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Medizinische Fakultät

16th

Leipzig Research Festival for Life Sciences

2020

ABSTRACT BOOK

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Preface

Dear Colleagues, Dear Guests,
we warmly welcome you to this year‘s

16th Leipzig Research Festival for Life Sciences of the Leipzig University.

Also in 2020, the Faculty of Medicine and the Faculty of Life Sciences are pleased by the great interest in participating in the Leipzig Research Festival of Life Sciences.

The form of scientific presentation shall offer a platform to all young life science scientists and physicians from the Leipzig scientific landscape for the presentation of their research results and scientific exchange. The high number of submissions illustrates the importance and appeal of this multidisciplinary scientific communication platform. The present abstract book shall illustrate to the interested public, politics and as well as current and potential industrial partners how multifaceted the activities and the successes of the Leipzig scientists and physicians are in the field of life sciences and medicine. The collection is at the same time a scientific »who is who« of Leipzig research to provide rapid problem solving by direct cooperation.

With special appreciation of the young scientists, the best poster presentations will once again be awarded with the prestigious Research Festival Leipzig awards. The new feature at the 16th Research Festival will be a short presentation of the award winners during the awards ceremony to give visitors an insight into the award-winning research. Moreover, this year the audience will have an opportunity to cast their vote on the presentations given by the scientific speakers.

In addition, we are pleased that we have once again received generous support from the research associations and scientific partners in medicine and in life sciences this year. These includes: the Faculty of Medicine and the Faculty of Life Sciences of the Leipzig University, the Center for Biotechnology and Biomedicine (BBZ), Leipzig; the Fraunhofer Institute for Cell Therapy and Immunology (IZI), Leipzig; the Innovation Center Computer Assisted Surgery (ICCAS), Leipzig; the Integrated Research and Treatment Center (IFB) Adiposity Diseases, Leipzig; the Max Planck Institute for Human Cognitive and Brain Sciences Leipzig, the Collaborative Research Center 1052 “Obesity Mechanisms“, Leipzig and the University Hospital Leipzig.

We hope, that our Research Festival in its 16th edition will once again serve its dual purpose to present innovative research results and to provide a contact forum for young and experienced scientists across hierarchical boundaries. Thus, the Research Festival accompanies and strengthens the forward-looking development of the biomedical and biotechnological location of the Leipzig University.

We would like to thank the organizing team and all partners for their dedicated cooperation for making the 16th Research Festival for Life Sciences possible.

Prof. Dr. Thomas Arendt
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Prof. Dr. Jens Meiler ist neuer Alexander von Humboldt-Professor der Universität Leipzig.
Als pharmazeutischer Chemiker und Bioinformatiker zählt er zu den weltweit renommiertesten Forschern auf dem Gebiet der computergestützten Wirkstoffentwicklung und forscht an der Schnittstelle von Biologie, Physik, Chemie und Informatik. An der Medizinischen Fakultät baut er seit Januar 2020 das neue Institut für Wirkstoffentwicklung auf. Dort bringt er rechnergestützte Verfahren und experimentelle Methoden gezielt zusammen, um neue Pharmazeutika zu entwickeln.

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Fakultät für Lebenswissenschaften

Die Fakultät für Lebenswissenschaften setzt sich aus den drei Instituten Biochemie, Biologie und Psychologie zusammen und verknüpft exzellente, interdisziplinäre Forschung mit forschungs- und praxisorientierter Lehre. Sie bietet 10 Studiengänge mit den Abschlüssen Bachelor of Science, Master of Science und Staatsexamen an.
Ein besonderes Charakteristikum der 1994 gegründeten und 2017 umbenannten Fakultät stellt die Zusammenführung unterschiedlicher naturwissenschaftlicher Disziplinen im Bereich Lebenswissenschaften dar. Die Studierenden, Forscherinnen und Forscher profitieren hierbei von den vielfältigen Kooperationen zwischen den unterschiedlichen Fachbereichen sowie mit anderen Fakultäten und anerkannten außeruniversitären Einrichtungen.
Zurzeit betreuen 29 Professorinnen und Professoren circa 1700 eingeschriebene Studierende und circa 500 Promovierende.
Die Forschungsbereiche der Fakultät spiegeln sich im „Cluster für Biodiversität, Ökologie und Evolution“, dem „Zentrum für Molekulare Wechselwirkungen in Biomedizin und Biotechnologie“ sowie dem „Zentrum für Neuro- und Verhaltenswissenschaften“ wider.

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The Fraunhofer IZI investigates and develops solutions to specific problems at the interfaces of medicine, life sciences and engineering. One of the institute's main tasks is to conduct contract research for companies, hospitals, diagnostic laboratories and research institutes operating in the field of biotechnology, pharmaceuticals and medical engineering.

The Fraunhofer IZI develops, optimizes and validates methods, materials and products for the business units Cell and Gene Therapy, Drugs, Diagnostics and Biosystems Technology. Its areas of competence lie in cell biology, immunology, drug biochemistry, biomarker, bioanalytics and bioproduction as well as process development and automation.

In these areas, research specifically focusses on the indications oncology, neuropathology, auto-immune and inflammatory diseases as well as infectious diseases and regenerative medicine.

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About the Institute

Research at the Max Planck Institute for Human Cognitive and Brain Sciences revolves around human cognitive abilities and cerebral processes, with a focus on the neural basis of brain functions-such as language, memory, music, and communication.

Our studies focus on the key coding principles of the brain enabling human thinking and the perception, planning, and generation of human cognitive abilities and cerebral processes, and analyse the interaction and common functional basis of their production and perception. We also investigate plastic changes in the human brain, the influence these have on various cognitive abilities, and on the neuronal and hormonal basis of modern diseases like high blood pressure and obesity. An additional focal point of research at the Institute is the further development of imaging methods such as magnetic resonance imaging for neurosciences. The MPI for Human Cognitive and Brain Sciences provides an exciting framework for these topical and alluring theoretical domains, with the full gamut of cognitive and neuroscientific methodology available under one roof.

The Institute currently consists of four departments:

- Neuropsychology (Angela D. Friederici)
- Neurology (Arno Villringer)
- Neurophysics (Nikolaus Weiskopf)
- Psychology (Christian Doeller)

A hallmark of the Institute and its research strategies is the dovetailing of research, development, and engineering. The centre draws on elaborate modern imaging techniques, which are gaining ground as part of more conventional behavioural approaches.

Our MPI at Stephanstrasse in Leipzig was established on 1 January 2004 by a merger between the former Leipzig Max Planck Institute of Cognitive NeuroScience and the Munich Max Planck Institute for Psychological Research. The new Institute, joining two centres of expertise into one, reflects the development of psychological and neuroscientific research, which are being conducted increasingly closer together. The centre in Leipzig has established exceptional conditions for cutting-edge interdisciplinary behavioural and neurobiological research into human cognition.

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Sonderforschungsbereich 1052
„Mechanismen der Adipositas“

SFB 1052
Obesity Mechanisms

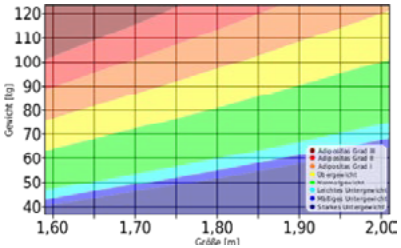
DURCH DICK UND DÜNN – EIN BLICK HINTER DIE KULISSEN DER ADIPOSITASFORSCHUNG

Was ist Adipositas?

Adipositas (von lateinisch „adeps“ = Fett) ist eine Ernährungs- und Stoffwechselkrankheit. Kennzeichen ist ein starkes Übergewicht mit einer starken Vermehrung des Körperfetts und krankhaften Auswirkungen. Nach Definition der Weltgesundheitsorganisation liegt ab einem Körpermasseindex von 30 kg/m² Adipositas vor. Ergänzend werden der Bauchumfang und das Taille-Hüft-Verhältnis zur Beurteilung herangezogen.

Die Adipositas wird unterschieden in drei Schweregrade: Grad I (BMI 30 – 34,9), Grad II (BMI 35 – 39,9) und Grad III (ab BMI 40).

In Deutschland ist fast ein Viertel der Bevölkerung von Übergewicht betroffen. Mit Adipositas werden verschiedene Begleiterkrankungen assoziiert, wie etwa Diabetes Typ 2, Bluthoch-druck, Fettleber, koronare Herzerkrankungen.



Was erforscht der Sonderforschungsbereich (SFB)?

Krankhaftes Übergewicht ist eine multifaktorielle Störung, die durch eine Kombination von Genetik, Verhalten, Lebensstil und Umweltfaktoren beeinflusst wird. Unser Anliegen ist es, neue Ziele und Mechanismen für therapeutische pharmakologische Herangehensweisen in der Behandlung von Adipositas und ihren Begleiterkrankungen zu identifizieren.

