acceptor. *m*-xylene was mineralized, as shown by the release of ^{13}C-CO_2. Two different species were dominant in the enrichment culture under all cultivation conditions, as revealed by Terminal Restriction Fragment Length Polymorphism (T-RFLP) analyses. One phylotype is affiliated to members of the genus *Desulfobacterium*, the other is related to *Epsilonproteobacteria*. The *Desulfobacterium* phylotype is believed to degrade *m*-xylene. The metabolic function of the *Epsilonproteobacterium* is not yet known. Further investigations are needed to obtain and elucidate the exact roles of these species. The preliminary protein analyses of both ^{12}C and ^{13}C xylene samples revealed that 23% of ^{13}C is incorporated in the majority of the peptides.

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POSTER 258

Fluorescent Modification of the Regenerative Chemokine SDF-1 α to Study Receptor Internalisation

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SDF-1 is a chemokine that plays a major role in trafficking of hematopoietic stem cells (HSC). Thus, it enables the formation of bone marrow during embryogenesis and later in adults it supports retention and homing of these cells in the bone marrow. Furthermore it is involved in organogenesis and regeneration, respectively.[1] Due to these promising features SDF-1α could serve as a therapeutic target. For studies on this small protein concerning its molecular properties as well as its therapeutic potentials, it needs to be modified chemically.
In order to reach these goals, the N-terminal segmet SDF-$1a_{1-49}$ has been cloned and expressed recombinantly in E. *coli* ER 2566, while the C-terminal segment SDF-$1a_{50-68}$ has been synthesized via solid phase peptide synthesis. Modifications are thereby introduced in the C-terminal segment at Lys^{56}, e. g.. Up to now carboxyfluorescein has been coupled to the e-amino group of the lysine residue. The two fragments then have been ligated by Expressed Protein Ligation (EPL), a subform of the Native Chemical Ligation (NCL).[2] The activity of the conjugate has been tested in an inositol 3-phosphate turnover assay as well as in chemotaxis assays. The potential of this compound to bind specifically to CXCR4-transfected HEK293 cells as well as to induce internalisation has been proven by fluorescence microscopy.[3]

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Assoziation: PbF III

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POSTER 259

Expression and Characterization of Human Interleukin-8 Analogs

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Despite modern techniques, implant rejection and wound healing are still significant problems in regenerative medicine. Improved biomaterials have been reported to be advantageous to conservative materials. However, it is necessary to control and limit the inflammatory potential of implants coated with biomaterial layers.
The chemokine interleukin-8 (IL-8, also named CXCL8) has been reported to mediate inflammatory processes and hence, the investigation of IL-8 interaction is a powerful tool to follow and estimate the inflammatory potential of biomaterials. IL-8 belongs to the family of CXC chemokines and selectively binds to the seven-transmembrane G protein-coupled receptors CXCR1 and CXCR2 with nanomolar affinity.
In previous work it could be shown that the C-terminal helix of IL-8 is not directly involved in the binding of the chemokine to hyaluronic acid. Whether this holds true for different biomaterials or extracellular matrix components have been investigated. Proteins with truncated C-termini were synthesized, as well as N-terminally reduced IL-8 segments. The hIL-8 N-terminus was expressed in E. coli and purified by affinity chromatography. C-termini were synthesized by solid phase synthesis (SPPS). Both fragments were fused by Expressed Protein Ligation (EPL) and characterization of these analogs was performed by analytical and biological methods.

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POSTER 260

New targets for stroke therapy – an in vitro approach

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Stroke is a leading cause of chronic disability in humans for which no effective treatment is available beyond a 4.5 hour time window, leaving more then 90% of patients untreated. The aim of our study was to analyse new therapeutically relevant molecules, which play a crucial role in the regulation of (patho-) physiological processes after stroke beyond this time window. Currently there are two protein families that we include as extremely promising and interesting candidates in our analysis, SUMOs (small ubiquitin like modifiers) and SENPs (SUMO proteases). We established an *in vitro* system which allows the subsequent functional study of these molecules during the ischemic stress response. Expression patterns show that SUMOs and SENPs are expressed in neural tissue under normoxic and ischemic conditions. Loss of function as well as overexpression experiments shall demonstrate their protective function during the regeneration process after oxygen glucose deprivation (OGD).
We hope that these and further studies help to elucidate the molecular signalling pathways activated after OGD, in order to enhance the therapeutic intervention during cerebral ischemia.

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POSTER 261

Cytochemical properties of perineuronal nets in the mice MNTB

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The medial nucleus of the trapezoid body (MNTB) is a prominent structure in the auditory brainstem and is involved in sound localization.
Principal cells are the typical MNTB neurons. They are contacted by the calyx of held, an excitatory giant axosomatic terminal ending. It is known that the mammalian MNTB comprises prominent perineuronal nets (PNs). However, the precise chemical composition of these PNs is not well-investigated.
PNs are a specialized form of extracellular matrix (ECM) and consist of large aggregating chondroitin sulphate proteoglycans connected to hyaluronan and tenascins. PNs enclose neurons of heterogenous subpopulations and occur in different shapes. To date, the function of PNs is largely unknown. Due to their high negative charge, caused by glycosaminoglycan and hyaluronan components, the PNs might be involved in local ion homeostasis. Furthermore there is evidence that PNs are involved in stabilization of synaptic contacts and exhibit a potential protective function in neurodegenerative diseases.
We investigated the chemical organization and structural appearance of PNs in the mice MNTB. We could show that PNs of principal cells in the MNTB consist of chondroitin sulphate proteoglycans, tenascin, link protein and hyaluronan. Thereby chondroitins of proteoglycans are 0-, 4- and 6-sulphated. In addition, we could demonstrate that net ensheathed principal cells of the mice MNTB express different carbohydrate residues detectable by distinct lectins.
Our results observe the chemical composition and shape of PNs in MNTB and indicate the complexity of this structure.

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POSTER 262

Vagus sensibel evozierte Potentiale – neurophysiologische Hirnstammdiagnostik?

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Sensibel evozierte Potentiale nach elektrischer Stimulation des kutanen Astes des N. vagus (VN-SEP) wurden erstmals von Fallgatter et al. (2003) beschrieben. Wir verglichen VN-SEP mit somatosensibel, durch elektrische Stimulation des N. trigeminus (T-SEP), und akustisch, durch Klicks (AEP), evozierten Potentialen und untersuchten mögliche parasympathische Effekte.
Bei 41 Probanden (Alter 28 ± 7 Jahre) wurden VN-SEP und T-SEP mit bipolaren Elektrodenverschaltungen (10-20 System) abgeleitet. Die Latenzen der Potentialkomponenten (P1, N1, P2 (VN-SEP); N13, P19 (T-SEP); I – V (AEP)) und die Peak-to-peak Amplituden wurden bestimmt. Der parasympathische Einfluss der Vagus- im Vergleich zur Antihelix-Stimulation wurde mittels Herzfrequenzvarianz (HFV) gemessen.
VN-SEP konnten bei allen Probanden nach Stimulation des Vagusinnervierten Hautareals nicht jedoch der Trigeminus-innervierten Antihelix reproduzierbar abgeleitet werden. Die Latenzen der VN-SEP (P1, N1) entsprachen denen der AEP Komponenten II und IV. Eine Korrelation zwischen den VN-SEP-, T-SEP- oder AEP-Latenzen fand sich nicht. Die interindividuelle Variabilität der Peak Latenzen (und Amplituden) war größer bei den VN-SEP (A1-Cz [ms]: P1 2,5±0,4; N1 4,7±0,9; P2 7,2±0,9) als bei den AEP (II 2,9±0,1; IV 5,1±0,2). Die HFV blieb durch sensible Vagus-Stimulation unbeeinflusst (p=0,06).
VN-SEP können verlässlich bei gesunden Probanden abgeleitet werden. Eine direkte Beeinflussung parasympathischer Aktivität war nicht nachweisbar. Die beachtliche interindividuelle Variabilität könnte den Einsatz bei Patienten mit vermuteten neurodegenerativen Erkrankungen einschränken.

Funding: formel1

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POSTER 263

The self, the body and the space: neglect as a theory of proprioceptive space

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The clinical neglect syndrom is still a subject of debate. This neurological disorder in space perception provokes a lot of different hypothesis about its character, its supramodality and the underlying mechanisms.
An interesting theory has been proposed that the crucial mechanism leading to neglect is a dysfunction of proprioceptive space, caused by a disturbed transformation of sensory input into a supramodal egocentric frame of reference. This egocentric coordinate system is centered on the midsagittal plane, but an unilateral brain lesion may lead to a deviation of the egocentric reference frame, as evidenced by an error when indicating 'straight ahead'.
In this study we tested the proposed proprioceptive dysfunction and the supramodal character of neglect by employing a model of neglect utilizing the effect of a vibration on left and right neck muscles on visual and auditory 'straight ahead'-orientation in healthy volunteers. We found that neck vibration leads to a shift in auditory determined subjective centre. This shift is similar for right and left stimulation. Neck vibration leads to a shift in visually determined subjective centre. This effect is smaller and only holds for left side stimulation.
These results support the hypothesis that an egocentric proprioceptive coordinate system is needed to establish space perception in the visual and auditory modality. Dysfunction of this proprioceptive space can induce a neglect-like deviation in 'straight ahead'-orientation.

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POSTER 264

Development of a non integrating lentiviral gene transfer system to slow down progressive neurodegeneration

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Alzheimer's disease (AD) is the most common neurodegenerative disorder with an enormous socio-economic burden on the aging society. The clinical symptoms and the neurodegeneration of AD are caused by accumulation of extracellular plaques and neurofibrillary tangles. Currently, causes of the disease are still unknown and there is neither an effective prevention nor a therapy treatment. Gene therapy is one promising method for preventing or even healing different serious diseases. Here we propose a new gene therapeutic tool, which ensures neuron-specific, long-lasting and regulated transgene expression in the CNS for further gene therapeutic applications. Non-integrating (NI) lentiviral vectors are tools of choice for our strategy. These vectors have the ability to infect specific neuronal cells, induce no or low immune response and the normal cell functions are not negatively affected. The safety risk of insertional mutagenesis may be avoided by the use of integration-deficient lentiviral vectors. Our concept to prevent neuronal cell death is based on neuroprotective effects of cell cycle inhibitors (cdkis), which block the cell cycle re-entry of neurons. Here, we present initial results to assemble NI lentiviral vectors, which can regulable express relevant physiological cdkis of the INK4 and Cip/Kip family.The neuron specific expression is enabled by neuron specific promoters an will be regulated by Tet-On/tet-Off system. We have established expression vectors for different cdkis and analysed their effects *in vitro*.

Supported by SMWK 7-7531.50-02-0361-07/2, ERANet Neuron, Afi Project 984.000-150 and formel.1 (2009).

Assoziation: PbF IV

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POSTER 265

Striatal synaptic plasticity in mutant mice carrying a humanized FOXP2

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Aims and Methods: There is evidence that two amino acid substitutions in the transcription factor FOXP2 were positively selected during human evolution and are linked to aspects of speech & language. These substitutions (T303N, N325S) occurred after the split of humans from chimpanzees 5-6 million years ago. Recently we have shown that mice carrying these human specific changes show increased long term depression (LTD) of corticostriatal glutamatergic transmission following high frequency stimulation in medium spiny neurons. Results: We show that the effects on synaptic plasticity are specific to medium spiny neurons since cerebellar purkinje cells, which also highly express Foxp2, show no alteration in their synaptic plasticity. To study the underlying mechanisms, we tested the involvement of dopamine and glutamate, known mediators of striatal neuronal plasticity. First results indicate that dopamine D2R activation is not only required for LTD in wild type but also for the enhanced effect in transgenic animals. In addition, the NMDAR antagonist APV blocks the enhanced effect in transgenic animals, but does not significantly affect LTD in wild type animals. Additional recordings indicate no change in NMDAR subunit expression, suggesting a modification of NMDAR function. Conclusion: Our findings support the hypothesis that humanized FOXP2 modulates specifically synaptic plasticity of medium spiny neurons via dopamine and NMDA receptors.

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POSTER 266

An advanced technique in immunohistochemical tissue characterization allows more-complex outcome measurement in preclinical stroke studies

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Background. As a result of numerous translational failures in the field of stroke, a more-complex perspective of tissue salvaging is required, including functional constructs like the neurovascular unit (NVU) and blood-brain barrier (BBB). The present study aimed on a novel quantification method of BBB damage and detection of stroke-impaired tissue after experimental cerebral ischemia. Methods. Middle cerebral artery occlusion (MCAO) was induced in Wistar rats using an embolic model, which is closest to the human condition. BBB permeability was assessed by intravenously applied fluorescein isothiocyanate (FITC)-tagged albumin (≈70 kDa) and biotinylated rat IgG (≈150 kDa), given 4 or 24 hours after MCAO. Immunohistochemical conversion of these markers into a diaminobenzidine label allowed size calculations of BBB-impaired tissue. Results. In ischemia-affected areas, FITC-albumin and biotinylated rat IgG displayed a similar leakage, which can be quantified by fluorescence microscopy and at light-microscopical level. Specific NVU components were addressed by using NeuN and HuC/D for neurons, rat endothelial cell antigen-1 (RECA) and laminin for vessels, lectins (from tomato, potato and *Griffonia simplicifolia*) for vessels and microglial subpopulations, S100ß for astroglia, as well as ionized calcium binding adaptor molecule 1 (Iba), CD68 and CD11b for activated microglia, neutrophils and macrophages. Conclusions. FITC-albumin and biotinylated rat IgG as BBB markers in combination with the specific detection of NVU components might facilitate a more-complex outcome measurement in experimental focal cerebral ischemia.

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POSTER 267

Prä-Stimulus-Vigilanz beeinflusst Reaktionszeit einer visuellen Diskriminationsaufgabe

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Die individuelle Reaktionszeit gesunder Probanden variiert beträchtlich im Verlauf der experimentellen Durchführung von Diskriminationsaufgaben. Es existieren kaum Studien, die den während des Experiments fluktuierenden Wachheitszustand des Probanden als potentiellen Einflussfaktor auf die intra-individuelle Reaktionsschnelligkeit beleuchten. Der Leipziger Algorithmus zur Klassifikation von Vigilanzstadien (VIGALL) ermöglicht auf Grundlage von EEG-Aufzeichnungen die sekündliche, automatische Bestimmung des Wachheitszustandes im experimentellen Verlauf. Wir nahmen an, dass die Probanden während des hoch-vigilanten EEG-Stadiums A schneller reagieren als während des weniger wachen EEG-Vigilanzstadiums B.
Während einer 15-minütigen EEG-Ableitung führten 24 gesunde Studentinnen eine visuelle Diskriminationsaufgabe durch. In 400 Trials wurden Targets „X" und Distraktoren „O" für jeweils 300ms im Abstand von 2000ms präsentiert. Die Probanden wurden instruiert beim Erscheinen des Targets so genau und so schnell wie möglich per Knopfdruck zu reagieren. Auf Grundlage der simultan aufgezeichneten EEG-Daten wurde das Vigilanzstadium jeweils eine Sekunde vor der Präsentation des Stimulus mithilfe des computerbasierten Vigilanzalgorithmus VIGALL klassifiziert.
Entsprechend unserer Hypothese reagierten die Probanden bei hoher Prä-Stimulus-Vigilanz (Stadium A) schneller als bei geringer Prä-Stimulus-Vigilanz (Stadium B).
Durch die automatische Bestimmung des Wachheitszustandes mittels VIGALL könnte perspektivisch die intra-individuelle Varianz neuro-kognitiver Messungen durch simultane EEG-Ableitung besser kontrolliert werden.