Der Sonderforschungsbereich konzentriert sich dabei auf drei Schwerpunkte: **Überernährung, Fetteinlagerung und Entzündung sowie Adipokine** (Hormone im Fettgewebe).

Überernährung

Aus evolutionärer Perspektive war es für unsere Vorfahren wichtig, dass in nahrungsreichen Zeiten überschüssige Kalorien in den Fettzellen gespeichert werden konnte. In Mangelzeiten konnte der Körper darauf zurückgreifen. Heute kann diese Speicherfunktion zu Adipositas führen, weil der Körper diese Reserve nicht in Anspruch nehmen muss. Wir wollen die evolutionäre Vergangenheit dieser genetischen Veränderungen verstehen. Und welche Unterschiede es zwischen Populationen gibt und in welchem Umfang diese Unterschiede für die Anfälligkeit für Krankheiten des Energiestoffwechsels vorhersagbar sind.

Fetteinlagerung und Entzündung

Es gibt verschiedene Arten von Fettgewebe: weißes, braunes und beiges Fettgewebe.
Die Speicherung von Fett in Fettzellen geschieht vorrangig über **weißes Fettgewebe**, das nur schwer abgebaut werden kann.

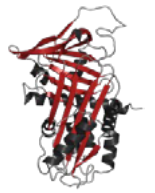

Weißes Fettgewebe.

Vor allem die viszerale Fetteinlagerung (in der Bauchhöhle) wird mit der Neigung zu Komplikationen assoziiert. Uns interessiert, welche genetischen Faktoren die Anzahl der Adipozyten (Fettzellen), Unterschiede in der Fettverteilung (viszeral oder subkutan) und ihre Assoziation mit Stoffwechselstörungen bestimmen. Mit Hilfe der Fettgewebebank in Leipzig sollen Gene identifiziert werden, die darin involviert sind.

In den Fokus der Forschung gerät derzeit das **braune Fettgewebe**. Es ist an der Thermogenese beteiligt, bei der weißes Fettgewebe in braunes umgewandelt wird. Wenn der Mensch leichter Kälte ausgesetzt wird, kann so die Körpertemperatur erhalten werden. Es kann auch durch Sport aufgebaut werden. Braunes Fettgewebe wird in der Forschung mit Gewichtsverlust und der Unterdrückung von Stoffwechselerkrankungen (z. B. Diabetes) in Verbindung gebracht.

Adipokine (Fettgewebshormone)

Das Fettgewebe sondert zahlreiche Hormone ab. In den letzten Jahren wurden zahlreiche Adipokine identifiziert. Unser Anliegen ist es, für ausgewählte Adipokine ihre Funktion, ihre molekularen Ziele und ihre potentielle klinische Relevanz als Biomarker oder in der Behandlung von Adipositas und deren Begleiterkrankungen zu definieren.


Struktur des Adipokins SerpinA12 (Vaspin) pdb:4FI8

Was ist der SFB?

Der Sonderforschungsbereich 1052 vereint Wissenschaftlerinnen und Wissenschaftler aus den Bereichen Anatomie, Biochemie, Biophysik, Chemie, Dermatologie, Endokrinologie, Genetik, Kardiologie, Labormedizin, Neurologie, Pädiatrie, Physiologie.

Beteiligte Einrichtungen sind die Universität Leipzig (Medizinische Fakultät; Fakultät für Lebenswissenschaften; Fakultät für Chemie und Mineralogie), das Universitätsklinikum Leipzig, das Max-Planck-Institut für Evolutionäre Anthropologie, das Max-Planck-Institut für Kognitions- und Neurowissenschaften und die Ben-Gurion-Universität in Beer-Sheva, Israel.

Gefördert von der Deutschen Forschungsgemeinschaft DFG

Poster 1

Scavenging of bone catabolic proteins by sulfated-GAG modified functional materials

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For guided tissue regeneration, surface properties of bone substitution materials are of high relevance. Our approach is to modify 3-armed methacrylated oligolactid-based macromer matrices [1] that have been shown to improve bone defect healing in diabetic rats [2].
By generating macromer-derived polymer films, we are able to analyze the surface properties of equally composed scaffolds [3].
For the current study, we decided to incorporate a small molecule anchor into the polymer films to bind a suitable linker molecule subsequently. Accordingly, methacrylate carrying films readily reacted with Jeffamine to homogeneously amino-functionalized film surfaces.
Surface decoration with sulfated glycosaminoglycans (sGAG) covalently bound to the linker is intended to improve bone defect regeneration by taking advantage of their shown ability to scavenge bone-catabolic proteins.
For proof of concept, sGAG decorated films were incubated with a solution of DKK-1 (8 ng/ml), a known wnt antagonist. After 24 h, less DKK1 was determined in the supernatant then the controls. Via fluorescence labeling of the protein, we were able to confirm, visualize and quantify the binding of DKK1 to the films.
Finally, we seeded osteoblast-like SaOS-2 cells on the functionalized films and applied osteogenic medium. Again, significantly less DKK-1 was found in the medium above modified films within 6 days as compare to control films. As a result, these cells showed higher calcium accumulation indicating improved osteogenic differentiation on sGAG-modified surfaces.
Overall these studies provided first insights in the mechanisms and effects of scavenging as an approach towards an improved bone regeneration.

References:
[1] Loth, Acta B. 2015;26:82-96
[2] Picke, Biomaterials 2016, 96:11-23
[3] Müller, Acta B. 2017, 51:148-160

Poster 2

Presentation of a biocompatible and efficient nucleic acid delivery system - In-vivo and in-vitro studies of new cationic lipoplexes

Giselbrecht J.[1], Bussmann J.[2,3], Langner A.[1], Wölk C.[1,4]

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Cationic lipids in combination with a helper lipid complex therapeutic DNA and are an efficient system to transport nucleic acids into cells. In the last decade cationic lipids are an often used transfection agent because of their high loading capacity, low cytotoxicity, low immunogenicity and absence of oncogenic risk. After an extensive physico-chemical analysis, the biocompatibility of newly designed lipoplex formulations gets into focus of our research activity. What will happen after systemic application of the lipoplexes?
Therefore various *in-vitro* and *in-vivo* assays regarding their hemocompatibility, biodistribution and pharmacodynamic activity are necessary. For evaluating the interactions of the cationic lipoplexes with blood components we performed hemolysis assay, particle size measurement and complement activation assays.
For *in-vivo* studies an animal model gives the opportunity to estimate the behaviour and toxicity of the lipoplexes in the organism. The zebrafishembryo as an *in-vivo* model has many advantages because of their small body size and optical transparency for studying the delivery of nanomedicines [1]. Especially the optical transparency allows observing the biodistribution direct in the living animal by microscopic observation. In addition, the experiments on Zebrafishemryos do not count as animal testing as long as they are completed before day 5 after fertilization.

References:
[1] Campbell, F., et al., Directing Nanoparticle Biodistribution through Evasion and Exploitation of Stab2-Dependent Nanoparticle Uptake. ACS Nano 2018

Poster 3

Interaction of Neuronal Cells with Electrode Materials

Abend A., Steele C., Zink M.

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Deep brain stimulation of neuronal cells with neuroelectrodes is already employed for medical treatment of different diseases such as epilepsy and Parkinson's. Additionally, coupling of neuronal cells to multielectrode and lab-on-a-chip materials offers new perspectives in *in-vitro* assessments ranging from neuronal network formation to drug testing. However, many biomaterials lack the ability to promote adhesion of neurons important for biomaterial performance. Employing the human glioblastoma cell line U87-MG as well as the human neuroblastoma cell line SH-SY5Y, we investigate the neuronal cells' adhesion dynamics, bioactivity as well as network formation on custom-made electrode materials composed of gold, indium tin oxide, titanium nitride with and without nanocolumnar surface patterning.

Poster 4

Overcoming the mucosal barrier by zeta potential changing nanoparticles

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Mucosal drug delivery is predominantly influenced by diffusion barrier of mucus gel layer and absorption barrier of epithelium. Overcoming these two barriers require different or even opposite surface properties of the nanocarrier systems. Hydrophilic and negatively charged nanocarriers permeate mucus gel layer rapidly, whereas hydrophobic and preferably positively charged nanocarriers interact more efficiently with epithelium. Herein, we developed zeta potential changing polymeric nanoparticles (NPs) via surface phosphorylation in order to overcome these two barriers. Polymeric NPs were prepared via in situ gelation between cationic chitosan and anionic chondroitin sulfate followed by phosphorylation using hexokinase. These phosphorylated NPs (pNPs) exhibited a zeta potential of -12.7 mV resulting in significantly enhanced mucus permeation.
A remarkable amount of phosphate was released upon incubation with isolated as well as cell associated alkaline phosphatase (AP) shifting zeta potential from negative to neutral. Moreover, pNPs displayed no toxic effects on Caco-2 cells. Due to the cleavage of phosphate substructures on the surface of the NPs by AP, uptake of these NPs by epithelial cells was increased almost 2-fold. Findings of this study suggest that zeta potential changing NPs might be a promising tool for mucosal drug delivery.