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POSTER 268

Differentiation of neuron-like cells from rat fibroblast-derived induced pluripotent stem cells in vitro

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Induced pluripotent stem cells (iPSCs) are adult somatic cells which have been reprogrammed to a pluripotent state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells (ESCs). They raised the possibility that in vitro differentiation may provide an invaluable source of cells for tissue replacement or repair without the controversial use of embryonic material.
The aim of the present study was to establish a protocol for the in vitro differentiation of rat fibroblast-derived iPSCs into neural lineage cells.
Reprogramming of Lewis rat adult fibroblasts was performed by viral transduction. Thereafter, the cells were cultured on mitotically inactivated rat embryonic fibroblasts in the presence of LIF. IPSC colonies were selected by appearance of ESC morphology and mechanically picked for passaging. Floating embryoid bodies (EBs) were harvested and plated onto tissue culture dishes with serum-free medium containing N2 supplement and bFGF. After 8 days, the mitogen bFGF was withdrawn and 5 % FCS was added.
A few days after EB attachment, cells radially migrated away from the EBs and showed various types of morphologies. As from day 14, many cells converted to a neural phenotype and could be detected by phase contrast microscopy. To confirm those first results of the differentiation procedure, immunostaining with antibodies against MAP2, Nestin and GFAP will be performed as well as expression profiling of neural markers over time. However, the rat iPSCs are able to form embryoid bodies and have the potency to differentiate into cells with neuron-like morphology.

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POSTER 269

Purinergic signaling in cochlear nucleus

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ATP plays an important role in the CNS by functioning as a neurotransmitter, cotransmitter and neuromodulator. In the peripheral auditory system, purinoreceptors of the P2 family contribute strongly to signaling in the cochlea, but little is known about the effects of purinergic neurotransmission in the central auditory system. Recently, it was shown *in vitro* that activation of P2 receptors evokes bursts of action potentials in spherical bushy cells (SBCs) of the cochlear nucleus (CN), the first central station in the ascending auditory pathway. Here we further examine the role of P2 receptor mediated signalling in CN of Mongolian gerbil, by conducting extracellular recordings *in vivo* with simultaneous iontophoretic drug application. P2 receptor agonist ATP and P2X selective antagonist TNP-ATP were applied during both spontaneous and sound-evoked SBCs activity. Three age groups were tested: shortly after hearing onset (P13-16), subadults (P20-23) and adults (P>45). Our results show significantly increased firing rate of SBCs during the ATP administration in P13-16 and P20-23 groups, but not in adult gerbils. Application of TNP-ATP induced rapid and persistent decrease in SBCs action potential firing in both preadult groups. The percentage of neurons reacting to either of administered drugs was higher in the P13-16 group compared to P20-23 group. These data suggest that purinoreceptor function is developmentally regulated. ATP seems to play an important role in the activity of SBCs in young gerbils, but purinergic signalling is diminishing after hearing onset and is completely absent in adult cochlear nucleus.

Assoziation: PbF IV

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POSTER 270

Desynchronisierte Abschnitte im Ruhe-EEG: sLORETA basierte Subklassifikation.

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Ziel der hier vorgestellten Arbeit war es, zu zeigen, dass sowohl hoch- , als auch niedrigvigilante, desynchronisierte Abschnitte im Ruhe-Elektroenzephalogramm (Ruhe-EEG) vorkommen können. Weiterhin sollte versucht werden, diese EEG-morphologisch ähnlichen , aber hinsichtlich der zugehörigen Vigilanz sehr verschiedenen Zustände mittels EEG-Tomographie (sLORETA: standardized low resolution electromagnetic tomography, hirnfunktionelle Bildgebung) zu unterscheiden.
Hierzu wurden die desynchronisierten Abschnitte von 9 ausgewählten Ruhe-EEGs in eine Hochvigilanz- und eine Niedrigvigilanzgruppe eingeteilt, und nach erfolgter Bildgebung statistisch verglichen. Die Zuordnung zu einer der beiden Gruppen erfolgte anhand des Vorhandenseins (niedrige Vigilanz) oder des Fehlens (hohe Vigilanz) von, für die Einschlafphase charakteristischen, langsamen Augenbewegungen (SEM) im synchron zum EEG aufgezeichneten Elektrookulogramm (EOG).
Es wurden zwischen beiden Gruppen signifikante Unterschiede ($p<0.005$) der relativen Aktivität im Theta-Band (4-8 Hz) für den medialen Temporallappen (MTL, BA 27,28,34,35,36) sowie Teile der tertiären Sehrinde und benachbarte Areale (BA 19,20,38) festgestellt. Der Vergleich einer, auf diesen Unterschieden basierenden Klassifizierung desynchronisierter Zustände mit der SEM-basierten Unterscheidung wurde durchgeführt, wobei eine gute Übereinstimmung der Methoden festgestellt werden konnte. Die Zuordnung beider Gruppen zu verschiedenen Vigilanzniveaus wurde durch signifikante Unterschiede hinsichtlich der zugehörigen Herzfrequenzen (höher für desynchronisierte Zustände ohne SEM) bestätigt.

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POSTER 271

Generation of transgenic mice expressing affinity-tagged fluorescent P2X2 receptors

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Increased understanding of the neurobiology of pain gives the chance to translate these mechanistic insights into better diagnosis and treatment. Therefore knowledge of the precise tissue distribution of specific receptors is crucial to understand pain processing. The involvement of purinergic receptors in nociception has attracted prominent attention. Extensive evidence supports particular an important role for P2X2 containing receptors in sensory neurotransmission.
To facilitate the morphological and functional identification of neurons carrying P2X2 receptors, we have generated a transgenic mouse strain, expressing a red fluorescent P2X2 receptor subunit as fusion protein including two affinity tags under the control of its own promoter. This mouse model was generated by recombination-mediated genetic engineering using the suitability of bacterial artificial chromosomes (BACs), an efficient method to construct vectors for subsequent manipulation of the mouse genome.
The expressed fluorescence will allow for a comprehensive microscopic mapping of the distribution of P2X2 receptors in vivo and guide the identification of neurons for functional analysis. The tandem affinity tags can be exploited to isolate these receptors from native tissues for biochemical analysis and co-purification of receptor-interacting proteins for mass spectrometric identification.
In summary, this transgenic mouse model should provide a rich resource to enable new insights into P2 receptor localization and function in developmental, physiological and pathophysiological processes.

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POSTER 272

Characterization of striatal hNPCs and their development under different oxygen concentrations

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The main function of the striatum is the control of voluntary movements. The degeneration of GABAergic medium spiny neurons within the striatum lead to loss of motor control and involuntary movements as seen in Huntington's disease. Up to now there is no effective therapy against this ailment. Among others cell replacement therapy is considered as a promising approach, but still suffers from the restricted availability of human striatal cells.
Over the past years, we were able to improve the long-time cultivation of human neural progenitor cells (hNPCs) and also their differentiation into neurons. To gain further insights into the mechanism influencing the development of hNPCs in vitro, we have produced hNPCs cultures that were derived from medium spiny neurons, the main neuronal population in the striatum (app. 95%), and we have examined the influence of different oxygen conditions on these cells.
Quantitative real-time PCR (qRT-PCR) analyses revealed that oxygen conditions modulate the expression of striatal markers during proliferation (Pax6, Dlx1) and differentiation (Darpp32, Ctip2). Hypoxia (3%) stimulates the expression of mRNA of specific markers of proliferation during the late period of cultivation, while normoxia (5%) increases the expression of striatal differentiation markers. However, such changes were not detected when proteins were analyzed. Therefore, the effects of low oxygen concentrations need to be addressed in more detail.

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POSTER 273

Cerebrospinal fluid hypocretin-1 (orexin A) levels in mania compared to unipolar depression and healthy controls

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Background: Impairment of sleep- wake cycles and circadian rhythm are found in human narcolepsy which is characterized by deficiency of hypocretin (hcrt) or its receptors. A disturbed electroencephalography (EEG) based vigilance regulation is also found in affective disorders such as major depressive disorder (MDD) and mania. For the first time, in the present study hcrt-1 levels were investigated in patients with a manic episode and compared with age-matched patients with MDD and controls.
Methods: 15 subjects were enrolled in the study after admission to hospital:
5 manic (mean YMRS 15.6 ± 2.9) and 5 age- matched patients with MDD (mean HDRS 11.6 ± 8.0), and 5 age-matched controls without any neurological or psychiatric disorder. Cerebrospinal fluid (CSF) hcrt-1 levels were measured in all three groups using a fluorescence immunoassay (FIA).
Results: Mean hcrt-1 level in manic patients (77.3 ± 20.7 pg/ml) did not differ significantly compared to patients with MDD (75.6 ± 15.7 pg/ml MDD) or controls (74.9 ± 19.3 pg/ml). Hcrt-1-levels and severity of disease did not show a significant association.
Conclusion: In the present study, for the first time hcrt-1 levels in manic patients were investigated but did not reveal significant differences neither compared to age-matched patients with MDD nor healthy controls without any psychiatric or neurological disorder.

* Schmidt FM, Brügel M, Kratzsch J, Strauss M, Sander C, Baum P, Thiery J, Hegerl U, Schönknecht P. *Cerebrospinal fluid hypocretin-1 (orexin A) levels in mania compared to unipolar depression and healthy controls.* Neurosci Lett. 2010 Oct 8;483(1):20-2.

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POSTER 274

Development of signal transmission at the Mouse Calyx of Held in vivo

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Synaptic transmission at the calyx of Held is known for its high reliability and fast signal transmission. In the present study we investigated the development of these properties *in vivo* in P8-P28 mice focussing on developmental changes within spontaneous discharge patterns around hearing onset. We used extracellular recordings to measure single-unit activity in the medial nucleus of the trapezoid body which enable simultaneous acquisition of pre- and postsynaptic activity reflected by a complex voltage signal. To precisely quantify the timing and the relative size of the single components, we developed a fitting algorithm which (I) decomposes the complex waveform of individual transmission events into the presynaptic action potential (AP), the excitatory postsynaptic potential (EPSP) and the postsynaptic AP and (II) at the same time accounts for overlaps between components from one or consecutive transmission events. Before hearing onset, we found signal transmission to be unreliable and of high variability in transmission delay. Also, EPSP and postsynaptic AP amplitudes were depressed strongly as a function of preceding activity. Around hearing onset (P12-P14) signal transmission gained the properties found at the mature calyx of Held, i.e. reliable in transmission with a low variability in both the transmission delay and in the amplitude of the EPSP as well as postsynaptic AP. Though activity-dependent depression was still seen in APs, EPSP depression no longer seemed to play a prominent role. In summary, we found the calyx of Held to mature just in time for the onset of acoustically evoked signal processing.

Assoziation: PbF IV

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POSTER 275

Imaging genetics of FOXP2 in dyslexia

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Dyslexia is a developmental disorder, affecting about 5-12% of all school-aged children. Genetic influence is estimated larger than 50%, however, the link between genetic variants and phenotypic deficits is largely unknown.
One of the most prominent genes influencing speech and language development is *FOXP2*. Our aim was to investigate a possible role of genetic variants of *FOXP2* in dyslexia using imaging genetics, combining functional magnetic resonance imaging (fMRI) and genetics to investigate the relevance of certain genetic variants for brain activation.
We initially applied a case / control study (N=245) for prioritisation of *FOXP2* polymorphisms for use in imaging genetics. Nine variants were analysed, rs12533005 showed strongest association with dyslexia. Therefore, relevance of carriage of the putative risk variant rs12533005-G for brain activity was studied by imaging genetics. In fMRI, the contrast of a rhyming task vs. fixation revealed a significant main effect for the factor "genetic risk" in a temporo-parietal area known for its role in phonological processing as well as a significant interaction effect between the factors "disorder" and "genetic risk" in activation of inferior frontal brain areas. In addition, this variant was shown to alter expression of *FOXP2* transcripts *in silico* as well as *in vivo* in human tissue. Hence, our data support a role of *FOXP2* genetic variants in the processing of language and phonology relevant for the development of dyslexia and demonstrate to our knowledge for the first time a possible framework for the application of imaging genetics in dyslexia research.

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POSTER 276

Influence of Smad6 on Synaptic Proteins and Vesicle Release in Neurons

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Smad proteins are transcription factors strongly involved in neuronal development and differentiation. Recently, we demonstrated that in neurons the subcellular localization of the phosphorylated receptor associated Smads 2 and 3 is disturbed under neurodegenerative conditions such as Alzheimer´s disease (AD)[1]. Preliminary experiments revealed that also Smad6, an inhibitory Smad, is expressed in neurons. Lately, Smad6 was shown to directly affect exocytosis of enzymes in pancreatic acinar cell[2]due to a functional interference with a homologue N-terminal sequence of the synaptosome-associated protein (SNAP) 25 interacting protein, which is involved in the vesicle release in pancreatic as well as neuronal cells. Combining both results, we raised the question, whether Smad6 also affects vesicle release in neurons, a process which is altered in the AD brain. We demonstrated a different subcellular localization of Smad6 in hippocampal neurons of human control and AD brain. Western blot experiments revealed increased Smad6 protein levels in AD samples. To examine the impact of Smad6 on the vesicle release we used mouse GT1-7 cells, an in vitro model for Gonadotropin releasing hormone (GnRH) secreting neurons. Smad6 was both reduced and enhanced using siRNA knockdown of Smad6 and induction via BMP2. The GnRH was measured by a Enzyme-linked Immuno Assay. To exclude an effect on the vesicle release only due to a modified expression of synaptic proteins their RNA levels under Smad6 reduction and enhancement were examined by Realtime-PCR.

1 Ueberham, U. et al. Eur J Neurosci. 2006 24(8):2327-34,
2 Nakamura H.Gut 2008 57:788-798.

Assoziation: PbF IV

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POSTER 277

Purification and characterization of tau aggregation intermediates

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Tau protein, which is mainly located in the axonal part of neurons is a microtubule- associated protein and plays an important role in Alzheimer´s disease. Tau protein regulates stability of microtubules, which are essential for neurite extension and axonal transport. In neurodegenerative diseases tau protein is hyperphosphorylated and the ability to bind to microtubules is lost. Due to this loss of function, more non-binding tau protein exists and forms aggregates, which are beta-sheet containing adducts of the protein in the cytoplasm. Aggregation of tau monomers to filaments is a multistep process via intermediate states. These tau aggregation intermediates may be involved in the toxicity.
Using recombinant tau protein we found that a short aggregation time (~24 h) produces more toxic tau species than a long aggregation time (~48 h). This was shown by cellular viability of SH-SY5Y cells and leakage of artificial phospholipid vesicles. Based on these results, we speculate that tau oligomers are more toxic than fibrils. In our present study we separated different tau aggregation products (monomeric, oligomeric and filamentous tau) from each other by gel filtration. To characterize the toxicity of the different aggregated forms, we characterized fractions with regard to protein size, beta sheet content and toxic effects in cell lines.

(gefördert durch DFG HO 2368/4-1)

Assoziation: PbF IV

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POSTER 278

Exploration of the ATP binding pocket at the P2X3 ion channel

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P2X3 receptors (P2X3R) are ATP-gated cation channels, which are mainly expressed in nociceptive sensory neurons and play an important role in pain signalling. To facilitate the development of specific antagonists for pain therapy, a detailed knowledge of receptor structure and function is required. By means of whole-cell patch-clamp recordings in HEK293 cells we investigated the effect of different modifications in the binding pocket in comparison with the wild type response to identify the exact binding position of ATP. Simulation of receptor-currents in a kinetic model (Karoly et al., 2008) gives us additional information about the binding-gating-desensitization process of the receptor. Based on our homology model, developed from zebrafish P2X4R and previous studies, we chose 15 amino acid residues, which are located in the supposed binding site. So far, 9 mutants were analyzed with ATP analogues like 2-MeSATP, α,β-meATP, BzATP, β,γ-meATP, ATPγS, dATP, CTP and GTP. In most cases, we observed a decrease in the receptor activity by maintaining the agonist preference order. As an exception we found mutant K176A, in which this order changed and agonists with a modified phosphate chain, including the P2X1/3 selective agonist α,β-meATP, failed to induce currents. This could be an evidence for the involvement of Lysine at position 176 in the activation process of the receptor by interacting with the phosphate chain of agonists. Investigations with further mutants are in progress to identify such specific amino acid-agonist interactions in detail.

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POSTER 279

The significance of the low voltage-gated potassium channel subunit Kv1.1 for the processing of sound source location in mice

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Voltage-gated potassium (Kv) channels containing Kv1.1 subunits are strongly expressed in neurons that fire temporally precise action potentials (APs). In the auditory system, AP timing is relevant to sound source localization by integrating interaural differences in time (ITD) and intensity (IID) of sound inputs to both ears. In mammals, the first nucleus to encode IIDs is the lateral superior olive (LSO), which integrates excitation from the ipsilateral ventral cochlear nucleus and contralateral inhibition mediated via the medial nucleus of the trapezoid body. We previously reported a weakened, delayed and temporally less precise AP transmission along this pathway in Kv1.1 knockout (*Kcna1*$^{-/-}$) mice. Here, we investigate the influence of these effects on IID processing by LSO neurons and by potential target neurons in the inferior colliculus (IC). IID sensitivity was measured using *in vivo* single-unit recordings in *Kcna1*$^{+/+}$ and *Kcna1*$^{-/-}$ mice to evaluate genotype-specific changes in integrating excitatory and inhibitory inputs. In *Kcna1*$^{+/+}$ mice, IID sensitivity in the LSO ranged from +30 (excitatory stimulus more intense) to -20 dB (inhibitory stimulus more intense). In *Kcna1*$^{-/-}$ mice, IID sensitivity was restricted to positive IIDs corresponding to ipsilateral sound positions. Whereas IID sensitivity in IC neurons seems wild-type like on the population level, manipulation of temporal relation of excitation and inhibition revealed the significance of Kv1.1 for the maintenance of latency disparities shaping IID sensitivity on the midbrain level. These results imply a fundamental role of Kv1.1 for the integration of excitation and inhibition required for correct sound source localization.

Assoziation: PbF IV

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POSTER 280

Morphine dependent regulation of PSA-NCAM expression in differentiated SH-SY5Y cells.

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Recently it was shown that the expression of PSA-NCAM (*Polysialic acid neuronal cell adhesion molecule*) in the post-mortem hippocampus of heroin addicts is positively correlated with the measured morphine blood concentration. These data suggest an increased expression of PSA-NCAM due to chronic heroin abuse. To verify these findings, the SH-SY5Y human neuroblastoma cell line, whose neuroblast-like cells can be differentiated to a dopaminergic neuronal-like phenotype, was used. The cells were treated with morphine to investigate the expression of PSA-NCAM compared to untreated cells. Naloxone was used as an antagonist.
The SH-SY5Y cells were subcultured in 96-well tissue culture plates and differentiated. After day 12, the differentiation was complete as indicated by typical neuron-like phenotype. Morphine and naloxone were added to the culture medium. A cellular ELISA protocol was adapted and performed to measure optical densities (OD).
There was no evidence for cytotoxic effects of morphine on differentiated SH-SY5Y cells. A significant increase of the OD (N = 224) was measured with 10, 50 or 200 μM morphine compared to the OD of controls. The effects were reversible after co-administration of 10 μM naloxone.
In conclusion, the *in vitro* results suggest a specific increase of the expression of PSA-NCAM by chronic morphine in a concentration dependent manner, confirming the findings from previous human *post mortem* studies. The alteration of PSA-NCAM expression is believed to be a neuroplastic or regenerative response to morphine which could explain drug-related limitations of central nervous system function.

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POSTER 281

Gender determines obesity's impact on reward-based learning and underlying brain structure

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The prevalence for obesity is higher in women and gender differences in the regulation of body weight are well documented. To investigate gender-dependent influences of obesity, we assessed reward-related behavior, known to be crucial for the control of energy consumption, and underlying brain structure. For both genders, we show that gray matter volume correlates with obesity in regions coding the value of food (i.e. Nucleus Accumbens, Orbitofrontal cortex), suggesting an overestimation of food reward value which may bias eating behavior towards hedonic food choices. Only in women, we show that obesity-related changes in executive function indeed generalize to other reward-related behaviors than eating. This, together with additional structural changes in putamen and prefrontal cortex suggests maladaptive plasticity in which behavioral control is progressively dominated by habit-like as opposed to goal-directed behavior. These findings are important for the understanding of gender differences in the development of obesity and for designing gender-appropriate treatments.

Funding: life

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POSTER 282

Characterization of the unfolded protein response in hNPCs

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The structural integrity of the cellular proteome is of eminent importance for all living cells. Proteins must be correctly folded and assembled to fulfil their functions as assigned by the genetic code. The accumulation of misfolded and unfolded proteins in endoplasmic reticulum (ER) induces ER stress, activating the unfolded protein response (UPR).
The aim of our study is to explore the role of the UPR in stem cell proliferation and differentiation using human neural progenitor cells (hNPCs) in vitro. These cells require low oxygen for maintaining there stem cell potential and we hypothesize that preserving immaturity requires activation of the UPR.
As a first step, we examined mRNA and protein levels of key UPR genes such as XBP1, GRP78 and ATF6 in proliferating cells cultivated under different oxygen conditions (21% vs. 3%) as well as in differentiating cells. Our results show no effect of oxygen conditions on the expression of UPR genes. On the other hand, there was a prominent downregulation of UPR specific mRNA during differentiation compared to proliferation. These data suggest that the UPR has a role in stem cell maintenance. Our current experiments aim to modulate the UPR and identify UPR dependent pathways that promote stemness of hNPCs.

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POSTER 283

The influence of different transcription factors on the metabolism of the amyloid precursor protein (APP)

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Alzheimer's disease is characterized by the deposition of b-amyloid peptides (Ab·) in senile plaques. Ab· is generated from the amyloid precursor protein (APP). APP expression is controlled by a promoter containing the unique CAGA motif, which is a consensus sequence for Smad proteins. These are important transcription factors of the TGF-b superpathway and strongly deregulated in neurons of AD patients.
In astrocytes a Smad dependent APP synthesis has been reported, which confirms the relevance of TGF-b in this process. However, contradictory data were also published. Previous own results with transgenic TGF-b mice demonstrated no detectable influence of TGF-b on APP expression. Moreover, convincing information concerning neurons is also not available. Summarizing these results the question arises whether TGF-b and APP are connected by Smad signalling.
We have considered this problem and examined the impact of Smad proteins on APP expression and metabolism in primary neurons derived from normal and transgenic APP mice. Using antisense strategy we knocked down Smad expression and determined intracellular and secreted APP. In contrast we also have stimulated the Smad activation by administration of factors composing the TGF-b superfamily.
In our experiment we have included cdk4, which is overexpressed in AD, probably regulated by Smad proteins and potentially involved in the phosphorylation of APP, a process which was recently shown to effect the generation of APP fragments. For cdk4 we have also performed a siRNA treatment to examine the APP metabolism.

Assoziation: PbF IV

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POSTER 284

Purinergic signaling in developing auditory brainstem neurons in vitro

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Early in development of the auditory and visual system, endogenously generated spontaneous patterns of neuronal activity can provide an important instructive signal for the refinement of sensory maps before the actual function commences. In the auditory system, bursting activity before hearing onset (postnatal day 12) is primarily generated in the cochlea by ATP-mediated activation of the cochlear inner hair cells. Such bursting activity has been also observed in several nuclei along the ascending auditory pathway, where it supports survival of target neurons, tonotopic refinement of afferent connections, and adjustment of synaptic strength. In the present study we conducted combined whole cell recordings and Ca^{2+} measurements in acute brainstem slices from Mongolian gerbil to investigate development of purinergic signaling in neurons of the auditory brainstem circuit. Our results show that extracellular ATP evokes Ca^{2+}-dependent bursting in neurons expressing purinergic P2 receptors. However, the expression of P2 receptors is developmentally and topographically regulated. The P2 receptor-mediated responses (membrane depolarization, inward current and intracellular Ca^{2+} signal) peak during the first postnatal week, but they are strongly down-regulated after hearing onset, consistent with its developmental role. Moreover, the expression of P2 receptors seems to be restricted to certain auditory brainstem nuclei and only to distinct neurons within the respective nuclei, suggesting that purinergic signaling might play a specific role in organization of developing neuronal circuits.

Assoziation: PbF IV

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POSTER 285

Adult adherent neural progenitor cells (NPCs): Occurrence of functional P2X-receptors

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The aim of this project was to elucidate whether cultured adherent neural progenitor cells (NPCs) of the subventricular zone (SVZ) of adult mice express functional P2X receptors (P2XR). Whole-cell patch clamp recordings and calcium imaging were used to characterize the functional expression of P2XR, which was further supported by immunocytochemical stainings. In these adherent cultures, we identified the P2X7R as the predominantly expressed member of the P2X family. Inward currents in response to ATP and the preferential P2X7R agonist Bz-ATP were largely increased in a reduced divalent cation solution. The responses evoked by Bz-ATP and ATP decreased with the age of the adherent cultures. This current reduction could be prevented when growth factors (EGF, FGF-2) were reapplied every day. The use of non-specific and specific antagonists (PPADS, P2X1-7; A438079, BBG, P2X7; TNP-ATP, P2X1-3; NF449, P2X1) in patch clamp and Ca^{2+} imaging experiments provide further evidence for the functional expression of the P2X7R. Moreover Zn^{2+} and alkaline / acidic pH modulated the Bz-ATP evoked signals in patch clamp as well as in Ca^{2+} imaging experiments. Using NPCs derived from P2X7R knockout mice, indicated that the Bz-ATP or ATP induced currents are mainly due to the activation of P2X7R. These results demonstrate that the P2X7R is functionally expressed in adherent cultures of NPCs from the SVZ. Furthermore growth factors may play a pivotal role in the expression of this receptor subtype.

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POSTER 286

Metabolism modulates Ca2+ signaling in astrocytes

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Astrocytes are important brain cells providing metabolic support to neurons as well as contributing to brain signaling. These different functional levels have to be highly coordinated to allow for proper cell and brain function. In astrocytes, Ca^{2+} signaling is the main signaling event, occurring either in single cells (Ca^{2+}-oscillations) or as intercellular signaling (Ca^{2+}-wave). We hypothesized that these Ca^{2+}-signaling events might be modulated by the cellular metabolism and especially the NAD^+/NADH-redox state. Neurotransmitters like dopamine increase cellular NADH via a receptor mediated activation of protein kinase A (PKA) and glycolysis. This increase in NADH accelerated intercellular Ca^{2+}-waves dependent on gap junctions. In addition, increasing the NADH content of astrocytes directly either by blocking the respiratory chain or by addition of extracellular NADH also accelerated Ca^{2+}-waves. In contrast, while application of NADH alone has no effect on the frequency of spontaneous Ca^{2+}-oscillations, it strongly enhances the change in Ca^{2+}-oscillation frequency induced by dopamine. Therefore, astrocytes appear to distinguish between these two different types of Ca^{2+}-signals in respect to their metabolic regulation. In conclusion, we provide evidence that astroglial metabolism signals back to modify Ca^{2+}-signals, which will probably also result in a modified response of astrocytes to neuronal signaling.

Assoziation: PbF IV

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POSTER 287

Astrocyte-specific deletion of the cytoskeletal adaptor protein vinculin in mice

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Astrocytes play an active role in the brain, including structural and metabolic support of neurons as well as transmitter release. Astrocytic processes are in close contact to blood vessels, other brain cells and synapses and these processes are formed and retracted within minutes. For the interaction of astrocytes with the surrounding extracellular matrix and neighboring cells the formation of localized contacts is required. One common adaptor of cell-matrix and cell-cell adhesions is the protein vinculin which structurally and functionally links the cell adhesion receptors to the actin cytoskeleton. To analyze the role of vinculin in astrocytes, we generated a transgenic mouse model allowing inducible astrocyte-specific inactivation of vinculin by using Cre-loxP technology. Genotyping of single astrocytes isolated from different brain regions demonstrated successful recombination of the floxed vinculin gene *in vivo*. Quantitative PCR showed a decrease of vinculin mRNA, while quantification of fluorescence images of single cells revealed the absence of vinculin in astrocytes in the knockout animals. Consequences of the vinculin-deficiency were tested by immunohistochemistry to look for alterations in the expression and localization of proteins involved in astroglial function. While numerous proteins important for astrocyte function were not affected by the loss of vinculin, preliminary data suggest a changed localization of the gap junction protein connexin43 in the astrocyte-specific vinculin-knockout mice. This may be important for the functional connection of cell adhesion and cell-to-cell coupling via gap junctions.

Assoziation: PbF IV

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POSTER 288

Split-Cre and split-CreERT2: versatile genetic coincidence detectors for precise analysis of cell populations in vivo.

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DNA recombination technologies such as the Cre/LoxP system have advanced and refined the analysis of gene and cell functions *in vivo*. By driving the expression of Cre recombinase under the control of a cell type-specific promoter, a cell type-specific modification of genes can be achieved. However, the precision of a single promoter driving Cre expression might not be sufficient to target a specific cell population. In the split-Cre system DNA recombination is controlled by coincidental activity of two promoters, thereby increasing spatial specificity of Cre-mediated DNA recombination. This system has been used to identify a special astroglial cell population *in vivo* which is defined by progenitor cells with simultaneous activity of the GFAP- and PLP-promoter. These progenitors are re-activated in several lesion paradigms. Furthermore, split-Cre has been used to analyse certain types of interneurons as well as adult neuronal stem cells. Finally, to allow temporal control of split-Cre-mediated DNA recombination we have now extended split-Cre by fusing split-Cre proteins with the tamoxifen inducible ERT2 domain derived from CreERT2. Split-CreERT2 shows an induction ratio of about 10 and EC50-values for its inducer 4-hydroxy-tamoxifen of about 50 nM indicating favourable properties for *in vivo* use. In summary, split-Cre and split-CreERT2 are powerful new tools of modern genetics allowing the further refinement of the analysis of gene and cell function in living animals.

Assoziation: PbF IV

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POSTER 289

Zelltypspezifische Modulation der Genexpression im Hypothalamus adipöser Mäuse

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Bei der Adipositas handelt es sich um ein starkes Übergewicht, das durch eine über das normale Maß hinausgehende Vermehrung des Körperfettes mit krankhaften Auswirkungen gekennzeichnet ist. Die Mechanismen, die zu einer gestörten Energiehomöostase und zu Adipositas führen sind trotz intensiver Forschung noch nicht vollständig geklärt. Energieaufnahme und -verwertung werden durch ein komplexes Zusammenspiel von Fettgewebe, weiteren Organen sowie dem Gehirn reguliert. Der zentrale und wichtigste Regulator der Nahrungsaufnahme und der Kontrolle der Kalorienzufuhr im Gehirn ist dabei der Hypothalamus. Da im Gehirn eine enge funktionelle Interaktion zwischen Neuronen und Gliazellen besteht, ist anzunehmen, dass bei der Pathogenese der Adipositas sowohl Veränderungen in Neuronen als auch in Gliazellen eine Rolle spielen. Daher wurden Veränderungen in der Genexpression in Neuronen, Astrozyten und Mikrogliazellen im Hypothalamus adipöser Mäuse zelltypspezifisch untersucht. In transgenen Mäusen mit Expression fluoreszenter Proteine in Neuronen, Astrozyten bzw. Mikroglia wurde Adipositas durch Fütterung mit Hochfettdiät induziert. Die markierten Zellen wurden mittels FACS aufgereinigt und zelltypspezifische Genexpressionsprofile mittels DNA-Microarrays generiert. Erste Ergebnisse zeigen eine Vielzahl von Genen, deren Expression auch in Gliazellen durch die Hochfettdiät reguliert wird. Dabei finden sich auch Gene, die in genomweiten Assoziationsstudien mit Adipositas beim Menschen assoziiert wurden. Die umfassende Analyse der Expressionsdaten wird uns neue Einblicke in die zentrale Regulation der Adipositas ermöglichen.

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POSTER 290

Determinants of the NADH/NAD+ redox ratio in cultured primary astrocytes

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Astrocytes constitute an important cell population in the brain contributing to brain signalling and providing metabolic support. While for example the glutathione redox system has been studied extensively, little is known about another central redox system intimately linked to metabolic interaction within the brain, the NADH / NAD^+ redox pair. In primary cultures of murine cortical astrocytes, the redox ratio of NADH / NAD^+ was determined to be 0.64 (total NADx content 3 nmol / mg protein). NADH levels were found to be highly responsive to metabolic influence: upon blockade of NADH consuming pathways, the redox system was shifted to the reduced site by increasing the NADH content up to 175 %. Starvation led to a minimum of 0,5 nmol NADH / mg protein. Surprisingly, despite considerable changes in NADH, the NAD^+ level did not change in response to an altered glycolytic or oxidative metabolism and could only be slowly increased up to 180 % by the addition of precursor molecules of pyridine nucleotide synthesis. Vice versa, NADH levels were unaffected by this increase in NAD^+. Nevertheless, the amount of NAD^+ seemed to control the extent of NADH increase upon glycolytic stimulation. Therefore, both partners are elegantly tuning the NADH / NAD^+ redox ratio. To further investigate this relationship in vivo, we are currently establishing a transgenic mouse model with chronically decreased NADH content.