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Poster 5

Generation of human lung organoids from placental- and umbilical cord-derived progenitor cells

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2 Universität Leipzig, Pädiatrisches Forschungszentrum, Abteilung für Neonatologie, Leipzig, Germany*

Background:
Human lung organoids (hLOs) are a useful model to study lung development and pulmonary diseases. Several groups established hLOs from embryonic or induced pluripotent stem cells; however, ethical issues and genetic modifications limit their applicability. To circumvent these difficulties, our aim is to use progenitor cells from the placenta and the umbilical cord (UC), clinical byproducts and the youngest source of adult stem cells, to generate hLOs.

Methods:
Human epithelial progenitor cells (EpiPC) were isolated from the amniotic epithelium of the placenta and the UC epithelium by different protocols. The obtained EpiPC were differentiated towards lung identity at the air-liquid interface using Pneumacult™ medium, conditioned medium from fetal rat lung fibroblasts and distal lung epithelial cells, or a defined medium. Subsequently, the expression of progenitor and lung cell markers was determined. Furthermore, endothelial and multipotent stroma cells were isolated from the UC for co-culture with EpiPCs to generate hLOs.

Results:
The conditions for the isolation and cultivation of EpiPC were established to ensure a reproducible protocol. The EpiPC showed the definitive foregut endoderm markers SOX17, Nkx2.1 and FoxA2 after isolation and maintained them during culture. Moreover, EpiPC can be differentiated into cells expressing the lung-specific markers Aqp5, pro-SP-C and CCSP. Co-culture of EpiPCs with primary endothelial cells in Matrigel led to the formation of 3D spheres with some cells expressing epithelial EpCAM and alveolar pro-SP-C.

Outlook:
The placenta and the UC are convenient sources of EpiPCs. The generated hLOs need further characterization and optimization to improve their differentiation into organoids with lung-specific function.

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Poster 6

Tyrosine-modified PEI for highly efficient nucleic acid delivery *in vitro, ex vivo* and *in vivo*

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Universität Leipzig, RBI Clinical Pharmacology, Leipzig, Germany

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Introduction:
The delivery of small interfering RNAs (siRNA) is a promising approach for the target-specific knockdown of pathologically overexpressed genes. A major challenge is the safe and efficient delivery of siRNAs esp. for *in vivo* application. The cationic polymer polyethylenimine (PEI) is a promising delivery system. However, while their high charge densities efficiently complex and protect the payload, PEIs are also associated with cytotoxicity, colloidal aggregation and often moderate transfection efficacy. Chemical modifications are a promising strategy for further improvement.

Methods:
We developed a set of novel tyrosine-modified PEIs. These were studied for optimal siRNA complexation conditions and other physicochemical properties. The biological and toxicological behavior of the siRNA complexes was characterized *in vitro*. Finally, the most promising complexes were further evaluated *in vivo*.

Results:
Gene silencing efficacies up to >90% were found in different cell lines and not associated with appreciable cytotoxicity. Incubation in the presence of serum, freezing or lyophilization of nanoparticles indicated excellent colloidal and biophysical stability. In *ex vivo* studies based on a tumor tissue slice model, a profound knockdown of GAPDH was found on mRNA and protein levels. In a pre-clinical *in vivo* study in colon carcinoma xenograft-bearing mice, tyrosine-PEI/siRNA nanoparticles targeting the anti-apoptotic oncogenes survivin and PLK-1 showed strong tumor-inhibitory effects and knockdown of the target proteins by ~50% without adverse effects.

Conclusion:
The chemical modification of PEI with the amino acid *L*-tyrosine strongly improved the physicochemical stability, reduced the toxicity and increased the bioactivity of nanoparticles *in vitro*, *ex vivo* and *in vivo*.

Poster 7

Surface-Mediated Gene Delivery from functionalized Polyelectrolyte Multilayer Scaffolds in Tissue Engineering

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In recent decades, the development of therapeutic strategies in which the drug is a nucleic acid, is an important research focus in gene therapy. A major challenge for the establishment of gene therapy is still the overcoming of biological barriers by means of suitable delivery systems. A new strategy for nucleic acid delivery systems is the encapsulation or immobilization of gene vectors within biomaterial surfaces. This allows the DNA to be positioned in cellular microenvironment to achieve localized and efficient gene delivery to tissues or cells.

In this study, we have developed a polye ayered film (PEM-film) that permits both, the immobilization and release of DNA from the surface of glass cover slips. Our approach makes use of the layer-by-layer method for the assembly of nanostructured thin films consisting of alternating layers of hyaluronic acid and chitosan. Here, lipid/DNA complexes (lipoplexes), consisting of novel cationic lipids are embedded within PEMs. We focused on effective loading of the PEMs with DNA and on the intensive surface characterization using confocal fluorescence microscopy, ellipsometry, AFM and SEM. In addition, interactions with C2C12 myoblasts, e.g. cell adhesion and cell viability were investigated.

In summary, a system based on hyaluronic acid and chitosan could be produced which on the one hand can be loaded effectively with DNA and on the other hand can trigger localized surface-based transfection on C2C12 cells. Surface- und cell studies show that the PEM-scaffold is a nanostructured system which is capable of cell adhesion to extracellular matrix and very good cell viability. First *in-vivo* experiments were carried out in which a good transfection could also be achieved with our established system.

Poster 8

Lipophilic arginine esters: Promising alternative to well-established cationic surfactants being used in pharmaceuticals

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Hydrophobic ion pairing (HIP) of hydrophilic macromolecular drugs with oppositely charged lipophilic counter-ions has been emerging as a novel strategy to facilitate their incorporation into lipid-based drug delivery systems. Various types of anionic and cationic surfactants as counter-ions are being widely used for this purpose. Regarding their use in pharmaceuticals, toxicity and non-biodegradability of well-established surfactants are questionable especially in the case of long term treatment of chronic diseases.

Therefore, in this study, cationic ester surfactants based on natural material arginine (Arg) were synthesized and evaluated for their ion-pairing potential with hydrophilic macromolecular drugs. Arg was linked to medium and long aliphatic chains (C_9 and C_{16}) via an ester bond.

Structures were confirmed by FTIR and ^{1}HNMR. Both esters were evaluated regarding critical micelle concentration (CMC), toxicity on Caco-2 cells, biodegradability by trypsin and ion-pairing with heparin and daptomycin as model anionic polysaccharide and peptide drugs, respectively. CMC of Arg esters was 7.5 mM and 2 mM with C_9 and C_{16} fatty chains, respectively. Arg esters were biodegradable (>90%) and were significantly less cytotoxic in comparison to well-established cationic surfactants. They were able to efficiently precipitate heparin (>95%) and daptomycin (>80%) from their aqueous solutions.

Based on all these results, arginine esters seem promising alternative to well-established cationic surfactants for ion-pairing as well as other pharmaceutical applications.

Poster 9

Kinase signaling mediates mesenchymal stem cell conditioned medium-induced Na^+ channel activity in fetal lung cells

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Background:
Impaired alveolar fluid clearance (AFC) and structural lung immaturity can lead to respiratory failure in preterm neonates. AFC is driven by vectorial Na^+ transport accomplished by the epithelial Na^+ channel (ENaC) and the Na,K-ATPase. Mesenchymal stem cells (MSCs) are suggested to harbor therapeutic potential for respiratory diseases, although effects on lung maturation have not been addressed. Beneficial effects of MSCs are attributed to paracrine signaling, i.e. growth factors involved in fetal lung development.

Aim:
We addressed whether MSC conditioned medium (MSC-CM) is able to stimulate lung branching morphogenesis and Na^+ transport in primary rat fetal distal lung epithelial (FDLE) cells and if inhibition of growth factor signaling attenuates the effect of MSC-CM.

Methods:
MSCs were isolated from umbilical cord. Effects of MSC-CM on Na^+ channel activity and expression were determined by Ussing chamber analysis and qPCR in FDLE cells. Lung maturation and branching morphogenesis were analyzed in fetal rat lung explants.

Results:
Fetal lung explants cultivated in MSC-CM displayed an enhanced structural maturation. Moreover, MSC-CM significantly ameliorated ENaC and Na,K-ATPase activity and gene expression. Inhibition of growth factor receptors did not prevent the stimulating effect of MSC-CM on Na^+ channel activity, however inhibitory studies of PI3-K downstream targets showed a significant reduction of MSC-CM mediated ENaC activity.

Conclusion:
The results demonstrate that MSC-CM increases Na^+ transport in FDLE cells, possibly attributable to PI3-K signaling, and improves branching morphogenesis. Therefore, MSC-CM can stimulate lung structural and functional maturation *in vitro* and might represent a future therapeutic option for preterm infants.