Assoziation: PbF IV

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POSTER 291

P2Y1 nucleotide receptor stimulation in the prefrontal cortex impairs working memory

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The medial prefrontal cortex (mPFC) is thought to be the highest order association area in the cortex involved in cognitive and pre-executive processes like working memory. $P2Y_1$G-protein coupled receptors ($P2Y_1$Rs) are sensitive to extracellular ATP/ADP and widely distributed in the brain. Their importance in cerebral functions is nearly unknown.
By immunofluorescence and confocal laser scanning microscopy we confirmed $P2Y_1$Rs on fibers and cell bodies of neurons and on astrocytes within the rat mPFC. We investigated behavioral responses to $P2Y_1$R stimulation by microinfusion of the agonist MRS2365 or vehicle into the rat mPFC. Sensorimotor gating measured by prepulse inhibition of the acoustic startle response was impaired by MRS2365. In social novelty discrimination, the attentional capabilities were reduced by MRS2365. The delayed non-matching to position (DNMTP) task used to assess short-term spatial memory and sustained attention was performed after training of the DNMTP rule in operant boxes. The drugs were administered before the last session which included random delays of 0, 8 or 16 sec in the trials. The accuracy in the DNMTP task was decreased by MRS2365 with increasing delay accompanied by enhanced nose pokes and magazine entries, whereas the time to complete the session was decreased, pointing to impaired working memory and enhanced impulsivity and perseveration.
Microdialysis suggests the modulation of the afferent dopaminergic transmission by $P2Y_1$R stimulation. The data demonstrate that $P2Y_1$Rs are involved in attentional processes, working memory and executive functions often affected in psychiatric diseases.

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POSTER 292

Expression and function of the SDF-1 chemokine receptors CXCR4 and CXCR7 in primary rat microglia

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The CXC chemokine, stromal cell-derived factor-1 (SDF1), binds to the chemokine receptors, CXCR4 and CXCR7, and is assumed to play a prominent role in the injured nervous system as well as in malignant brain processes. Proposed functions of SDF-1 in the injured CNS include the control of migration, proliferation, and/or differentiation of primary astroglia, oligodendroglia, and neuronal progenitors. In addition, SDF-1 promotes growth and metastasis of gliomas. Although microglia represent another known target of SDF-1, the specific functions of the chemokine on this neural cell type still remain elusive. Especially, only sparse data are available on the effects of SDF-1 on primary microglia. This issue is further intrigued by our recent demonstration that in contrast to the current view, CXCR7 does not represent a decoy chemokine receptor in astrocytes, but actively mediates SDF-1 signalling.
We now demonstrate that primary rat microglia exhibit similar high expression levels of CXCR4 and CXCR7. We further reveal that about 70% of the cells co-express CXCR4 and CXCR7 at their cell surface. On the functional level, we found that SDF-1 induces the migration of primary microglia. A subsequent screen for activated signalling molecules/pathways revealed that SDF-1 leads to the dose-dependent activation of Erk-1/2 and Akt, but not of p38, and PKC. Importantly, SDF-1-dependent activation of both signalling molecules persisted in primary microglia with depleted expression of CXCR4. Collectively, our findings unravel that SDF-1 is functional in primary microglia and affects these cells predominantly through CXCR7.

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POSTER 293

Microinjection of iron into the mouse brain leads to oxidative stress followed by neurodegeneration

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Oxidative stress is one of the key-factors in the development and progression of neurodegenerative diseases like Alzheimer`s (AD) and Parkinson`s disease (PD). It is known that free radicals produce oxidative damage, which affects neuronal components and leads to neuronal loss in brains of AD patients. Beside copper, iron is believed to contribute to oxidative stress in AD brains by catalyzing the generation of free radicals. In particularly hydroxyl radicals ($OH^{\cdot}$) lead to neurodegeneration by damaging cell membranes and DNA. Here, we analyze degenerative effects of iron in the mouse brain. Therefore, wildtype mice were microinjected with 0.2μl of a 20mM solution of ferric chloride into the left barrel field. Mice of the control group received an equal volume of 0.9% NaCl with the pH adjusted to the ferric solution. After 24h alternatively 72h the mice were perfused intracardially under deep anesthesia. Brains were removed, sectioned and analyzed using Fluorojade-staining as well as H2AX-labelling to visualize neuronal degeneration. These methods help us to assess the degree of damage, caused by iron-induced oxidative stress. Surprisingly, the range of neurodegeneration in the brain was smaller after 72h in comparison to 24h. This suggests an early start of regenerating processes that will be analyzed in future projects.

Assoziation: PbF IV

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POSTER 294

Neurons associated with aggrecan-based perineuronal nets in subcortical regions are protected against tau pathology in Alzheimer's disease

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The biological basis for the selective vulnerability of neurons in Alzheimer's disease (AD) is elusive. Aggrecan-based perineuronal nets (PNs) of the extracellular matrix have been considered to contribute to neuroprotection in the cerebral cortex. In the present study, we investigated the organization of the aggrecan-based extracellular matrix in subcortical regions known to be preferentially affected by tau pathology in AD. Immunocytochemistry of aggrecan core protein was combined with detection of neurofibillary degeneration. The results show that many regions affected by tau pathology in AD, such as the basal nucleus of Meynert, the dorsal thalamus, hypothalamic nuclei, raphe nuclei, and the locus coeruleus were devoid of a characteristic aggrecan-based extracellular matrix. Regions composed of nuclei with clearly different intensity of tau pathology, such as the amygdala, the thalamus and the oculomotor complex, showed largely complementary distribution patterns of neurofibrillary tangles and PNs. Quantification in the rostral interstitial nucleus of the medial longitudinal fascicle potentially affected by tau pathology in AD revealed that tau pathology was not accompanied by loss of aggrecan-based PNs. Neurofibrillary tangles in net-associated neurons were found extremely rarely in the pontine reticular formation. We conclude that the low vulnerability of neurons ensheathed by PNs previously described for cortical areas in AD represents a more general phenomenon that also applies to subcortical regions. The aggrecan-based extracellular matrix of PNs may thus, be involved in neuroprotection.

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POSTER 295

Effect of various stress conditions on processing of vascular endothelial amyloid precursor protein

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Endothelial cells (EC) of the cerebral microvasculature co-exist in proximity with neurons and astrocytes, forming a functional neuro-glia-vascular unit. In pathologic situations such as hypoxia, each of these cells secrete cell-type specific factors that may, when produced in excess, be toxic. In particular, the vascular endothelial growth factor (VEGF) is produced and secreted by EC in response to hypoxic or ischemic stress. The observation of enhanced VEGF expression in brains of Alzheimer patients in vicinity to β-amyloid (Aβ) plaques, suggests a link of VEGF upregulation and formation and/or deposition of Aβ. Indeed, our studies in brain slice cultures and primary neuronal cells provided evidence of a role of VEGF in processing of the amyloid precursor protein (APP; Bürger et al., 2009, 2010).
The present study stresses the hypothesis that various pathogenic conditions such as hypoxia and oxidative stress may affect processing of APP in EC. EC derived from Tg2576 mouse brain were subjected to hypoxia or hydrogen peroxide for various periods of time and the effect on APP metabolism was examined by assessment of APP cleavage products such as sAPPβ and Aβ using ELISA and Western blotting. Both hypoxia and incubations of EC by hydrogen peroxide resulted in up-regulation and secretion of VEGF into the culture medium. The data obtained so far support a role of hypoxia and oxidative stress in the pathogenesis of Alzheimer´s disease by affecting APP processing in vascular EC.
A.M. is recipient of PhD stipendship by the DAAD. S.B. gratefully acknowledges the receipt of scholarship by the Hans und Ilse Breuer Stiftung.

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POSTER 296

Bassoon speeds vesicle reloading at a central excitatory synapse

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Objective: The large scaffold protein bassoon is a central component of the presynaptic cytomatrix at the active zone (AZ), the site where vesicles release their neurotransmitter content. Deletion of bassoon has been reported to impair AZ formation and to partially silence synapses, but its molecular role remains largely unclear. Here, we investigate cerebellar mossy fibre to granule cell synapses, which are characterized by rapid vesicle recruitment at a limited number of release sites, in control and bassoon knockout mice. Methods: We recorded spontaneous miniature EPSCs, EPSCs evoked by low-frequency stimulation, and EPSCs during and following trains of high-frequency stimulations at individual MF-GC connections. Results: Basal synaptic transmission was normal in bassoon knockout (*bsn*$^{-/-}$) compared to control mice. During sustained synaptic transmission, however, synaptic depression was more pronounced in *bsn*$^{-/-}$ mice. In addition, recovery from depression was slower compared to control. Quantitative analysis indicated that the release probability and the number of readily releasable vesicles were normal but that the rate of vesicle recruitment was reduced by ~30% in *bsn*$^{-/-}$ mice at both room and physiological temperature. Conclusion: These results provide evidence that bassoon supports vesicle recruitment at the AZ of glutamatergic central synapses.

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POSTER 297

Doubling of release sites with normal release probability compensates for postsynaptic blockade within minutes at Drosophila active zones

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How can synapses change the probability of neurotransmitter release during synaptic plasticity? While synaptic release probability depends on the number of release-ready vesicles and the vesicular release probability, a dissection of both parameters during synaptic plasticity is difficult. Here we use the well established presynaptic homeostatic compensation upon interference with postsynaptic glutamate receptors at the *Drosophila* neuromuscular junction as a model for plastic alterations of synaptic release probability. As a genetic tool to induce synaptic homeostasis, we used animals lacking the glutamate receptor (GluR) subunit IIA and expressing only the IIB-type receptor (GluRIIB). Combining short-term plasticity analysis, cumulative excitatory postsynaptic current analysis and quantal short-term plasticity modeling, we found an increase in the number of release-ready vesicles during homeostatic compensation. Consistently, in fluctuation analysis, the number of release-ready vesicles was almost doubled in GluRIIB animals compared to controls. Quantitative confocal image analysis revealed an increase in the amount of the active zone protein Bruchpilot and stimulated emission depletion (STED) microscopy showed an enlargement of the presynaptic cytomatrix structure during homeostatic compensation. Furthermore, we analysed homeostatic compensation on a shorter timescale by incubation with the GluR blocker Philanthotoxin and found similar alterations. Our results demonstrate that synaptic homeostasis regulates the number of release-ready vesicles on the time scale of minutes to weeks by structural protein redistributions.

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POSTER 298

Dendritic calcium pumps limit the spread of long-lasting synaptic calcium signals

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In spiny dendrites of cerebellar Purkinje neurons, repetitive stimulation of afferent parallel fibers (PFs) induces sustained calcium signals, which are thought to trigger the induction of certain forms of long-term depression (LTD; Eilers et al., Learning & Memory, 1997). These calcium signals remain relatively constant both in their amplitude as well as in their spatial extend during ongoing synaptic activity. At the border between active and inactive dendrites, the intracellular calcium concentration forms a gradient that drops e-fold from ~600 nM to resting values over 3.8 μm. Given high concentration of the mobile endogenous calcium buffers calbindin and parvalbumin, such steep gradients were rather unexpected. We analyzed the spatial profile of the calcium signals with a combination of imaging experiments and mathematical approximations. Our analysis predicts that neither the exogenous calcium indicator dye nor endogenous buffers significantly influence the shape of the calcium gradient. Instead, the capacity of dendritic calcium clearance mechanisms determines the steepness of the gradient and, correspondingly, the spread of dendritic calcium signals.

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POSTER 299

Inhibition of VEGF signaling differentially alters processing of APP in primary cultured neurons, astrocytes and endothelial cells

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The upregulation of the vascular endothelial growth factor (VEGF) in response to hypoxic, or ischemic stress as well as in brains of Alzheimer patients in vicinity to β-amyloid (Aβ) plaques, suggests a link of angiogenesis, VEGF upregulation and formation of Aβ. In testing this hypothesis, brain slices, primary neuronal, astrocytic, and vascular endothelial cells that over express the Swedish mutation of human amyloid precursor protein (APP), were exposed by VEGF, and the effect on APP metabolism was examined. VEGF exposure of brain slices resulted in a transient increase in the APP β-cleavage product sAPPβ, and reduced formation of Aβ, accompanied by decreased β-secretase activity, as compared to controls. Exposure of neuronal cells by the VEGF receptor inhibitor SU5416 for 24 hours resulted into increased release of sAPPβ, and strikingly enhanced secretion of Aβ into the culture medium, which was accompanied by increased β-secretase activity. VEGF hardly affected APP processing in primary astrocytes, whereas incubation by SU5416 for 24h decreased the secretion of Aβ and sAPPβ into the culture medium, as compared to controls. The SU5416-induced effects could not be suppressed by the additional presence of VEGF, suggesting that SU5416 affects pathways apparently independent of VEGF receptor signaling. The data support our hypothesis of a role of VEGF in the pathogenesis of Alzheimer´s disease by affecting APP processing but differentially acting in cells forming the neuro-glia-vascular unit. Supported by Alzheimer Forschung Initiative (AFI) to R.S. S.B. is a recipient of a scholarship by the Hans und Ilse Breuer Stiftung.

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POSTER 300

COMP-Angiopoietin-1 changes the neuropathy profile of sciatic nerve in leptin-deficient ob/ob mice

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Peripheral diabetic neuropathy (PDN) is a serious complication of diabetes which carries the degeneration of sensory fibres, endoneural microvessels and high risk of pain. We have recently demonstrated that the neuropathic changes in sciatic nerve of leptin-deficient ob/ob mice occur prior to the development of advanced stage of diabetes. Since cartilage oligomeric matrixprotein (COMP)-Ang-1, a soluble, stabile form of Ang-1 promotes angiogenesis and nerve growth, we hypothesize that it could induce the regeneration of nerve fibres and endoneural microvessels in diabetic mice. In this study, COMP-Ang-1 [100ng/ml] or NaCl were i.p. injected into 3-month old, ob/ob or ob/+ mice for 7 and 21 days. Time course observations revealed that COMP-Ang-1 reduced fasting blood glucose level and plasma cholesterol in ob/ob mice compared with NaCl treatment. COMP-Ang-1 1) up-regulated expression of neurofilament 68 and GAP43; 2) recovered synthesis of endo-and perineural gap junction proteins such as connexin (Cx) 32 and Cx26 and 3) suppressed the expression of inflammatory factors: TNFa or Cx43 in sciatic nerve of ob/ob mice evaluated by Western Blot analysis. Moreover, COMP-Ang-1 treated ob/ob mice showed regeneration of small-diameter endoneural microvessels (visualized by FITC injection) compared with NaCl treatment for 21 days. Effects of COMP-Ang-1 corresponded to increased phosphorylation of Akt and p38MAP upon Tie-2 receptor. These findings strongly point that COMP-Ang-1 can promote the healing of degenerating peripheral nerve through enhanced neuritogenesis, microangiogenesis and suppressed inflammation in diabetic subjects.

Funding: formel1

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POSTER 301

Saffron and trans-crocetin inhibit the atp-induced calcium mobilisation in rat neuroblastoma cells

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Saffron, the dried stigmata of *Crocus sativus* L., is used in traditional medicine for indications like cramps, asthma and depressive mood. Studies indicate a neuroprotective potential of saffron. We found that an hydro-ethanolic saffron extract (CSE) and trans-crocetin, a carotinoid from saffron, act antagonistic on NMDA receptors. Another study showed, that trans-crocetin inhibits the ADP-induced platelet aggregation by decreasing intracellular Ca^{2+} release and extracellular Ca^{2+} influx.