Poster 10

Determination of mechanical properties of human cancellous bone from thoracolumbar spine and sacrum

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Objective:
The determination of material parameters of bone plays an important role in understanding its mechanical behaviour and interactions with implants. So far, no standardized method has been established so that material parameters found in the literature are subject to enormous variances. In order to create a reliable database that can be used for the creation of complex material models the mechanical properties of human cancellous bone are to be determined through compression tests using a self-developed test protocol.

Material and methods:
Tests were performed on fresh frozen human spinal column segments from body donors from the Institute of Anatomy at the University of Leipzig. A tenon cutter was used to extract standardized cylindrical test specimens with a diameter of 8 mm in the direction of the main physiological load. In total 58 test specimens were extracted from thoracic and lumbar vertebrae as well as the sacrum and then trimmed to a uniform length of 16 mm using a diamond band saw and a custom-made holding device. After determining the bone density the test specimens underwent mechanical compression tests according to DIN 50134.

Results:
The modulus of elasticity is 162.4 ± 73.3 MPa for thoracic vertebrae, 167.5 ± 65.7 MPa for lumbar vertebrae and 173.9 ± 106.2 MPa for the sacrum. The compressive yield strength is 1.03 ± 0.50 MPa for thoracic vertebrae, 0.81 ± 0.55 MPa for lumbar vertebrae and 0.86 ± 0.80 MPa for the sacrum. Furthermore, a tendency towards increasing strength properties with increasing bone density can be observed.

Conclusions:
Compared to the literature, the determined parameters are plausible and show a lower variance. Further testing is performed in order to increase the number of samples and to be able to derive valid material models.

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Poster 11

Analysis and reconstruction of sinusoidal extracellular matrix for human liver tissue engineering

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One challenge in liver tissue engineering is the reconstruction of extracellular matrix (ECM) to maintain hepatocyte-specific functions. The ECM used for cultivation does not reflect the essential composition of proteins present in the liver. Previous RNA-analysis emphasized non-parenchymal cells (NPC), e.g. stellate, Kupffer and endothelial cells as main sources of ECM. Aim of the present study is the investigation of NPC and primary human hepatocytes (PHH) for the ECM protein production, characterization of ECM stability in culture and to test identified ECM proteins for their ability to stabilize PHH cultures.

PHH and NPC were isolated from human liver tissue samples. After isolation, PHH and NPC were analyzed on transcriptional level (qRT-PCR) to visualize the activity of genes coding for three groups of matrix components: fibrillar collagen, membrane-specific and regulatory proteins. Additionally, NPC were cultured in 2D and PHH in 3D using Alvetex™ scaffolds. Analysis on transcriptional and protein level (mass spectrometry) will be performed after adherence and after 2, 4 and 6 days of culture. Identified key components of ECM will be tested for their ability to stabilize hepatic functions (Albumin, Urea, Phase I and II metabolism) in culture.

We expect NPC specific expression of ECM proteins, which change during culture in dependence of adaption and dedifferentiation. Successful identification of key players of ECM will allow the establishment of suitable ECM coatings. We expect that these coatings will allow stable culture conditions for PHH without loss of differentiation and thus a preservation of functionality. These data will be used in the development of hepatic co-culture models and micro tissues reflecting the *in vivo* liver architecture and functionality.

Poster 12

Ameliorated phenotype of Huntington mice after MSC administration

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With a worldwide increasing life expectancy, the prevalence of neurodegenerative diseases of the aging population ascends. Huntington disease (HD) is an autosomal dominant neurodegenerative disorder with neuroinflammation as hallmark. Pro-inflammatory cytokines are significantly upregulated. Cell-based therapies captured interest as potential treatment for HD and other neurodegenerative diseases. Mesenchymal stem cells (MSC) have shown beneficial effects to treat HD by intracerebral transplantation (ICT). MSCs possess a great therapeutic potential due to their immunomodulatory, regenerative and neuroprotective properties.
However, translation of ICT for human applications is difficult due to the highly invasive delivery method which poses high risk, additional damage and high side-effects. Our aim was to study a non-invasive, low risk application method, which is easily repeatable. Therefore, we want to study the beneficial effect of non-invasive intranasal administration (INA) of MSCs to reduce the neuroinflammatory phenotype in HD-mice.
The HD mouse model R6/2 carries an exon of the disease-causing human huntingtin (HTT) gene and shows physiological and behavioral phenotypes that recapitulate symptoms of HD patients, including neuroinflammation. MSCs were isolated from bone marrow of eGFP-transgenic mice. Cell were applied intranasally twice with 1×10^6 to R6/2 mice.
Up to 7.5 weeks after transplantation, MSCs were tracked in the brain. INA of MSCs reduced neuroinflammation and led to positive long-term effects weeks after application. The results of this study can contribute to improve cell-based therapies in regard to the non-invasive application method as it can easily be repeated. INA provides an effective delivery method to the brain [doi:10.3390/cells8060595].

Poster 13

Novel Approach for manufacturing of artificial trabecular bone models

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Objective:
The use of bone substitutes for biomechanical testing has several advantages, such as the renunciation of the use of human donor tissue. Donor tissue materials exhibit high intraindividual variations due to age, medical history, gender and other factors. For this reason there is a great interest in artificial test materials that reproduce the mechanical properties of bone tissue and entire bone structures.

Materials and Methods:
A total of 12 trabecular bone samples (Ø 8 mm x 16 mm) were extracted from the fresh frozen vertebrae using a tenon cutter in cranial-caudal direction and cut afterwards using a diamond band saw. Two types of trabecular bone models were extracted from µCT data in a procedure equivalent to human samples and manufactured using stereolithography. The first type resembles the original bone structure and a second model type was made by thickening the first one to increase the stiffness. Uniaxial compressive tests according to DIN 50134 were performed on all samples.

Results:
The modulus of elasticity is 167.5 ± 65.7 MPa for the lumbar vertebrae. The modulus of the first model type is 64.4 ± 6.1 MPa and 388.34 ± 92.7 MPa for the second one. The compressive strength for the lumbar vertebrae is 0.81 ± 0.55 MPa whereas the values for the first and the second model type are 1.3 ± 0.1 MPa and 12.1 ± 1.1 MPa.

Conclusion:
The manufactured models show highly comparable mechanical properties to human bone due to material aggregation. The production of valid artificial bone models using additive manufacturing is a possible alternative to existing manufacturing methods and can easily be applied to entire bone structures with further validation studies.

Poster 14

3D-Printing and Degradation Studies of Tubular Conduits from a 2-Component-Hydrogel Premix

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The peripheral nervous system possesses a limited, defect size-dependent capacity for regeneration after injury. Such injuries are still best clinically treated by autografts. Limited availability and associated comorbidities of such autologous tissues and an unmet clinical demand for larger transplants motivate research on artificial nerve guidance conduits (NGC).
A promising material class for the development of such NGCs are cross-linked hydrogels of both natural and synthetic origin. Our group developed an anhydride-containing oligomer for cross-linking of amine-containing natural hydrogel-forming materials, such as collagenous or gelatinous peptides. Manually fabricated 2-component (2K)-hydrogels from such peptides and different oligomers have previously been investigated for their use as artificial NGCs with encouraging results.
In order to progress these materials, this work explores the use of 2K-hydrogels in extrusion-based 3D-printing, a method which would allow for the fabrication of multi-channeled NGC with dimensions customized to the individual defect. As most commonly available 3D-printers are equipped with single cartridge extrusion print heads, a premixed formulation was developed. This formulation incorporated both components and an organic or inorganic base in a suitable concentration to generate a slowly gelling hydrogel. Characterization of reaction kinetics and printed constructs allowed for optimization of the formulation.
The resulting mixture yielded multi-channeled constructs with variable sizes, rectangular or round cross-sections and good stability. The 2-component-hydrogel constructs were investigated for their *in vitro* degradation behavior and found to feature a slow and continuous mass loss while retaining structural integrity.

Poster 15

In vitro investigations of the induction of invasive breast cancer cell phenotypes during crossing tissue interfaces

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During cancer cell invasion and metastasis cells encounter very different biochemical and biophysical properties of the extracellular matrix (ECM). Recently we could show that the local change of ECM microstructure (pore size) is a key to induce a very invasive and proliferative behavior of the breast cancer cell line MDA-MB-231, using an *in vitro* reconstituted step gradient of different collagen I networks. We now aimed to reveal insights on the mechanism of the induction of the phenotypic change at the ECM interface.
MDA MB 231 breast cancer cells were embedded into a dense collagen I compartment (pore size: 4 µm) and cell migration into a more porous compartment (6 µm) was investigated using long-term single cell tracking over several days as well as immunofluorescence. In agreement to previous experiments the migration behavior of cells changed from random to highly directional, accompanied by an increased proliferative activity. The latter was quantified by phospho histone 3 antibody staining of breast cancer cells after interface crossing. As we hypothesize mechanotransductional mechanisms to drive the persistent phenotypic change during crossing the matrix interface we also investigated immunostaining of mechanical elements of the nucleus such as emerin, as well as of the actin skeleton. By that we reveal insights in the impact of cytoskeletal forces on epigenetic changes, when cells exhibit a highly polarized cell state during crossing the matrix interface.
In sum, the developed biomimetic ECM interfaces provide an interesting model for the investigation of cancer cell invasion at tissue interfaces.