In this study we examined the influence of CSE and trans-crocetin on the ATP-induced increase of the intracellular calcium concentration ($[Ca^{2+}]_i$) in rat B104 neuroblastoma cells using a FURA-2-imaging system. ATP caused a concentration dependent (1 nM – 1 mM) increase of the $[Ca^{2+}]_i$ with a transient peak descending to a plateau phase. The maximum effect was induced by 100 μM. The basal level of $[Ca^{2+}]_i$ decreased in Ca^{2+}-free medium containing 1 mM EGTA. The ATP (100 μM) induced Ca^{2+} peak was reduced and the plateau phase was removed under this conditions, indicating an initial release of Ca^{2+} from intracellular stores and an influx of extracellular Ca^{2+}.

CSE (200 μg/ml) decreased the ATP-induced Ca^{2+} mobilisation by 51.0 ± 3.1 %. The effect was concentration dependent (10-200 μg/ml) and still remained after a washout period of 15 min. Trans-crocetin 10 μM inhibited the ATP-induced Ca^{2+} mobilisation by 26.1 ± 2.8 %. The effect was concentration dependent (1-50 μM) but not reversible after a washout period of 15 min.

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POSTER 302

Facilitation at recurrent Purkinje neuron synapses of calbindin-D28k mutant mice

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Aims and Methods: Neighboring Purkinje neurons (PNs) connect each other via recurrent axon collaterals, which form synapses that switch from paired-pulse depression to facilitation (PPF) during postnatal development [1]. It has been suggested that saturation of the high-affinity Ca^{2+}-binding protein calbindin-D28k (CB), which is abundantly expressed in PNs, underlies facilitation [2]. Here we addressed this hypothesis using paired electrophysiological recordings from wild-type (WT) and CB mutant mice. Results: We confirm that PPF occurs at WT synapses of 8 to 12 days-old mice with a paired-pulse ratio of ~1.5 at 5 ms interstimulus intervals (ISI). We find that PPF mainly results from a high failure rate of ~45% in the first release process that declines to ~25 % for the second release (at 5 ms ISI). In CB mutants PPF was not significantly different from the WT, but the failure rate in both, the first and second response were significantly increased. Conclusion: These findings argue against the hypothesis that saturation of CB is the dominant factor governing PPF at recurrent PN synapses, but suggest that CB could be part of the presynaptic cytomatrix, possibly involved in linking release sensor and Ca^{2+} channels.

Supported by the DFG.

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POSTER 303

Non-viral gene delivery as an innovative shuttle-system to target neurons in vivo

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Neurodegeneration in Alzheimer's disease might, at least in part be due to an incomplete re-entry of neuronal cells into the cell cycle resulting in neuronal dedifferentiation and apoptosis.
Application of the physiological inhibitors of the cyclin dependent kinases 4 and 6, critical gatekeepers of the cell cycle, might prevent cell cycle re-entry and, thus exert neuroprotective effects. Especially $p16^{INK4a}$ is the most promising inhibitor because it can constitute stable binary complexes with both, cdk4 and cdk6, and has already shown to protect neurons against neurotoxic damage *in vitro* and *in vivo* by our working group.
Here we present an approach of a therapeutical tool for neuron-specific gene transfer of cell cycle inhibitors into the brain to delay or even to prevent neurodegeneration. In our experiments we used the polycation polyethylenimine (PEI) coupled with specific antibodies (ab) possessing high affinity to surface receptors of the target cell. Complexation between PEI/ab-PEI and a $p16^{INK4a}$-GFP-vector was determined *in vitro* by transfection and binding studies in cell culture and *in vivo* by stereotactic injection into the hippocampus and the medial septum of mice. Our results show that this system can successfully be used for non-viral gene delivery *in vitro* and *in vivo*. Furthermore, injection of $p16^{INK4a}$ complexed with PEI/ab-PEI exhibits a neuroprotectic effect on cells subjected to neurotoxic damage with N-Methyl-D-Aspartic acid (NMDA). This was analysed by Fluoro-Jade staining and immunohistochemical application of specific neuronal and cellular markers.

Assoziation: PbF IV
Funding: formel1

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POSTER 304

Species-specific differences in glutaminyl cyclase expression in mammalian brain

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Glutaminyl cyclase (QC) converts N-terminal glutam(in)yl residues into pyroglutamate (pE), thereby stabilizing these peptides. Recently, it has been shown that QC also plays a pathogenic role in Alzheimer's disease by generating the disease-associated pE-Abeta from N-terminally truncated Abeta peptides *in vivo*. However, the brain region- and species-specific expression of QC as well as its subcellular localization are largely unknown. Therefore, the present comparative immunohistochemical study was performed to reveal the cellular localization of QC in different brain regions of four mammalian species: mouse, rat, cat and dog.
We observed robust QC expression by many hypothalamic neurons, moderate QC expression by a low proportion of neurons in hippocampus and neocortex, and by a high percentage of Edinger-Westphal nucleus and locus coeruleus neurons in brains from mice and rats. Brains from other mammalian species which are reported to display Abeta pathology, such as dog and cat, were also evaluated for QC expression and QC immunoreactive neurons were generally found in the same brain regions as demonstrated for mice and rats. In all species investigated, the density of QC immunoreactivity in individual neurons was highest perinuclearly and declined towards the cellular periphery.
Our data indicate that QC is expressed in brain regions and by neuronal populations affected by Abeta pathology in Alzheimer's disease. Moreover, there are substantial differences in cortical QC expression levels between mammalian species which should be considered when using laboratory animals as *in vivo* models to study QC functions.

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POSTER 305

Human traumatic brain injury induced astrogliosis – involvement of P2Y1 receptors?

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Traumatic brain injury (TBI) is an important cause of death and disability in humans. TBI is highly correlated with the induction of astrogliosis, characterized by qualitative and quantitative changes of astrocytes. Knowledge of specific receptors (R) and transduction mechanisms involved in astrogliosis are crucial for diagnosis and treatment. In previous *in vivo* studies in rats after mechanical injury we have shown the involvement of purinergic receptors, e.g. the P2Y1R in gliotic- and anti-apoptotic processes. The aim of the present study was to verify a possible influence of this subtype in astrogliosis in human brain.
Based on human post mortem autopsy material of TBI patients, astroglial reaction around the traumatic area in the prefrontal cortex was investigated using histology, immunohistochemistry and Western blot techniques.
The results indicate that TBI in human is associated with an elevated expression of the number of GFAP-positive cells and protein content in relation to the post traumatic period as well as with a time-dependent up regulation of the P2Y1R expression in the peritraumatic area. To confirm the localisation of this subtype we performed multiple immunofluorescence studies indicating the astrocytic character of P2Y1-positive cells. Furthermore, after TBI the expression of other markers for neuronal and glial cells as well as apoptosis was investigated.
In conclusion, present data show for the first time the involvement of the P2Y1R subtype in injury-induced astroglial reaction in human, suggesting specific roles of purinergic receptors in glial cell pathophysiology in neurodegenerative diseases.

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POSTER 306

Untersuchungen zum Wissenserwerb von Nichtmedizinern im Fach Anatomie

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Naturwissenschaftlern, die sich im Rahmen einer postgradualen Ausbildung im Fach Anatomie fortbilden möchten, können auf Grund von Zeitmangel nur knapp bemessene Präsenzveranstaltungen wahrnehmen. Ergänzende Lehrbücher sind oft zu viel zu ausführlich und konfrontieren den Leser mit einer Vielzahl lateinischer Fachtermini.
Deshalb wird derzeit geeignetes Arbeitsmaterial für eine E-Learning-Plattform entwickelt, gefördert durch Mittel aus dem europäischen Sozialfond.
Eine zweistufige quasi-experimentelle Studie ging der Frage nach, ob interaktives (Lösungen müssen selbst erarbeitet werden) oder reproduktives Lernen (vorgegebener Text) zu besseren Ergebnissen führt. Der aktuelle Wissenstand wurde durch einen Vortest aus 20 multiple choice-Fragen erfasst und danach die Teilnehmer in drei etwa gleich starke Gruppen eingeteilt. Beide Interventionsgruppen bekamen Lehrmaterial gleichen Inhalts, aber verschiedener Ausführung, mit einem Evaluationsbogen im Anhang. Die Kontrollgruppe nahm nur an den Tests, aber nicht an der Intervention teil. Nach einer Woche wurde in einem Nachtest (27 offene Fragen) der Wissenszuwachs erfasst und mittels statistischer Verfahren ausgewertet.
Bewertet man den kurzfristigen Wissenszuwachs, ergeben sich keine signifikanten Unterschiede zwischen dem Lernen mit interaktiven bzw. reproduktiven Arbeitsmaterial. Das Erarbeiten der Lösungen nahm mehr Zeit in Anspruch, verspricht jedoch langfristig eine bessere Retention des Wissens.
Für die Implementierung des Arbeitsmaterial in die E-Learning-Plattform schlagen wir deshalb eine Synthese aus interaktivem Arbeiten und leicht nachschlagbaren Lösungen vor, um die Vorteile beider Methoden kombinieren zu können.

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POSTER 307

Modulation of the steady-state visual evoked potential (SSVEP) by overt and covert attention

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Flickering stimuli evoke an oscillatory brain response with the same frequency as the driving stimulus, called the SSVEP. SSVEPs are robust brain signals and thus play a major role in the development and use of non-invasive Brain Computer Interfaces (BCIs). We investigated the impact on SSVEP amplitudes when subjects either directly gaze at a flickering stimulus (overt attention) or covertly shift attention to such a stimulus.
A detection task was performed at the attended location in order to ensure that subjects shifted attention as instructed. Horizontal eye movements (allowed in overt attention but to be avoided in covert attention) were monitored by the horizontal electrooculogram. The modulation of SSVEP amplitudes by overt attention was larger than by covert attention. Additionally, overt attention changed the topographical distribution of SSVEP amplitudes on the scalp, with overtly attended stimuli eliciting the greatest amplitudes at central electrodes. These results show that navigating BCIs with SSVEPs can be more reliable with overt attention and highlight some of the challenges in developing BCIs for patients who lack control of eye movements.

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POSTER 308

Vergleichende Analysen der SDQ-Daten von Kindern mit einem psychisch erkrankten Elternteil im Vergleich zu den Ergebnissen des Kinder- und Jugendgesundheitssurveys (KiGGS)

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Einleitung: Bei den vorliegenden Analysen handelt es sich um die Ergebnisse des Projektes HELP-S: Hilfen, wenn Eltern psychisch erkranken in Sachsen. Bis zu 30% der ambulant versorgten Patienten in Deutschland haben mindestens ein minderjähriges Kind. Die Erkrankung eines Elternteils stellt eine hohe psychosoziale Belastung für Kinder dar und ist gleichzeitig ein Risikofaktor für die Entwicklung psychischer Störungen. Bisherige Studien fokussieren auf den stationären Kontext.

Methode: An einem Stichtag wurden Patienten, die mindestens ein minderjähriges Kind haben, in 43 Nervenarztpraxen in Sachsen mittels Fragebogen befragt. Für 105 Kinder liegen vollständige Informationen zum Strength and Difficulties Questionnaire (SDQ – Elternversion) vor. Der SDQ liefert, neben einem Gesamtproblemwert, Scores für die Subskalen emotionale Probleme, Hyperaktivitätsprobleme, Verhaltensprobleme, Probleme mit Gleichaltrigen und prosoziales Verhalten.

Ergebnisse: Fast die Hälfte der Eltern schätzte ihre Kinder im Alter von 3 bis 17 Jahre im SDQ als psychisch auffällig ein. In der Elternversion des SDQ erreichten 41,9% der Kinder grenzwertige oder auffällige Gesamtproblemwerte, nach dem Kinder- und Jugendgesundheitssurvey (KiGGS) weisen 18,5% der Kinder und Jugendlichen in der Allgemeinbevölkerung grenzwertige oder auffällige Werte im SDQ auf($t=4{,}322$ ($df=112$, $p<0{,}001$). Bei den Werten der Subskala „Prosoziales Verhalten“ zeigen sich keine signifikanten Unterschieden zwischen den Werten von Kinder psychisch erkrankter Eltern im Vergleich zu den Ergebnissen der KiGGS Studie ($t=-1{,}673$ ($df=104$, $p=0{,}097$).

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POSTER 309

Selective maintenance of intensity information accounts for transient spatially biased sensory processing in a tactile DMS task

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We used a delayed match-to-sample (DMS) task to investigate the impact of selection from short-term memory on a spatially specific neural correlate, the somatosensory N140. A pair of sample stimuli with differing magnitudes was presented simultaneously to both hands. The subsequent visual retro-cue determined the category (weak, strong) of the target. Participants were asked to maintain the target intensity and ignore the distractor. Spatially specific sensory processing was probed by irrelevant pulses that were presented shortly after the cue. Locations of samples, probes and test stimuli were randomized. Hence, spatial anticipation of tests was ruled out; maintenance of spatial properties was not required by the task. We found enhanced N140 amplitudes for probes that shared spatial properties (same hand) with the memorandum. This modulation was absent for test stimuli. We conclude that the selection of intensity information from a memory trace is mediated by transient spatial orienting mechanisms.

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POSTER 310

Die Erfassung transgenerationaler Effekte nach politischer Inhaftierung in der SBZ/DDR

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Aus Befunden der Psychotraumatologie kann geschlussfolgert werden, dass eine elterliche Traumatisierung auch Auswirkungen auf die Nachkommen haben kann. In einer Pilotstudie wurde erstmals die transgenerationale Weitergabe von politischer Traumatisierung in der SBZ/DDR untersucht. Indikatoren hierfür waren Psychopathologie, familien- (u.a. Bindung) und ressourcenspezifische Items (u.a. Resilienz).
Der eigens für die Studie entwickelte und von Experten validierte Fragebogen wurde an insgesamt 100 Kindern von ehemals politisch Inhaftierten versendet, die auf multimodalem Wege rekrutiert wurden (z.B. Aufrufe in Zeitschriften). Der Fragebogen enthielt standardisierte Screeninginstrumente (z.B. AAS, PHQ, GAD7, IES-R, RS) und themenspezifische Items. Die Ergebnisse wurden mit einer alters- und geschlechtsgematchten Repräsentativstichprobe verglichen.
Erste Datenanalysen der 37 TN (Ø=52J.; n=25 ♀) belegen stark erhöhte Depressivitäts- (d=.70) und Somatisierungswerte (d=.70) sowie höhere Angstdaten (d=.43). Bei 26,5% der Befragten liegt eine PtBs vor. Höhere Werte werden auch hinsichtlich des Bindungsmerkmals Distanzverhaltens berichtet (d=.27). Die Resilienz ist tendenziell niedriger als bei Vergleichspersonen (d=.13).
Im Vergleich zur Allgemeinbevölkerung berichten die Kinder ehemals politisch inhaftierter Personen in der DDR/SBZ erhöhte Werte im Bereich der affektiven Störungen, was für eine Vulnerabilität spricht. Zudem sind Bindungsmerkmale verändert, die Resilienz hingegen nicht in bedeutsamer Weise. Zukünftig müssen die Ergebnisse anhand größerer Fallzahlen überprüft und vermittelnde Mechanismen untersucht werden.

Funding: formel1

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POSTER 311

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

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Ziel: Der Verlust eines Kindes während der Schwangerschaft bedeutet für viele Eltern ein traumatisches Erlebnis, das mit anhaltenden Trauerreaktionen und bedeutsamen psychischen Belastungen bis hin zu psychischen Störungen einhergehen kann. Diese Studie untersucht die Wirksamkeit eines Internet-basierten Therapieprogramms für Eltern im deutschsprachigen europäischen Raum, die einen solchen Verlust erlebt haben.
Methode: In einer randomisierten Kontrollgruppenstudie wurden die weiblichen Teilnehmer (n= 83) zufällig entweder einer 5-wöchigen Internet-basierten Behandlung oder einer 5-wöchigen Wartelistenbedingung zugeordnet. Während der manualisierten kognitiv-behavioralen Therapie schrieben sie 10 Texte über ihre Verlusterlebnisse. Nach jedem zweiten Text erhielten sie ein individuelles Feedback von ihrer Therapeutin. Die Teilnehmerinnen der Kontrollgruppe durchliefen im Anschluss an die Wartezeit die gleiche Behandlung. Es wurden Prä- und Post-Messungen und ein 3-Monats-Follow-up durchgeführt, bei denen Trauer, posttraumatischer Stress, Depression und allgemeine psychische Gesundheit erfasst wurden.
Ergebnisse: Die Teilnehmerinnen der Behandlungsgruppe zeigten, verglichen mit den Teilnehmerinnen der Kontrollgruppe, hoch signifikante Verbesserungen hinsichtlich Trauer, posttraumatischem Stress, Depression und allgemeiner psychischer Gesundheit. Es ergaben sich mittlere Effektstärken, die über das 3-Monats-Follow-up stabil blieben.
Fazit: Das Internettherapieprogramm kann einen Beitrag dazu leisten, die Versorgungssituation für Eltern, die während der Schwangerschaft ihr Kind verloren haben, zu verbessern.

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POSTER 312

Bindungsvermeidung und automatische affektive Reaktion auf Gesichtsausdruck

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In vorliegender Studie wird die Beziehung zwischen Bindungsvermeidung und -angst im Erwachsenenalter und automatischer affektiver Reaktion auf emotionalen Gesichtsausdruck untersucht. Nach Mikulincer und Shaver (2003) sollten bindungsvermeidende Personen auf Nähewünsche bzw. Kummer anderer abweisend reagieren – nicht aber auf positive interpersonale Signale. Der mimische Ausdruck von Traurigkeit bzw. Freude obwohl unterschiedlicher Valenz signalisiert jeweils eine Aufforderung zu sozialer Interaktion und Annäherung. Die Methode des subliminalen affektiven Primings (Murphy & Zajonc, 1993) ermöglicht die Erfassung automatisch ablaufender affektiver Reaktionen. In unserer Studie wurde eine affektive Primingaufgabe 30 gesunden Erwachsenen vorgegeben, in der traurige und freudige Gesichter maskiert gezeigt wurden. Die Probanden füllten den Relationship Scales Questionnaire sowie Fragebogen zu Ängstlichkeit und Depressivität aus. Bindungsvermeidung korrelierte invers mit dem negativen (auf traurigem Gesichtsausdruck basierenden) affektiven Priming. Dieser Zusammenhang bestand unabhängig von Bindungsangst, allgemeiner Ängstlichkeit und Depressivität. Bindungsangst korrelierte mit keinem affektiven Primingscore. Demnach erscheint Bindungsvermeidung einen Einfluss auf die automatische affektive Reaktion auf traurige Mimik zu haben und könnte mit einer Reduzierung der spontanen affektiven Reaktivität auf Traurigkeit zusammenhängen.

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POSTER 313

Familiarity Influences the Rating of Emotional Pictures

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Paramedics are experts for the case of emergency so they are often exposed to unpleasant situations and accidents. We expected that paramedics would rate emotional unpleasant pictures with medical content (trauma, mutilations, accidents and injection) as less unpleasant and arousing compared to other unpleasant pictures (human and animal threat) as well as compared to a control group.
Fife paramedics and 12 students rated 135 pictures (45 neutral, 45 medical unpleasant and 45 other unpleasant pictures) from the International Affective Picture System (IAPS; Lang, Bradley & Cuthbert, 2008). Subjects were asked to rate valence and arousal of every picture on the 9-point Self-Assessment Manikin (SAM) scale. In addition, the participants rated the familiarity of each image on a 9-point scale.
First results showed that paramedics rated their group-specific picture set as less unpleasant, more familiar and less arousing compared to the control group and compared to other unpleasant emotional images.
A positive correlation was found for the familiarity and the valence of medical pictures as well as a negative correlation between familiarity and arousal. These first results suggest that a higher familiarity of the picture results in higher valence (i.e. less unpleasant) and lower arousal.

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POSTER 314

Impact of Impairment in Instrumental Activities of Daily Living and Mild Cognitive Impairment on Time to Incident Dementia – Results of the Leipzig Longitudinal Study of the Aged (LEILA75+)

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Background: Early diagnosis of dementia requires knowledge about associated predictors. The aim of this study was to determine the impact of mild cognitive impairment (MCI) and impairment in instrumental activities of daily living (IADL) on the time to an incident dementia diagnosis.
Methods: Data were derived from the Leipzig Longitudinal Study of the Aged (LEILA75+), a population-based study of individuals aged 75 years and older. Kaplan-Meier survival analysis was used to determine time to incident dementia. Cox proportional hazards models were applied to determine the impact of MCI and impairment in IADL on the time to incident dementia.
Results: 180 (22.0%) of 819 initially dementia-free subjects developed dementia by the end of the study. Mean time to incident dementia was 6.7 years (95% CI = 6.5-6.9). MCI combined with impairment in IADL was associated with a higher conversion rate to dementia and a shorter time to clinically manifest diagnosis. The highest risk for a shorter time to incident dementia was found for amnestic MCI combined with impairment in IADL: the mean time to incident dementia was 3.7 years (95% CI = 2.9-4.4) and thus half as long as in subjects without MCI and impairment in IADL.
Conclusions: Subjects with MCI and impairment in IADL constitute a high-risk population for the development of dementia. The consideration of impairment in IADL should constitute an important step towards an MCI concept being clinically more useful for prediction of dementia.

Funding: formel1, life

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POSTER 315

How 'social' is the social Simon effect?

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Many activities we perform in daily life are carried out together with other people. But how do we mentally represent other people's actions? The social Simon effect has been considered to provide an index for action co-representation. Here, we investigated whether joint-action effects in a social Simon task involve mechanisms of action co-representation, as measured by the amount of the mental incorporation of another person's action into one's own cognitive representation. We combined an auditory social Simon task with a manipulation of the sense of ownership of another person's hand (Rubber Hand Illusion). If the social Simon effect is mediated by action co-representation then the synchronous stroking should increase the size of this effect. However, we found the social Simon effect to be smaller in the synchronous as compared to the asynchronous stroking condition (Exp.1), suggesting that the social Simon effect reflects the representation of spatially separated action events rather than the co-representation of the other person's action. This effect is independent of the active involvement (Exp. 2) and the presence of another person (Exp. 3). These findings suggest that the 'social' Simon may be socially induced but is not really social in nature. Rather than requiring or necessarily reflecting the co-representation of the other person's action into an individual's own body and/or task representation, the effect seems to result from salient social or non-social actions or events that induce the coding of an individual's own action as left or right—a necessary condition for the Simon effect to emerge.

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POSTER 316

Disentangling prosodic and syntactic influences on the early left anterior negativity (ELAN)

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In auditory language comprehension, syntactic operations are the key element to build a sentence structure. Previous studies violating the local syntactic sentence structure have reported an early left anterior negativity (ELAN) of the event-related potential that peaks at around 100 – 200 ms. These studies strongly controlled for possible prosodic influences on the syntactic processes. However, a change in the prosodic contour occurred together with the syntactic violation. The goal of the present magnetoencephalography (MEG) study was to disentangle both superimposed influences on the ELAN. Neural activations elicited by a syntactic word category violation were compared to neural activations elicited by a prosodically incongruent sentence contour, in order to estimate the contribution of a prosodic incongruency to the ELAN effect. The results show a clear picture. Not only elicited the syntactic violation stronger superior temporal cortex activations than the pure prosodic violation in the 110 – 160 ms time window, but moreover showed a left-hemispheric bias that was not present for prosodically incongruent sentences. In addition, only the syntactic violation elicited a very early effect at around 60 ms. Thus, the current findings show that the ELAN effect cannot be attributed to the detection of an prosodic incongruency, but is primarily driven by syntactic structure building difficulties.

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POSTER 317

The assessment of changes in cognitive functioning: Age, education and gender specific Reliable Change Indices (RCIs) for older adults tested on the CERAD-NP battery. Results of the German Study on Ageing, Cognition and Dementia in Primary Care Patients

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Evolution and Molecular Diversity

Background/Aims: The diagnosis of dementia requires reliable evidence about decline in cognitive functioning over time. The CERAD-NP battery represents a commonly used neuropsychological instrument to measure cognitive functioning in the elderly. Normative data for changes in cognitive function that normally occur in cognitively healthy individuals is crucial to interpret changes in CERAD-NP test scores. *Methods:* As part of the German Study on Ageing, Cognition and Dementia in Primary Care Patients (AgeCoDe Study), a sample of 1450 cognitively healthy individuals, aged 75 years and older, was assessed three times at 1.5 year intervals over a period of 3 years using selected subtests of the CERAD-NP battery. Age, education and gender specific reliable change indices (RCIs) were computed for a 90% confidence interval. *Results:* Across different age, education and gender subgroups, changes from at least 6 to 9 points in Verbal Fluency, 4 to 8 points in Word List Memory, 2 to 4 points in Word List Recall and 1 to 4 points in Word List Recognition indicated significant (i.e. reliable) changes in CERAD-NP test scores at the 90% confidence level. *Conclusion:* Smaller changes in CERAD-NP test scores can be interpreted only with high uncertainty because of probable measurement error, practice effects and normal age-related cognitive decline. This study provides age, education and gender specific CERAD-NP reference values for the interpretation of cognitive changes in older age groups.

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POSTER 318

Does the Clock Drawing Test predict dementia? – Results of the Leipzig Longitudinal Study of the Aged (LEILA 75+)

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Background/ Aims: High conversion rates to dementia are known for MCI patients, but diagnosis of MCI is mostly very time consuming. Due to the fact that the Clock Drawing Test (CDT) is quick to administer, it will be of interest to compare the predictive validity of the CDT and of an MCI diagnosis for the diagnosis of dementia.
Methods: CDT scores and diagnosis of MCI were assessed at baseline and were compared between patients with incident dementia and those without (n= 384). Multivariate analyses, receiver operating characteristic analyses and values of sensitivity and specificity of the CDT were calculated.
Results: Individuals with incident dementia had significantly higher CDT scores at baseline than those without dementia. CDT also was a significant predictor of incident dementia after adjusting for other factors. But CDT reached a nonsatisfying sensitivity (68%) and specificity (65%). The area under the receiver operating characteristic curve of CDT was at 0.70 and therefore slightly lower than for MCI diagnosis (0.78).
Conclusions: Because of the only slightly lower predictive value of the CDT, its quick application and scoring compared to the MCI concept applied, it will be worthwhile to improve the CDT scoring system in order to increase the predictive validity in dementia.

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POSTER 319

Altersunterschiede in empathischer Akkuratheit: Gibt es Entwicklung vom Jugend- ins mittlere Erwachsenenalter?

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Die Fähigkeit, die Gefühle einer anderen Person richtig einschätzen zu können, spielt als kognitive Facette der Empathie in jedem Lebensalter eine wichtige Rolle, u.a. für altruistisches Verhalten, moralische Entwicklung und die Qualität zwischenmenschlicher Beziehungen. Die entwicklungspsychologische Forschung zu diesem Thema konzentriert sich jedoch vor allem auf die Kindheit. Ob sich die hier gefundenen altersbezogenen Gewinne auch bis ins Jugend- und Erwachsenenalter fortsetzen, ist bisher noch ungeklärt. Da jedoch eine ganze Reihe sozial-kognitiver und affektiver Fähigkeiten, die mit empathischer Akkuratheit zusammenhängen könnten (u.a. weisheitsbezogenes Wissen, kognitiv-affektive Komplexität), gerade in diesem Lebensabschnitt einen altersbedingten Zuwachs zeigen, gehen wir von einer kontinuierlichen Zunahme der empathischen Akkuratheit vom Jugend- bis ins mittlere Erwachsenenalter aus. Zur Überprüfung unserer Hypothese haben wir 90 männliche Probanden aus drei Altersgruppen (14-17, 25-35, 45-55) gebeten, die Gefühle von neun männlichen Targetpersonen einzuschätzen, die in Videofilmen von einer Minute Länge autobiographische, emotionale Situationen schildern. Unsere Annahmen konnten teilweise bestätigt werden. So wiesen Jugendliche geringere empathische Akkuratheit als junge und mittelalte Erwachsene auf. Letztere unterschieden sich jedoch in ihren Leistungen nicht voneinander. In weiteren Analysen soll nun untersucht werden, wodurch sich die gefundenen Altersunterschiede erklären lassen und welche Rolle motivationale Faktoren (Altersrelevanz der Filme) für das Ausmaß empathischer Akkuratheit spielen.

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POSTER 320

Die Lebensqualität krebskranker Eltern

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FRAGESTELLUNG: Eine Krebserkrankung verändert das physische und psychische Erleben der Patienten und kann z. T. massive seelische Belastungen und soziale Verwerfungen nach sich ziehen. Inwieweit das Vorhandensein von minderjährigen Kindern einen moderierenden Einfluss auf das Belastungserleben der Patienten und auf unterschiedliche Funktionen der Lebensqualität im Zeitverlauf hat, wird im Rahmen eines multizentrischen, von der Deutschen Krebshilfe geförderten Forschungsprojekts nachgegangen.
METHODE: Im Zeitraum von 2009 bis 2011 erfolgt eine schriftliche Befragung von onkologischen Patienten (n=200), deren Partnern und Kindern bis 18 Jahre zu insgesamt drei Zeitpunkten (nach Diagnosestellung und jeweils ein halbes Jahr später). Die über EORTC-QLQ-C30 erfasste Lebensqualität der Patienten mit Kindern unter 18 Jahren wird über statistisches Matching mit der Lebensqualität einer gleichaltrigen Kontrollgruppe aus kinderlosen Krebspatienten (n=51) verglichen. Zum ersten Erhebungszeitpunkt liegen aktuell Daten von etwa 140 Patienten vor.
ZWISCHENERGEBNISSE: Bei Elternschaft von minderjährigen Kindern weisen Krebspatienten im Vergleich mit kinderlosen Krebspatienten nach Diagnosestellung eine in vielen Bereichen niedrigere Lebensqualität auf, vor allem in sozial- und rollenbezogenen Dimensionen. Perspektivisch erlaubt die Auswertung der Längsschnittdaten Aussagen über mögliche Wechselwirkungen zwischen der Lebensqualität der Patienten und der psychosozialen Situation der Angehörigen.

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POSTER 321

Die ÄrztInnensicht auf das PatientInnen-ÄrztInnen-Gespräch

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Dass PatientInnen mit Arzt-Patienten-Gesprächen oft unzufrieden sind, ist Ergebnis zahlreicher Untersuchungen (z. B. Langewitz et al, 2002).
Doch wie sehen ÄrztInnen das ÄrztInnen-PatientInnen-Gespräch? Was ist Ihnen dabei wichtig, auf was achten Sie?
Im Rahmen einer Interviewstudie wurden 25 klinisch tätige ÄrztInnen mittels eines teilstrukturierten Interviewleitfadens befragt.
Die transkribierten Interviews wurden in Anlehnung an die thematische Inhaltsanalyse von Burnard (1991) ausgewertet. Insgesamt wurden aus den Interviews N = 115 Textpassagen zu der Fragestellung analysiert, die zu 32 Kategorien zusammengefasst wurden.
Die wichtigste Funktion des ÄrztInnen-PatientInnen-Gesprächs aus ÄrztInnensicht ist die „Informationsvermittlung". An zweiter Stelle steht die Kategorie „Vertrauen", damit ist sowohl Vertrauen in den Arzt wie auch Vertrauen in die Behandlung gemeint. An dritter Stelle wird die Verständlichkeit der Informationen betont, was für die Interviewten bedeutet ihren Sprachstil an die PatientInnen anzupassen bzw. verständliche Sprachbilder für die Informationen zu finden.Das entstandene vollständige Kategoriensysteme wird auf dem Poster vorgestellt und unter anderem in Bezug auf die ärztliche Aus- und Weiterbildung diskutiert.