Poster 16

Charged amphiphilic oligomers for nanoparticle stabilization – synthesis and aggregation behavior

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The search for improved drug delivery systems is necessary as highly selective APIs or nucleic acids for the treatment of cancer or autoimmune diseases are identified and developed. Polymeric or polymer coated nanostructures are of special interest as their physico-chemical properties can be tuned precisely during synthesis [1].
In this project we are focused on maleic anhydride (**MA**)-containing oligomers with different combinations of methoxy-poly(ethylene glycol) methacrylate (**PEG**) and tetradecylacrylate (**14**) as hydrophilic and lipophilic comonomers. The amphiphilic oligomers were synthesized by free radical polymerization (THF/18h/60°C/AIBN) of predefined comonomer mixtures using an established protocol [2]. The range of oligomers was extended with 4-acryloylmorpholine (**Mo**) as a chemically inert filler comonomer.
Pristine oligomers (**o14PEGMA** and **o14PEGMoMA**) were chemically analyzed by NMR and acid-base titration and finally fully hydrolysed to yield the polyanionic form. Dialysis was best suitable for purification of the anionic oligomers. Lyophilised oligomers were used to study colloidal aggregation behavior using a fluorescence probe [3].
Oligomers were successfully used to stabilize calcium phosphate nanoparticles and more extended studies are ongoing to correlate the aggregation properties of different oligomers with their stabilization capacity.
We strive to use this information for controlled oligomer design and functional modifications to adjust calcium binding and nanoparticle uptake.

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Poster 17

Bioactive hybrid glass scaffolds with controlled Ca^{2+}-release for bone tissue engineering purposes

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Recently, we successfully published a hybrid material from sol-gel derived silica based glass and functionalized 3- and 4-armed macromers. We processed it to heat sterilisable, biodegradable, mechanically stable and bioactive scaffolds.
After incubation in aqueous media, however, mechanical stability of these scaffolds was substantially reduced. In this study, we investigated, if a systematic variation of Ca^{2+} which is a prerequisite for bioactivity may lead to mechanically stable scaffolds with controlled release of Ca^{2+}.
In a first step, we successfully improved the scaffolds stability after incubation in aqueous media via reduction of Ca^{2+} content, but still observed a burst release due to missing integration of Ca^{2+} into the glass network. We therefore changed the way of Ca^{2+} incorporation and established a method to introduce melt-quenched Bioglass microparticles (Vitryxx®) (BG-MP) into the hybrid system.
Via systematic variation of BG-MP content, we found that approx. 3.5 % (m/m) could be integrated in pure hybrid glass formulations, whereas the supplementation of $CaCl_2$ in the sol allowed for higher BG-MP content up to 8.5%. BG-MP containing scaffolds showed a sustained Ca^{2+}-release over the incubation period (84 d) and no significant reduction in scaffolds mechanical strength. pH-changes between 0.1 and 0.45 pH units caused by the BG-MP depended on their amount and were significantly less pronounced compared to those observed when the same amount of BG-MP was incubated alone (up to 1.2 pH units). Even small amounts of BG-MP caused a prominent mineral deposition on a scaffold surface considered as bioactivity.

Poster 18

Adjustable Thermo-Responsive Materials from Three-armed Macromers for Cell Carrier and Implant Design

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Mechanical stimulation of cells during cultivation has become an effective strategy to direct cell differentiation towards a specific phenotype and increase tissue maturity. One scarcely explored strategy to apply such a stimulation is the use of a mechanically active polymer for cell carrier design. N-Isopropylacrylamide (NiPAAm) is a thermo-responsive polymer with a lower critical solution temperature (LCST) at around 32°C that has been excessively using in the design of thermos-responsive materials.

At physiological temperature (37°C), the polymer is condensed and presents a mildly hydrophobic surface. When the temperature is lower than LCST, the polymer becomes hydrophilic and takes up water which increases the bulk volume and biomaterial dimensions.
In this study we strive to develop a duroplastic material that can be processed into tissue engineering scaffolds and drug delivery devices. The material should exhibit a transition temperature at slightly below body temperature and should be supportive for cell adhesion, also below its LCST.

To this end, NiPAAm was copolymerized with hydrophilic and ionic so-monomers as well as trimethylolpropane triacrylate (TMPTA) for network formation and biodegradability. Duroplastic networks have been synthesized and material properties were correlated with chemical composition of the reaction mix. First data on cytocompatibility and cell material interactions are presented.

Poster 19

Protein delivery with oligomer-cross-linked albumin nanoparticles

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Nanoparticles (NP) are essential drug carriers and protein delivery vehicles. Natural polymers are excellent building blocks for NP for protein delivery because of their biocompatibility, biodegradability and the hydrophilic environment that they generate to stabilize embedded protein. In order to obtain sufficient NP stability, such materials have to be cross-linked.
To this end, we developed anhydride group-bearing oligomers in our group that have been proven suitable for the formation of gelatin hydrogels and the cross-linking of gelatin microparticles. In this project, we aim at formulating NP from albumin and reactive oligomers and integrate fluorescent probes as well as pharmacologically active molecules for intracellular delivery.
Oligomeric cross-linkers oPNMA, oPDMA, of different compositions, especially different anhydride contents, have been synthesized by free radical copolymerization of the comonomers. Albumin-NP (ANP) were fabricated by nanoprecipitation and subsequent cross-linking. A model protein, β-Galactosidase, was loaded to pre-fabricated ANP and was released over time to evaluate network properties and release kinetics. Cell culture experiments were used to evaluate the cytocompatibility of NP.
Oligomer-cross-linked ANP have been successfully fabricated within reproducible size range. In particular, the isoelectric point of cross-linked ANP correlated well with the cross-linker type and anhydride content. The loaded β-Galactosidase was released without significant activity loss over a period of 2.5–3.5 d. Fluorescently labelled ANP helped investigate their uptake characteristics by fibroblasts.

In summary, stable and homogenous oligomer-cross-linked ANP have been shown as adjustable therapeutic protein vehicles for intracellular delivery.

Poster 20

Interplay of macrophages and fibroblasts in heparin-modified 3D collagen-I matrices

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Wound healing is a complicated process requiring collaborative activity of different cell types. While fibroblasts (FB) and their differentiated phenotype, myofibroblasts, are essential for regeneration of damaged tissue through extracellular matrix synthesis, paracrine signaling between FB and macrophages (MΦ) is known to affect cell behavior.

Advanced *in vitro* models mimicking and modulating the interaction of both cells types represent promising systems for detailed investigation of immunomodulatory processes, especially in the context of disturbed wound healing. In our approach, a previously established co-culture model of primary human FB and M-CSF stimulated MΦ in defined 3D collagen I (Col-I) matrices was used to evaluate the possibility of modifying these with heparin and selectively 6ON-desulfated heparin.

Heparin's ability to bind soluble cytokines is hypothesized to alter paracrine interaction of cells. FB and MΦ were homogeneously incorporated into 2.5 mg/ml Col-I matrices of a defined microstructure, with 2 x 10^4 FB and 8 x 10^4 MΦ being present in one matrix. Heparin was subsequently adsorbed to these matrices. Stable immobilization of approx. 0.15 µg heparin per µg Col-I could be determined after 5 days, with 6ON-desulfated heparin being present at 0.05 µg.

A Wst-1 assay proved high viability of FB and MΦ which were present in the Col-I matrices during modification. In summary, we set up a biomimetic co-culture system of primary human FB and MΦ within a defined 3D matrix with optional modulation of cytokine binding via heparin and 6ON-desulfated heparin. Co-culture studies including gene expression analysis will be used to analyze the impact of modulating cytokine exchange accompanied by quantification of cytokine binding and gradient formation.

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Poster 21

Tailoring Network Structure of Collagen Type 1 by High-Energy Electron Irradiation

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Imitating mammalian's extracellular matrix is essential to investigate cell behavior like adhesion and migration *in vitro* and is of great importance for biomedical applications as well. Collagen as main component of the mammalian's extracellular matrix is well suited as biomimetic material due to its excellent biocompatibility and biodegradability.

Mostly, the fabrication of collagen type 1 matrices with defined networ pore size involves the usage of cytotoxic chemicals. Herein, we adjust the pore size by covalent crosslinking, using high-energy electron irradiation of 0 kGy, 50 kGy and 100 kGy. Thereby, electron beam treatment is an effective and noninvasive method to ensure biocompatibility without the need for further chemicals. In addition, the pore size dependence of collagen type 1 networks on protein concentration is examined, using 1 mg/ml, 2 mg/ml and 3 mg/ml. In this contribution, we present a method to tailor the hydrogel's pore size by adjusting the gel concentration and the irradiation dose.

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Poster 22

Characterizing Peptide-Receptor Interactions in Opioid Receptors with Molecular Dynamics Simulations

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Opioid receptors are peptide binding G Protein-Coupled Receptors (GPCRs) and belong to the class A GPCR subfamily. They are known for mediating pain response on a cellular level in our brain, spinal cord and peripheral neurons.
The μ-, κ- and δ- Opioid receptors represent three subtypes of this receptor class and are the major players in analgesia. Even though they all bind analgesic drugs their function has also been proven to be connected to stress response, mood and the reward system. The endogenous ligands for these receptors are peptides of individual length and sequence, binding to each of the opioid receptor subtypes with different affinities.
Some of them, products of proenkephalin and prodynorphin, share a characteristic N-terminal “message sequence” (N-YGGF...) and diverge in their C-terminal “address sequence”. Resolving the role of these differences in binding to each of the opioid receptor subtypes and connecting them to specific peptide-receptor interactions might help us to understand the dynamic binding process and specificity of these endogenous ligands.
We researched and compared the dynamic binding of the endogenous peptides Leu- and Met-enkephalin as well as the artificial peptide DAMGO to the three opioid receptor subtypes μ, κ and δ using Molecular Dynamics Simulations. In a total simulation time of ~ 30 μs we investigate the stability of the ligand inside the receptor binding pockets as well as differences in interactions based on diverging sequences and structural features of the orthosteric binding sites.
Our results will shed light on the importance of dynamics in peptide binding processes and how they can help us in understanding ligand specificity in GPCRs.

Poster 23

Residue Type Specific Dynamics of the Growth Hormone Secretagogue Receptor investigated by Solid-State NMR

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The Growth Hormone Secretagogue Receptor (GHSR) is a highly dynamic G Protein-Coupled Receptor with seven transmembrane domains. Upon ligand binding, GHSR undergoes a conformational change to an active state, crucial for signal transduction into the cells. Physiologically, GHSR plays a role in diverse functions such as sleep, immune response or food intake.
Previously, the uniformly ^{13}C-labelled GHSR in native-like membrane environment was characterized with respect to its dynamics and was shown to be highly flexible [1]. However, these results represent an average of the dynamics of all sites of the receptor. Therefore, we aimed to investigate the site specific and single residue dynamics of GHSR.
In order to characterize the dynamics of specific domains, amino acids clustering in the transmembrane domains, the loops and the C-terminus (intracellular side) were ^{13}C-labelled through an established cell-free expression strategy. The labeled GHSR was expressed in the precipitated form with a yield of up to 1.2 mg per 1 mL reaction volume and reconstituted in DMPC bicelles. Using DIPSHIFT NMR, the mobility of the C-H bonds of three ^{13}C-labelled amino acid types (methionine, arginine and histidine) has been investigated to determine the order parameter of motion for each domain.
As expected, the transmembrane domain is the most rigid part of the receptor, the loops and ends of helices are slightly more mobile while the C-terminus showed the highest mobility. In the next steps, the dynamics of single key residues, involved in ligand binding, in signal transduction or conserved among GPCRs (e.g. Trp$^{6.48}$) will be investigated.

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Poster 24

Detection of Conformational Dynamics of the Y_2 Receptor by Site-Specific Spin Labeling using NMR and EPR measurements

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The function of G protein-coupled receptors is intrinsically linked to their conformational heterogeneity. In conjugation with site-directed spin labeling, NMR and EPR provide powerful tools to access highly dynamic conformational states of these proteins. Here, nitroxide spin labels were coupled to single cysteines in the neuropeptide Y_2 receptor (Y_2R), which is essential in key physiological pathways. Various single cysteines were introduced into a functional cysteine-deficient Y_2R variant. The mutants were expressed by *E.coli* fermentation with yields of up to 10 mg of purified Y_2R per liter expression medium and functional reconstituted into a lipid bicelle environment. Successful spin labelling was confirmed by a CPM fluorescence assay.

A solid-state MAS NMR approach was established monitoring distance dependent paramagnetic relaxation enhancement effects between the spin labeled receptor and its site-specifically ^{13}C labeled ligand neuropeptide Y (NPY). First experiments have been performed with the Y_2R-A202$^{45.49}C$ mutant, which contains the spin label in close proximity to the ligand binding pocket. An enhanced relaxation rate was detected for the I28-Cd site in NPY, but not for residue A14, which is in good agreement with our structural model.

Furthermore, CW-EPR measurements with spin labels coupled to different intra- and extracellular sites have shown spectra with mobile and immobilized populations, indicating multiple dynamic conformational states of the receptor. Addition of intracellularly bound arrestin will be the next steps in order to investigate structural changes upon Y_2R activation. Moreover, the established labeling protocol will path the way for future long-range distance measurements using DEER spectroscopy.

Poster 25

Mechanistic insights into the specificity of glycosaminoglycan interactions with regulatory proteins using solution NMR

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Glycosaminoglycans (GAGs) represent a class of negatively charged linear polysaccharides binding regulatory proteins (e.g. chemokines/interleukins) and consequently actively participate in multiple cell signalling processes. Moreover, because of the high flexibility and varying sulfation pattern of the GAG there is no binding motif or recognition pattern known. However, the central question that still remains to be answered is the specificity of protein/GAG interactions. Is the binding exclusively driven by the electrostatic forces or does the sulfation pattern of the GAG plays the critical role?

For a better understanding of the protein/GAG interaction and its specificity we choose interleukin 8 (IL8) as a model system and analysed the interaction with anionic peptides with varying net charges and/or charge distribution to investigate the specificity of electrostatically driven interactions between proteins and polyelectrolytes using solution NMR. The ^{1}H-^{15}N HSQC (heteronuclear single quantum coherence) spectrum of IL8 provides the fingerprint signals, which correspond to the amino acid of the protein. Initial titration experiments with two designed negatively charged peptides (net charge of -5 and -7) show some shifting peaks upon increasing peptide concentration. From this observable chemical shift perturbation, a pattern of interacting residues arises, which is compared to the known binding epitope of known GAGs. Comparison of these epitopes will allow concluding about the specificity of electrostatically driven interactions between proteins and polyelectrolytes.

Poster 26

Investigation of the Structure and Dynamics of Lipid Models of the StratumCorneum Using NMR Spectroscopy

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The stratum corneum (SC) as the outermost layer of the human skin prevents the body from excessive water loss as well as xenobiotics. In this work, we studied a LPP (long periodicity phase) model of the intercellular lipids of the SC consisting of *N*-lignoceryl-D-*erythro*-sphingosine (Cer[NS]), *N*-(32-linoleyloxy)dotriacontanoyl-D-*erythro*-sphingosine (Cer[EOS]), a free fatty acid-mixture (FFA-mix, C16-C24 saturated) and cholesterol at a molar mixing ratio of 0.3:0.7:1:0.45. Model membranes were investigated by ^{2}H solid-state NMR spectroscopy at temperatures ranging from 25 °C to 80 °C. The four components Cer[EOS], Cer[NS], lignoceric acid (C24, FFA) and cholesterol, where specifically deuterated and measured in four separate mixtures each containing just one deuterated species. From this data, the phase composition and the order parameters of each deuterated molecule could be determined. The results show that most of the lipids are in a highly ordered orthorhombic (crystalline) state at physiological skin temperature while the linoleic acid of the Cer[EOS] molecule was found in an isotropic and highly disordered state at all investigated temperatures. This surprising observation provides further evidence for the unique role of Cer[EOS] as a modulator for the barrier properties of the SC. These results modify our understanding of the molecular structure and dynamics of the intercellular lipid matrix of the SC to better understand the barrier properties of the human skin.

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Poster 27

Thermophoretic trap for single amyloid fibril and protein aggregation studies

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The formation of aggregates of peptides is responsible for a number of neurodegenerative diseases. The individual steps of this aggregation from single soluble monomers or oligomers to highly ordered, insoluble amyloid fibrils, however, are commonly hidden in the ensemble average of common measurement techniques. The heterogeneity of the ensemble at all stages of the aggregation process hides the growth details such as secondary nucleation processes or fibril fragmentation.

I will present on my poster a method that is able to trap single amyloid fibrils freely diffusing in solution by utilizing a static temperature field which is generated by converting optical energy from a laser into heat with a nano-plasmonic metal structure. This thermophoretic trap allows us to extract a lot of properties of the individual fibrils, like their Soret coefficients characterizing the motion in a temperature gradient as well as the translational and rotational diffusion coefficients over time periods of at least several 10 minutes up to even hours.