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POSTER 322

Vermittlung von Gesprächsführung im Medizinstudium – Haltungs- oder technikorientiert

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Immerwieder kommt es bei der Vermittlung der GesprächsführungstechnikAktives Zuhören zu dem Disput, ob es primär eine Technik sei oder vielmehr eine Haltung, die man seinem Gesprächspartner gegenüber einnimmt. Auch in der Literatur gibt es eine sehr facettenreiche Darstellung, die beide Sichtweisen abdeckt. Ziel der vorliegenden Untersuchung war es daher, die Auswirkungen auf das Gespräch zu untersuchen,wenn Aktives Zuhören einmalmit demSchwerpunkt Technik und einmal mit dem Schwerpunkt Haltung vermittelt wird. Es wurden zwei Gruppen á 6 TN rekrutiert, die jeweils 3 1/2 Stunden im Aktiven Zuhören mit dem jeweiligen Schwerpunkt geschult wurden. Vor und nach der Schulung mussten die TN jeweils ein Gespräch mit einer standardisierten Schauspielpatientin (SP) führen, das per Video aufgezeichnet wurde. Mittels Fragebogen wurden die TN und die SPs zusätzlich um eine Einschätzung des Gesprächs gebeten. Nach erster Sichtung der Daten schneidet die Technik-Gruppe am schlechtesten bei der Bewertung der Zufriedenheitmit den Gesprächen ab. Obwohl die TN dieser Gruppe quantitativ häufigerAktives Zuhören angewendet haben, ist die Zufriedenheit der SPsmit den Gesprächen der Haltungsgruppe um ein Vielfaches höher.

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POSTER 323

Geschlechtsspezifische horizontale und vertikale Segregation bei Ärztinnen und Ärzten

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Hintergrund: Nahezu 70% der Humanmedizinstudierenden sind inzwischen Frauen. In der weiteren beruflichen Laufbahn lässt sich ein deutlicher geschlechtsspezifischer Schereneffekt beobachten. Neben der vertikalen Segregation zeigt sich eine geschlechtsspezifische Wahl der fachärztlichen Weiterbildung.
Fragestellung: Welche Deutungsmuster der ÄrztInnen hinsichtlich ihrer beruflichen Entwicklung tragen zu dieser geschlechtsspezifischen Verteilung bei?
Methode: Mit der Methode des „theoretischen Samplings" (Glaser et al. 1967) wurden themenzentrierte Interviews zur Arbeits- und Lebenssituation mit neun ÄrztInnen in der fachärztlichen Weiterbildung und einer Fachärztin geführt. Es wurden jeweils Frauen und Männer aus geschlechtstypisch segregierten Bereichen, sowie einem nicht-segregierten Fachgebiet interviewt. Die vollständig transkribierten Interviews wurden sequenzanalytisch nach der Methode der Objektiven Hermeneutik (Oevermann 2001) und nach dem Prinzip der „minimalen und maximalen Kontrastierung" (Kelle et al. 1999) ausgewertet.
Ergebnisse: Allgemein zeigte sich ein männlich konnotiertes, hegemoniales Anforderungsmuster für an großen Krankenhäusern angestellte ÄrztInnen, was sich sowohl in Bildern der „großen Chirurgie" als Maßstab für die eigene Facharztwahl als auch in Bildern von OberärztInnen vor dem Hintergrund der eigenen beruflichen Pläne und Wünsche widerspiegelte.
Diskussion: Die Rigidität dieses Anforderungsmusters führt zu Diskriminierungen gegenüber real oder vermutet davon abweichenden Personen. Folglich erleben Frauen ihr subjektives Passungsverhältnis im Arbeitsalltag konflikthafter als Männer.

Funding: formel1

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POSTER 324

Soziodemografische Daten und die Einstellung zur Laryngektomie 1 Jahr nach der Operation

Schock J[1,2], Vogel HJ[1], Plontke S[3], Singer S[4], Keszte J[4], Brähler E[4], Breitenstein K[5], Böhm A[6], Gose A[4], Matthäus C[7], Heim ME[8], Pabst F[9], Kluge A[10], Guntinas-Lichius O[11], Oeken J[12]

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Fragestellung: Wer bereut seine Entscheidung zur Laryngektomie ein Jahr nach der Operation?
Methode: Multizentrische Länggsschnittstudie (12 HNO-Kliniken) mit 6 Befragungsszeitpunkten (hier ausgewertet: t4 = 1 Jahr nach der Laryngektomie). Die Einstellung zur Operation wurde mit dem Fragebogen zur psychosozialen Anpassung nach der Laryngektomie (FPAL, De Maddalena und Pfrang, 1990) erfasst, die Schichtzugehörigkeit über Nettoeinkommen, Schulbildung und beruflicher Stellung bestimmt.
Ergebnisse: Über 70% der Laryngektomierten (84 von 114) sind sehr zufrieden mit ihrer Behandlungsentscheidung. Es gibt keine statistischen Unterschiede zwischen den Geschlechtern und den Altersgruppen. Unterschiede wurden zwischen sozioökonomischen Schichten festgestellt: Mittelschicht ist zufriedener (n=67; 10% Bereuen) als Unter- (n=41; 17% Bereuen) und Oberschicht (n=6; 33% Bereuen).
Fazit: In der Bewertung der Laryngektomie unterscheiden sich Männern und Frauen bzw. die Altersgruppen nicht. Personen aus sozialer Ober- und Unterschicht bereuen ihre Entscheidung häufiger. Psychosoziale Veränderungen einer Laryngektomie werden von Personen des Mittelstands am besten kompensiert. Zukünftiger Forschung bleibt es, hierfür Erklärungen zu finden und Zusammenhänge mit Lebensqualitätsaspekten zu untersuchen.

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POSTER 325

Psychosoziale Unterstützung laryngektomierter Karzinompatienten durch Patientenbetreuer im Akutkrankenhaus – Longitudinaldaten einer multizentrischen Studie

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7 Klinikum Bavaria Kreischa
8 Universitätsklinikum Jena
9 Klinikum Chemnitz
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Fragestellung: Wie häufig nehmen Betroffene im Akutkrankenhaus die psychosoziale Unterstützung der Patientenbetreuer der Selbsthilfegruppen des Bundesverbandes der Kehlkopfoperierten e.V. in Anspruch und wie zufrieden sind sie damit?
Methodik: Multizentrische Längsschnittstudie (12 Kliniken) mit insgesamt 6 Befragungszeitpunkten (hier ausgewertet: t3 = Ende der Anschlußheilbehandlung). Zur Erhebung der Daten wurden strukturierte Interviews durchgeführt.
Ergebnisse: Mehr als 90% der 224 Befragten finden das Angebot der Klinikbetreuung wichtig, 42% der Studienteilnehmer nahmen es in Anspruch. Ein Großteil der Befragten bewertete die Betreuung als gut bis sehr gut. Grund für eine Nichtinanspruchnahme war meist fehlende Kenntnis über die Möglichkeit eines solchen Angebotes.
Fazit: Laryngektomierte Karzinompatienten profitieren von einer Patientenbetreuung durch Selbsthilfegruppen in der akuten Behandlungsphase. Dennoch sind viele Betroffene nicht ausreichend über diese besondere Form der psychosozialen Unterstützung informiert bzw. wird sie nicht flächendeckend angeboten. Eine Verbesserung der Zusammenarbeit von Kliniken und Selbsthilfegruppen wäre daher wünschenswert, um mehr Patienten den Kontakt zu einem Betreuer zur ermöglichen.

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POSTER 326

Patienten-Information in Leichter Sprache – Chance zur Erhöhung der Patientensouveränität

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Im Art. 9 der Konvention über die Rechte behinderter Menschen wird der barrierefreie Zugang zu Kommunikation und Informationen als Grundlage einer selbstständigen und selbstbestimmten Lebensgestaltung gefordert. Art. 25 fordert das Recht auf Information und Aufklärung in der gesundheitlichen Versorgung. Das nationale Gesundheitsziel „Gesundheitliche Kompetenzen erhöhen, Patientensouveränität stärken" verweist auf die Bedeutung informierter, aufgeklärter Patienten. Menschen mit Behinderungen oder eingeschränktem Sprachverständnis bleiben davon oft ausgeschlossen. Durch Informationssangebote in Leichter Sprache kann die Situation für diese Patientengruppen verbessert werden. Die Sprache folgt festen Regeln für Wörter, Sätze und Layout. Der Text wird durch Bilder unterstützt. Zielgruppen für Leichte Sprache sind Menschen mit unterschiedlichen Behinderungen wie kognitive Beeinträchtigungen, Hör- oder Sehbehinderungen, Hirntumoren, Schädel-Hirn-Verletzungen, Schlaganfällen, demenziellen Erkrankungen, aber auch Nichtmuttersprachler mit geringen Sprachkenntnissen.Im Kommunikationsprozess zwischen medizinischem Personal und Patient kommt es oft dazu, dass Menschen mit den genannten Beeinträchtigungen nicht in die Kommunikation einbezogen werden. Verständliche Informationen zu allen gesundheitsrelevanten Fragen zu bekommen ist ein Menschenrecht! Im Poster werden Beispiele aus Patienteninformationsmaterialien in Leichter Sprache vorgestellt. Bisher entwickelten wir Informationsmaterialien zum Thema Mamma-Ca und Prostata-Ca, zu Schwangerschaft und zu Pränataldiagnostik und Schwangerschaftsverhütung.

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POSTER 327

Epidemiology of Depression in Old Age – Results of the Leipzig Longitudinal Study of the Aged (LEILA 75+)

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Background: In order to assess future needs of the health care system for prevention and treatment, information on epidemiology of depression among the highest age groups is required. However, most previous studies just focused on prevalence and incidence rates of late life depression across the entire old age. Methods: For a population-based sample of 1,265 elderly individuals aged 75 years and older, prevalence and incidence rates as well as risk factors of depression were determined. Individuals were requested every 1.5 years over six waves. Depression was assessed dimensionally by the CES-D (Center of Epidemiologic Studies Depression Scale) and categorically by the SCID (Structured Clinical Interview for DSM-IV). The prevalence rates were 1.0% for Major Depression, 2.5% for Minor Depression according to DSM-IV and 38.2% for depressive symptoms according to CES-D. The rates increased for Minor and depressive symptoms with rising age. Risk factors were divorced or widowed marital status, low educational level, poor self-rated health status, stressful life events, and poor social network. The incidence rates were 6.9 per 1000 person-years (py) for Major Depression, 16.6 per 1000 py for Minor Depression and 33.9 per 1000 py for depressive symptoms. Discussion: Since depressive symptoms are common in oldest age and associated with broad categories of risk factors, latest-life depression represents an important public health issue. Employment of comprehensive geriatric assessment to ascertain depressive symptoms and its concomitants could help to improve treatment success.

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POSTER 328

„Ich bin froh, dass es ihn gibt" – Behinderte und chronisch kranke Mütter in Sachsen

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Hintergrund: Menschen mit Behinderungen sind oft Empfänger gesellschaftlicher Diskriminierung und Missachtung. Sind sie auf Förderung, Hilfe und Begleitung angewiesen, werden sie schnell als Last der Gesellschaft empfunden. Behinderte schwangere Frauen oder behinderte Frauen mit Kinderwunsch müssen sich für diesen rechtfertigen und stehen später unter dem Druck, dem mütterlichen Ideal mehr als nichtbehinderte Frauen entsprechen zu müssen.
Methode: Im Auftrag der Roland-Ernst-Stiftung für Gesundheitswesen Sachsen wurde eine 10%ige Zufallsstichprobe von ca. 15.000 in Sachsen gemeldeten schwerbehinderten Frauen der Altersgruppe 25-45 Jahre mit einem anerkannten Grad der Behinderung von mind. 50 gezogen. Der Rücklauf betrug 33% (N=525), wovon insgesamt 56% Kinder hatten. Davon konnten 98 für eine vertiefende schriftliche Befragung zu ihren Erfahrungen als Mutter gewonnen werden.
Ergebnisse: Unterstützung bei der Gestaltung der Mutterrolle erfahren die Betroffenen vor allem durch die eigene (Herkunfts-) Familie, den Partner und den Freundeskreis. Geistig behinderte Mütter werden am seltensten von ihren Familien unterstützt, geistig behinderte und psychisch kranke Mütter am seltensten von anderen Müttern.
Akustische Verständigungsschwierigkeiten, Orientierungsprobleme, fehlende Zeit oder Kraft der Mutter, schlechte (zeitliche und räumliche) Erreichbarkeit der Einrichtung sowie Ängste auf Seiten der Mütter sind Einschränkungen, die innerhalb der Kita oder Schule berichtet wurden.
Ihre Ressourcen sehen die Mütter selbst in Form von emotionaler Nähe, großzügigem Zeitbudget und der Vermittlung von Eigenständigkeit und humanitärem Handeln.
Die Mütter empfehlen anderen Frauen mit Behinderungen/chronischen Erkrankungen, ihren Unterstützungsbedarf klar zu benennen und weniger ängstlich zu sein, Hilfen anzunehmen. Sie selbst wünschen sich weniger bürokratische Hürden und mehr finanzielle Entlastungen, Unterstützung im Alltag und Betreuungsmöglichkeiten sowie medizinisch-therapeutische Weiterentwicklungen.

Diskussion: Partnerschaft und Familienplanung sind wichtige Bestandteile im Leben von behinderten/chronisch kranken Frauen und stellen heutzutage keine Ausnahme mehr dar. In der Gestaltung der Mutterrolle erfahren (mit Ausnahme der geistig behinderten Frauen) behinderte/chronisch kranke Mütter vielfältige Unterstützung und wenig gesellschaftliche Ausgrenzung, was für eine zunehmende Toleranz gegenüber dieser Personengruppe spricht.

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POSTER 329

HELP-S: Hilfen, wenn Eltern psychisch erkranken in Sachsen – Ergebnisse eines multizentrischen Forschungsprojekts zur Situation von Familien mit einem psychisch erkrankten Elternteil in Sachsen

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Einleitung: 26,5% der psychiatrischen Patienten in Deutschland haben minderjährige Kinder. Mehr als die Hälfte dieser Kinder haben einen spezifischen Hilfebedarf, der nur in 54% der Fälle gedeckt ist.
Methode: In unserer Studie wurden an einem Stichtag in 43 Nervenarztpraxen in Sachsen alle Patienten mit mindestens einem minderjährigen Kind mit einem Fragebogen zu soziodemographischen Angaben, Stärken und Schwächen eines Kindes, dem spezifischen Bedarf in ihrer Familie nach Hilfsangeboten, genutzten Hilfsangeboten und Gründen keine Hilfen in Anspruch zu nehmen befragt (N=128). Neben dem standardisierten Strengths and Difficulties Questionnaire (SDQ) wurde ein auf der Grundlage von 26 Experteninterviews entwickelter Fragebogen zur Bedarfserfassung und zur Nutzung von Hilfen eingesetzt.
Ergebnisse: An der Stichtagbefragung nahmen überwiegend Mütter teil (78%). Die vorwiegenden Diagnosen waren Depression und Angststörungen. Insgesamt gaben die Patienten einen hohen und sehr komplexen Bedarf nach Hilfsangeboten für sich und ihre Kinder an. 42% der Kinder erreichten in der Elternversion des SDQ grenzwertige oder auffällige Gesamtproblemwerte. Mehr als 20% der Kinder waren bereits wegen psychischen oder Verhaltensauffälligkeiten in Behandlung. Am häufigsten wurden dabei Angebote der Kinder- und Jugendpsychiatrie, Angebote des Jugendamtes und Wohnangebote für Eltern und Kind genutzt. Die häufigsten Gründe keine Hilfen in Anspruch zu nehmen waren, dass die Kinder vom Thema psychische Erkrankung ferngehalten werden sollen, Angst vor Ausgrenzung und Vorurteilen und dass keine Angebote bekannt sind.

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POSTER 330

Lebenszufriedenheit und Gesundheitsbezogene Lebensqualität bei Migranten und Nicht-Migranten – welche Rolle spielen migrationsspezifische Faktoren?