Repeating the measurement for several single fibrils allows us to extract a length dependence of the translational and rotational diffusion coefficients being in line with theoretical predictions. Due to the high sensitivity of the rotational diffusion coefficient on length changes, we are furthermore able to study the growth of single fibrils down to a few 10 nm, i.e., below optical resolution, in the presence of monomers or monitor secondary nucleation events and fragmentation which have not been seen directly before.

Thus, our trap offers a promising platform for investigations of molecular interactions and provides a deeper insight into individual growth stages of amyloid fibrils.

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Poster 28

Retinal implant: Selective electrical activation of retinal pathways

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Purpose:
Bionic implants exist which restore limited sight to the blind by electrically stimulating the neural tissue of the eye called the retina. Current implants stimulate all cells of the retina at the same time, however the retina has dozens of cell types which each carry a different visual message to the brain. In this work, we show how designing an electrical stimulus based on the preferred input of selected cell types can selectively activate the ON and OFF pathways of the retina. This improved specificity should improve bionic vision by making images sharper.

Methods:
We extamined amplitude-modulated electrical pulse trains for differential activation of the ON and OFF pathways. Such activation was examined mouse retina using a microelectrode chip (MEA) to record and stimulate epiretinally.

Results:
Noise-embedded, sine-wave, pulse train modulations were sufficient to elicit ON or OFF RGC-specific activation, depending on the direction of the modulation (decreasing or increasing cathodic pulse amplitude, respectively). RGCs receiving ON pathway input responded more strongly to upward cathodic pulse train modulations, whereas RGCs receiving OFF input responded more strongly to downward modulations.

Conclusions:
Deriving amplitude-modulated electrical pulse trains from the electrical input filter is a useful method to find out specific stimuli eliciting ON and OFF RGC pathway inputs. Eventually, by proving that pathway-specific activation via the implant is possible, we hope to foster the development of new retinal implants that integrate the natural visual coding used in healthy eyes.

DFG: HO 622/1-1

Poster 29

O Protons where art thou? Kinase Inhibitors in Lipid Membranes with NOESY and more

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We investigated the interaction of three different FDA approved Kinase inhibitors (Ceritinib, Imatinib and Ruxolitinib) with POPC lipid membranes.
To observe the orientation of the molecules inside the membrane as well as their influence, we applied 1H,2H and 31P NMR techniques measuring cross relaxation rates, order parameters of the POPC acyl chain and chemical shift anisotropy respectively.
All investigated inhibitors show an increase in the chemical shift anisotropy, meaning a decrease in the headgroup mobility. Ceritinib and Ruxolitinib are shown to increase acyl chain movement, while Imatinib decreases it.
The localisation of the different chemicals was determined by the cross relaxation rates of some inhibitor protons to the POPC protons, with all chemicals arranging themselves in the glycerol region. Wide distribution functions however indicate that the molecules remain very mobile inside the membrane.

Poster 30

Elongated Cells Fluidize Malignant Tissues

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Tissue morphology changes during tumour progression. In 2D cell cultures, different tissue states, such as fluid, jammed and nematic, are linked to cell shapes. While it is not clear if these results hold true in three dimensions, they suggest to investigate cell shapes and tissue states of matter in 3D. To explain cell motility in tumors, we compare 3D cell spheroids composed of cells from a cancerous and a non-cancerous cell line.

Through spheroid fusion experiments and live cell tracking, we show that the epithelial sample behaves solid-like and the malignant sample is fluidized by active cells moving through the tissue. Full 3D-segmentations of the samples show that the fluid-like tissue has elongated cell shapes. This links cell shapes to cell motility and bulk mechanical behaviour.

We reveal two active states of matter in 3D tissues: an amorphous glass-like state with characteristics of 3D cell jamming, and a disordered fluid state.

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Poster 31

Development of a universal measurement set-up for the biomechanical examination of acetabular fractures

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Due to the high complication rates of current treatment methods for acetabular fractures, an improved solution is being researched. Biomechanical examinations must be carried out beforehand. The experimental arrangements of current studies merely can analyse special fracture gaps on the artificial bone.
For further development of treatment methods and for investigation of the fracture movement at the acetabulum, a test rig is being developed. It must allow a repeatable examination of different acetabular fractures with artificial and human bones.
The development of the test bench is carried out under consideration of created test protocols and guidelines. The dimensioning of the components is based on the insights of evaluated CT data. The corresponding orientation of hip bones is defined on the basis of literature.

The attachment point for the testing machine is created by embedding the hip bones on the symphysis and the iliac tuberosity in casting resin. By using a special embedding construction, the load situation during walking is simulated anatomically correct and reproducible. A rotatable plate aligns the embedded iliac tuberosity according to the desired fracture examination and can be viewed by an optical measuring system. The final evaluation with two artificial hip bones of different sizes provides evidence that the functionality is independent of the sample geometry.

With the developed test rig the fracture gap movement at the acetabulum of artificial and human bones can be examined individually. Furthermore, statements about the biomechanical behaviour of different treatment methods can be made before clinical studies.

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Poster 32

Formation of a ß2AR*-Gs_{GDP} intermediate complex

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X-ray crystallography and cryo-electron microscopy structures of receptor G protein complexes show hallmarks of receptor and G protein activation. In all these complexes, the C-terminal α5 helix of Gα binds deeply into the binding pocket of the activated receptor (R*). In contrast, recent hydrogen-deuterium exchange mass spectrometry and X-ray footprinting mass spectrometry data of the β2-adrenoceptor Gs system show that α5 remains dynamic for a long period of time suggesting an intermediate GDP-bound β2AR*-Gs_{GDP} complex as the first specific receptor G protein interaction [1]. The existence of an intermediate R*-G_{GDP} complex was initially demonstrated by kinetic and single-molecule fluorescence resonance energy transfer analysis [2,3]. The recent X-ray structure of the β2AR construct with a fused Gαs carboxyl-terminal 15 amino acid peptide (PDB-id: 6E67) shows a binding mode of α5 that significantly differs from the X-ray structure of nucleotide-free β2AR*-Gs (PDB-id: 3SN6) [4]. In order to investigate whether that mode of interaction represents the β2AR*-Gs_{GDP} complex, we analyzed the spontaneous formation of the β2AR*-Gs_{GDP} complex in long all-atomistic classical molecular dynamics simulations.

Results are discussed with regards to the role of structural intermediates for coupling specificity and for receptor catalyzed G protein nucleotide exchange.

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Poster 33

Stress Fiber vs. Cortical Contractility and its Relevance for Tissue and Cancer Development

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It is the current perception that cell contractility is solely based on a force dipole like interaction requiring stress fibers that pull between cellular adhesion sites for migratory and invading purposes. However, our observations suggest a clear differentiation between stress fiber and cortical contractility.

We investigate on one hand suspended cells, lacking stress fibers and adhesion points, regarding active cortical contractility and on the other hand adhered cells, in an ECM environment displacing biomechanical properties based on oriented actin stress fiber contractility. Epithelial cells assemble a strong actomyosin cortex providing cortical tension exhibiting mechanosensitive contractile behavior. In contrast mesenchymal cell cortices behave less contractile, while they express more prominent stress fibers generating stronger contractile forces in 3D collagen gels.

We propose an actomyosin rearrangement from cortical to stress fiber structures during epithelial–mesenchymal transition.

We investigate the formation of cell-cell contacts up to the formation of cell spheroids, which is accompanied, for epithelial cells, with rearrangement of their contractile actomyosin cortices building up a collective actomyosin cortex surrounding the aggregates. This collective actomyosin rim results in round shaped cell spheroids which suggests a high cortical tension similar to surface tension. In contrast, mesenchymal cells, do not form stable cell-cell contacts neither collective actomyosin rims, due to lacking cortical contractile potential, suggesting low surface tension like behavior.

All together, we reveal a significant contribution of cortical contractility in tissue development of epithelial cells, while reduced impact for cancer development of mesenchymal cells.

Poster 34

A lipid bilayer membrane model system for hydrogel microparticle based biosensors

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A large amount of small molecule active substances exist in the environmental water system, mainly as reminiscent excreted drugs from the human body, such as beta-blockers. To monitor aqueous systems and quantify these small molecule drugs, cost-intensive, analytical techniques like mass spectrometry or liquid chromatography are commonly used. The so-called soft colloidal probe (SCP) technique represents an alternative, low cost method to quantify small molecules with high sensitivity in the pM range. SCPs are elastic hydrogel microparticles functionalized with the target analyte. SCP interaction with an immobilized binding partner (e.g. receptor) on a transparent biochip and competitive interference with free analyte in solution leads to a differential adhesion of SCP on the biochip surface, which is optically detected.