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Der Zusammenhang zwischen migrationsspezifischen Lebensumständen, der gesundheitsbezogenen Lebensqualität (GLQ) und der allgemeinen Lebenszufriedenheit (LZ) wurde theoretisch beschrieben und einer empirischen Analyse unterzogen. Mittels des SOEP-Datensatzes wurden 21.079 Personen, davon 2.971 (14,1%) Migranten, in Bezug auf die subjektiv eingeschätzte GLQ (erhoben mit SF-12) und generelle LZ untersucht. Es handelte sich um eine vergleichende Analyse zwischen Migranten und Nicht-Migranten, sowie zwischen verschiedenen Migrantengruppen. Es wurden keine praktisch relevanten Unterschiede zwischen Migranten und Nicht-Migranten in deren Einschätzungen der GLQ und der generellen LZ gefunden. Es zeigten sich jedoch Einflüsse der migrationsspezifischen Faktoren Aufenthaltsdauer, Einreisealter und Herkunftsland. Migranten mit längerer Aufenthaltsdauer schätzten ihre psychische LQ und die allgemeine Lebenszufriedenheit niedriger ein. Migranten, die bei der Einreise nach Deutschland älter als 40 Jahre waren, schätzten ihre körperliche LQ am niedrigsten ein. Außerdem haben Migranten türkischer Herkunft sowohl ihre physische LQ als auch ihre LZ am niedrigsten eingeschätzt, während Migranten aus westeuropäischen Ländern den höchsten Wert für die körperliche LQ und Migranten osteuropäischer Herkunft höchste LZ angegeben haben. Die Ergebnisse dieser Arbeit verdeutlichen, dass der unter dem Begriff Migranten subsumierter Bevölkerungsanteil eine sehr heterogene Gruppe darstellt. Es wird deutlich, dass der Bedarf an einer weiterführenden systematischen Untersuchung der aufgestellten Fragen auf epidemiologischer Ebene besteht.

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POSTER 331

The Film Festival „AUSNAHMEZUSTAND" (State of Emergency) – Do feature films and documentaries on mental health reduce stigma and influence help-seeking attitudes?

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Aim: From October 2008 until June 2010, the association *Irrsinnig Menschlich* e.V. from Leipzig carried out the German-wide film festival „Ausnahme|zustand", on the subject of mental health, for the second time. The festival was on tour in more than 70 cities, aiming to give a podium to the topic mental health and to inform and entertain an adolescent audience that has not been in close contact with the subject before.
Methods: A pre-post test was carried out to look for the effect of feature films and documentaries on social distance of the adolescent audience towards mentally ill people and on the change in help-seeking attitudes. A total of 582 students with a mean age of 16 could be questioned during the film festival in Leipzig.
Results: As the results show, the effect on the viewers' social distance strongly depends on the content of the feature films and documentaries: a reduction as well as an increase of social distance was identified. For one of the films, no significant change was found. Concerning help-seeking attitudes, the effect also depends on the feature film or documentary with one feature film showing no change. Age, gender, and knowing someone with mental health problems also turned out to be decisive factors influencing the development of social distance and help-seeking attitudes.
Conclusions: Feature films or documentaries about mental illness can reduce stigma or influence help-seeking attitudes, but effects strongly depend on the particular film.

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POSTER 332

Isolation of iridoid glucosides from Euphrasiae herba by droplet counter-current chromatography and their structure determination

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Euphrasia officinalis is a hemiparasite belonging to the family of Orobanchaceae. It grows unattached or attached to various host plants in grasslands of Eurasia. Traditionally but not evidence based used for various eye sufferings it is also known as eyebright (Augentrost). Typical active constituents beside phenolics such as phenylethanoids, lignans, phenolic acids and flavonoids are iridoids like aucubin, catalpol, euphroside, melampyroside, boschnaloside and others. Interestingly, the transfer of iridoids from the host plant to Euphrasia species was described, too.
For isolation of iridoid glucosides from Euphrasiae herba a practicable droplet counter-current chromatography method was developed according to iridoid isolations from Premna japonica. On the basis of TLC pre-experiments the solvent system CH_2Cl_2:MeOH:H_2O:n-PrOH 9:12:8:1 was used in descending mode. The iridoid enriched sample was obtained from a methanolic extract by separation against apolar solvents and by a column chromatography with Al_2O_3. Hence, aucubin and melampyroside were found. After purification of further fractions on a RP18 column 8-epi-loganin, gardoside methyl ester, ipolamiide and shanziside methyl ester were isolated for the first time from Euphrasia species. The structures of isolated iridoids were established by spectroscopic evidence. Thus the results obtained provide possible marker compounds useful for future pharmacopoeial analytics as well as for pharmacological investigations on eye diseases.

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POSTER 333

Micellar electrokinetic capillary chromatography (MECC) for rapid analysis of Dipsacus sylvestris Huds. (Dipsacaceae) and differentiation from other Dipsacus species

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The biennial Dipsacus sylvestris HUDS. (Dipsacaceae), introduced to Europe in antiquity, grows to a basal rosette with a strong tap root in its first year of cultivation, followed by the flowering period in the second year. Significant constituents are phenolic acids, flavonoids, iridoids and bis-iridoids. In opposite to the well-established Traditional Chinese Medicine (TCM) plant Dipsacus asperoides CHENG., D. sylvestris has mainly historical usage.
To characterize possible antiinfectious compounds different extracts of Dipsaci sylvestris radix were analysed by TLC, capillary zone electrophoresis (CZE) and micellar electrokinetic capillary chromatography (MECC) allowing the differentiation from the TCM drug. Especially MECC (λ = 234 nm; borate buffer 45 mM, SDS 20 mM, pH 9.4) yields typical fingerprint electropherograms mainly consisting of iridoids and phenolic acids. MECC results showed reproducibility of peak areas and relative migration times.

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POSTER 334

Eine Analyse von Biologie-Schulbüchern unter besonderer Berücksichtigung des Themas Tierschutz

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In Deutschland besitzt Tierschutz Staatszielcharakter und ist seit dem 01.08.2002 im Grundgesetz verankert. Nicht nur alleine hieraus ergibt sich die Forderung nach einer angemessenen Behandlung des Themas im (Biologie-)Unterricht, sondern auch aus der prinzipiellen Überlegung, die Schüler zur Wertschätzung der Natur anzuleiten. „Von daher ist die Auseinandersetzung mit der Frage, wie wir mit Tieren umgehen (sollten), ein wesentlicher Bildungs- und Erziehungsaustrag, der sein Ziel darin findet, die Kinder zu sich und ihrer Umwelt gegenüber verantwortungsbewusst handelnden Menschen zu erziehen“ (LÄNGLE 2008, S. 28).
Bei der Vermittlung des Tierschutzthemas kommt dem Schulbuch eine große Bedeutung zu, kann es doch von Schülern und Lehrern in vielfältiger Weise genutzt werden. Zudem hat das Schulbuch einen erheblichen Anteil an der Unterrichtsvorbereitung vieler Lehrer (LOIDL 1980).
Gegenstand der Untersuchung ist die Umsetzung des Themas Tierschutz in Biologielehrbüchern für die Klassenstufen 5 und 6. Mithilfe eines eigens entwickelten Analyseschemas wurden exemplarisch zehn Schulbücher charakterisiert und beurteilt. Ein Ziel der Untersuchung war es, positive Charakteristika herauszuarbeiten, um sie als denkbare Vorgabe für mögliche Schulbuchverbesserungen vorzustellen.

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POSTER 335

7-Chloro-6-desoxy-harpagide, a major iridoid glucoside from Leonurus cardiaca L. (Ph. Eur.)

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Continuing our search for possible cardioactive single constituents of primary and refined antiarrhythmic extracts of *Leonurus cardiaca* we report herewith the isolation of a chlorinated major iridoid glucoside besides the known ajugol, ajugoside and galiridoside. The structure of 7-chloro-6-desoxy-harpagide was determined by ESI-MS and 1d/2d $^{1}H/^{13}C$ NMR spectroscopical experiments. This unusual chlorinated iridoid has been found only once, namely in the related Lamiaceae *Physostegia virginiana* with the not very comprehensible name ‘stegioside I’. Thus this compound may prove useful as analytical marker substance as well as possible pharmacologically active compound, as for example shown for the anxiolytic activity of an iridoid enriched preparation from *L. cardiaca.*

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POSTER 336

UNTERSUCHUNG ZUM KNOCHENSTOFFWECHSEL AN EINEM PRIMATENMODEL

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Die Knochenphysiologie und -pathologie des Menschen unterscheiden sich deutlich von den bekannten Versuchstieren, somit sind humanrelevante Tiermodelle, wie Primaten, dringend von Nöten. Ziel unserer Studie war die Analyse von Einflussfaktoren auf die mittels Computertomografie (CT) gemessene Knochendichte (BMD).
In dieser Studie wurden 58 adulte Weißbüschelaffen (*Callithrix jacchus*) mit einem Alter zwischen 7 und 180 Monaten in drei Gewichtsgruppen eingeteilt: Gruppe 1 (< 300g; n=12), Gruppe 2 (300g-400g; n=26) und Gruppe 3 (> 400g; n=20). Neben der Bestimmung von Kalzium (Ca), Phosphor (Pi), alkalischer Phosphatase (AP) und Estradiol (E2) im Blut, wurde die Messung des totalen BMD (mg/cm^3) und planen BMD (g/cm^2) des 3. und 4. Lendenwirbels mittels eines LaTheta LCT-100A™ *in vivo* Scanner durchgeführt.
Das BMD bei der Gewichtsgruppe 1 (plane BMD: median: 0,158 g/cm^2; total BMD: median: 438,8 mg/cm^3) war signifikant ($p<0,001$) niedriger als bei Gruppe 2 (plane BMD: median: 0,163 g/cm^2; total BMD: median: 443,4 mg/cm3) und Gruppe 3 (plane BMD: median: 0,1904 g/cm^2, total BMD: median: 496,5 mg/cm^3). Ebenfalls wurde eine signifikante ($p<0,005$) lineare Korrelation zwischen BMD und AP, sowie Ca (jedoch nur bei den männlichen Affen) gefunden. Keine linearen Beziehungen fanden sich zwischen BMD und Phosphor oder dem Alter der Tiere, sowie zwischen E2 und Ca, P oder AP.
Schlussfolgernd lässt sich sagen, dass bei steigendem Körpergewicht die Knochendichte, sowie die AP des Weißbüschelaffen zunehmen. Diese Ergebnisse decken sich mit den humanen Befunden und spiegeln die Relevanz der Weißbüschelaffen als Tiermodel für Untersuchungen von Veränderungen im Knochenstoffwechsel wieder.

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POSTER 337

Quantitative Measurement of Genomic-wide Transcription Factor Protein Domain Co-occurence

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Transcription Factor (TF) typically cooperate to activate or repress the expression of target genes. TFs play critical roles in essentially everydevelopmental function, from the proliferation and differentiation of stem cells to the maintenance of differentiated cells in the adultorganisms.The combination of de novo gene predictors and subsequent HMM-based annotation of SCOP domains in the predicted peptides that leadsto consistent estimates with acceptable accuracy has been determined. In particular, it can be utilized for systematic studies of the evolution ofprotein domain occurrences and co-occurrences. As an application, we have considered seven major classes of TF : zinc-finger (znf), leucine-zipper,winged-helix, Bromo, Brct ,KRAB and HMG-box (hmg). Znf, leucine-zipper, winged-helix, and hmg are DNA binding domain. We have found that differenttypes of DNA binding domains systematically avoid each other throughout the evolution of Eukarya. In contrast, DNA binding domains belonging tothe same superfamily were readily co-occur in the same protein. Meanwhile,we try to determine the domain cooccurence of znf with other non TF domains, namely WD40, Phd, Ring, and tpr. However, we found highexpectations and no oberservations neither for our predictions nor for SF. This indicates avoidance. The utilized non TF domains having the samefunction, which are mediating protein-protein interaction. KRAB and ZNF domain have different function, and they cooccured. It could be concluded that different domain with the same function will tend to avoid, while different domain with different function will tend to cooccur.

Assoziation: PbF III

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POSTER 338

Genetic variability of two lacertid lizard species in fragmented habitats in Bulgaria

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Habitat loss, fragmentation, and structural changes of habitats are considered to be the major causes of an increasing rate of species extinction in recent decades. However, some species seem to be at a greater risk in fragmented landscapes than others. To investigate the effect of recent anthropogenic habitat fragmentation, a project was set out analyzing the genetic variability of the Sand Lizard (*Lacerta agilis*) and the Green Lizard (*L. viridis*) in Bulgaria. Whereas the latter species is broadly distributed in the country, *L. agilis*, and especially the subspecies *L. agilis chersonensis* is rare. Both species face severe habitat fragmentation in some regions of their occurrence and are hence suitable models to study the impact of habitat reduction and isolation employing genetic markers. Due to their differing distribution range, comparing the genetic variability of both species will provide insights into the differential fragmentation sensitivity between habitat specialists and generalists. Therefore, we sampled 20 individuals per population in four fragmented and two non-fragmented populations each of *L. agilis* and *L. viridis*. Subsequently, the DNA was isolated and 21 to 24 microsatellite loci were analysed. Additionally, we characterised the landscape in terms of habitat size, distance among habitat patches, and dispersal barriers among the sampled populations to find potential correlations to the genetic results. First results of this analysis will be presented on the poster.

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POSTER 339

Venom analysis of Glycera (Glyceridae, Annelida) using a transcriptomics approach

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Animal venoms exist in many phyla and a surprising convergence of protein families recruited as toxins is documented. Investigations were conducted for most venomous taxa including snakes, lizards, spiders, scorpions and cone snails. Despite its richness in potentially venomous species, none such data is available for Annelida. We conducted the first analysis of the venom of Glycera (Glyceridae, Annelida) using Next Generation Sequencing of the venom gland transcriptome. The convergent recruitment of proteins into the venom is discussed.

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POSTER 340

A survey of the expression of developmental genes in adult myzostomids (Protostomia, Myzostomida)

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Myzostomids are minute, soft-bodied, marine worms that have been associated with echinoderms since the Carboniferous age. Due to their long history as host-specific ectocommensals or parasites, they developed a deduced body plan that complicates the revelation of their phylogenetic relation to other metazoan taxa. While many of their morphological characters show congruence with annelids (e.g., ladder-like nervous system, parapodia-like structures, trochophora larvae), recent molecular analysis revealed incongruent results supporting a close relationship to either Platyhelminthes or Annelida. For subsequent phylogenetic analyses we sequenced the transcriptome of pooled adult individuals of the protandric *Myzostoma cirriferum* with Solexa Sequencing Technology. 36 million short paired-end reads have been assembled with the Abyss assembler which generated around 30,000 transcripts of>200bp size. Longest transcripts were above 8,000bp. Functional annotation using BLAST searches revealed the presence of a wide range of genes classified in Gene Ontology to biological processes related to development. These include ANTP-class genes like *hox* genes, *fox* genes, *NKx* genes, and others. Additionally, genes related to the *wnt*-pathway and other transcription factors were found to be expressed in adult myzostomids. Here we present a summary of our findings, draw conclusions for the phylogenetic position of myzostomids and speculate about the presence of these classes of genes in the investigated adult worms.

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POSTER 341

Association and evolutionary studies of the melatonin receptor 1B gene (MTNR1B) in the self-contained population of Sorbs from Germany

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List of topics

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Objectives: Several polymorphisms of the melatonin receptor 1B gene (*MTNR1B*) have been shown to be associated with elevated fasting plasma glucose and impaired early insulin release. The aim of this study was to assess effects of *MTNR1B* variants on traits related to the metabolic syndrome in the self-contained population of Sorbs from Germany. Since the prevalence of rs4753426 has recently been reported to be associated with sunshine duration, we also evaluated natural selection in vertebrates and human populations at this locus.
Material and Methods: Five single nucleotide polymorphisms (SNPs) representing all linkage disequilibrium groups within the *MTNR1B* locus were genotyped in 937 Sorbs for association analyses on metabolic traits related to type 2 diabetes mellitus (T2DM). The associations were assessed by regression analyses. Signatures of selection between species were investigated with phylogenetic analysis by maximum likelihood (PAML) and various tests of population genetic measures (e.g. Fst, Tajima's D) were performed.
Results: Previously reported association between *MTNR1B* variants (rs10830963, rs4753426) and OGTT derived indices of beta cell function (HOMA-B) could be replicated in the present study. PAML-analyses showed that the gene was strongly conserved between species, but on the lineage leading to human adaptive selection was present. Population genetic measures also indicated natural selection.
Conclusions: Our data support the physiologic importance of *MTNR1B* in the context of glucose homeostasis and suggest evidence of selection at this locus.

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