We develop a new biochip platform to immobilize relevant receptors in a native functional environment using supported lipid bilayers (SLB). By that a multitude of drugs interacting with membrane proteins, like GPCRs, should be addressed. We investigated two types of SLB, a native membrane preparation and an artificial lipid bilayer on solid surfaces with and without maleic acid copolymer cushion layers. Confocal laser scanning microscopy and fluorescence recovery after photobleaching were used to characterize the different approaches in terms of success and homogeneity of SLB and mobility of lipids and membrane proteins.

The results revealed that native membrane preparations do not only for a direct preparation of SLB while artificial lipid bilayers can be achieved with varying mobility in dependence on the underlying support. Ongoing experiments, using as exemplary analyte beta-blockers, will reveal the applicability of the SLB system in SCP technique.

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Poster 35

Vaspin internalization into adipocytes is receptor mediated and initialized by interaction with cell surface GAGs

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Vaspin is a member of the serpin family and so far, there are two known protease targets, KLK7 and KLK14. Vaspin administration to diet-induced obese mice reduces inflammation in adipose tissue and improves insulin action, parameters seriously affected by obesity.

Investigating the cellular fate of vaspin using a fluorescently labeled vaspin, we observed substantial internalization of vaspin into 3T3-L1 pre-adipocytes. We then found internalization into human pre-adipocytes as well as differentiated 3T3-L1 cells yet only marginal internalization into HEK293 and HepG2 cells. Competition with unlabeled wt vaspin and incubation with the inhibitor chlorpromazine lead to significantly decreased vaspin uptake. These data provide strong evidence for an active receptor-mediated internalization process. The LDL receptor-related protein (LRP1) is a clearance receptor for serpin-enzyme complexes in the circulation. Initial data showed, that the presence of RAP, a ligand of LRP1, significantly inhibited vaspin uptake giving first indication that LRP1 mediates vaspin internalization.

Previously, we have elucidated the binding of vaspin to glycosaminoglycanes in the ECM. Therefore, we used a non-heparin-binding vaspin variant to investigate whether GAG binding is a prerequisite for receptor-mediated internalization. Indeed, we observed a significant reduction of internalization for this variant.

Together, we provide strong evidence for a receptor-mediated vaspin internalization process that is initiated via GAG binding and subsequent interaction with LRP1. Further work aims to elucidate the effects of vaspin internalization on signal transduction pathways activated by vaspin. This will greatly enhance the understanding of beneficial effects of vaspin in adipose tissue and obesity.

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Poster 36

The adhesion GPCR *mayo/CG11318* in the alimentary and excretory system of *Drosophila melanogaster*

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To date, only two homologs associated with adhesion G protein-coupled receptor (aGPCR) had been described in *Drosophila*, limiting the use of the fly as a model to investigate other aGPCR layouts. We work with the newly discovered aGPCR, *CG11318*, which we renamed mayo, to investigate its role in *Drosophila melanogaster.* Our experiments show transcriptional expression of mayo throughout the gastrointestinal canal and in the anal pads of larvae. With the help of the null mutant and rescue lines, we are carrying out loss-of-function studies. Since the anal pads are involved in ion absorption and excretion, we tested the ion absorption in $mayo^{KO}$ animals and investigated their survival in hyperosmolar environments. This uncovered a reduction of ion absorption in $mayo^{KO}$, and decreased survival of hyperosmolar exteriors upon loss of *mayo* in larvae. In larvae and adults, $mayo^{KO}$ showed differences in gut length. This provides a basis for future experiments that will be determining the molecular and physiological function of *mayo*.

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Poster 37

A new approach in the production of Antimalarials from Nature – Excretion of compounds from *Triphyophyllum peltatum* in liquid cultures

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The West African tropical liana *Triphyophyllum peltatum* Airy Shaw, is a rare, part-time carnivorous, and the only species of its genus in the Dioncophyllaceae family. It contains several different naphthylisoquinoline alkaloids and naphthoquinones shown to be remarkably effective against various diseases, in particular against malaria. However, important further investigations are still missing for the development of therapeutic drugs. The biggest bottleneck is the limited natural availability of these compounds in sufficient quantities since total synthesis is complex and hence not economic. *In vitro* cultures represent an interesting approach, but this method requires the cultures to be sacrificed to harvest the compounds.

Therefore, we want to investigate the excretion of *T. peltatum* compounds in *in vitro* liquid cultures. Root cultures were incubated in the dark with 1/4 liquid MS medium under moderate rotation. After 15 days, the medium was collected and extracted with dichloromethane and ethyl acetate. The evaporated extracts were analyzed by HPLC and LC-MS. The dichloromethane extract showed a strong yellow color and HPLC analysis revealed a major peak, which could be identified as droserone by comparison with an authentic reference compound.

The HPLC analysis of the ethyl acetate extract revealed a major peak with UV absorption maximum at 284 nm and one of the minor peaks showing UV spectra and retention time characteristics of the naphthylisoquinoline alkaloids. Further analysis is required to identify these compounds. We conclude that the excretion of *T. peltatum* metabolites in liquid cultures is a promising approach to produce antimalarial compounds. The next steps will focus on further structural investigations and experiments to increase overall yield.

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Poster 38

KS0365 is a new and potent TRPV3 agonist

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The transient receptor potential channel TRPV3 is a thermosensitive, non-selective, Ca^{2+} permeable channel primarily expressed in the skin. Recent studies indicate a critical role of TRPV3 in several aspects of skin physiology and in the development of skin disorders. Due to the lack of highly potent, selective and specific modulators of TRPV3, so far only limited progress has been made to understand how TRPV3 influences skin homeostasis. We here describe the identification of a novel TRPV3 agonist KS0365. KS0365 activated TRPV3 channels with an EC_{50} of 7.3 ± 1.3 µM. The Ca^{2+} influx in response to KS0365 was further enhanced in cholesterol-enriched cells. In contrast to the outwardly rectifying TRPV3 currents evoked by 2-APB, HEK_{mTRPV3} cells responded to KS0365 application with a linear current, indicating a fully activated TRPV3 channel.

KS0365-mediated Ca^{2+} entry and inward currents through TRPV3 were blocked by the non-specific TRPV channel blocker ruthenium red. KS0365 was also effective in activating endogenously expressed TRPV3 channels in m308k mouse keratinocytes with an EC_{50} of 25.0 ± 3.1 µM for cholesterol-enriched cells. In MTT cell viability assays, KS0365 induced cytotoxic effects in HEK_{mTRPV3} cells, but not in the parental HEK cell line. In a migration assay performed on m308k cells, KS0365 led to a 1.7-fold acceleration of the scratch closure compared to non-treated cells. Notably, co-stimulation with KS0365 and epidermal growth factor (EGF) resulted in a 3.6-fold acceleration of the scratch closure after 12 hours, which was abrogated by ruthenium red, indicating that the increased cell migration in response to KS0365 and EGF is mediated by TRPV3.

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Poster 39

Design, synthesis and biological evaluation of a series preferential HDAC6 inhibitors structurally derived from HPOB

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Histone deacetylases (HDACs) and histone acetyltransferases (HATs) control the dynamic status of histone acetylation, which plays an important role in the regulation of gene expression. The hyper-acetylation of histones is generally associated with transcriptional gene activation. Conversely, the hypo-acetylation of histones is correlated with transcriptional gene repression. HDACs remove the acetyl groups from acetylated histones, resulting in a closed chromatin configuration that blocks the access of the transcription machinery to DNA, and suppress gene expression.

HDACs consist of eleven zinc-dependent enzymes, which are further divided into four different classes, including class I (HDACs 1, 2, 3,8), class IIa (HDACs 4, 5, 7, 9), class IIb (HDACs 6, 10), and class IV (HDAC11). Notably, in many different cancer types an overexpression of these enzymes was found to repress the expression of tumour suppressor genes. Consequently, HDACs have been investigated as promising anticancer targets and HDAC inhibitors emerged in the last decade as valuable epigenetic anticancer drugs. In this study, we report a new class of preferential HDAC6 inhibitors structurally derived from the well-established HDACi HPOB. These new compounds are accessible by a straightforward microwave-assisted UGI-4-component synthesis.

The half maximal inhibitory concentration was improved by iterative cycles of synthesis and *in vitro* testing against the HDAC isoforms 1 and 6 leading to a hit compound with an IC_{50} value < 10 nM. All compounds were further tested for their cytotoxicity against three different leukemia cell lines. Strikingly, several compounds exceeded the activity of the lead compound HPOB and the most promising compound displayed submicromolar activity against all three cell lines.

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Poster 40

Transformation of carnivorous plants: A mechanism to produce pharmacological active compounds

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A wide variety of carnivorous plants can produce and secrete well-defined digestive fluids consisting of pharmacological active secondary metabolites and digestive enzymes.
This digestive fluid is secreted out of the plant cell and could be harvested very easily without harsh cleaning steps.
Our aim is to research the transport mechanisms of enzymes in the digestive fluid and modify the secreting system to produce pharmaceutical relevant substances in defined compartments of carnivorous plants.
The success of a transformation and a good transformation efficiency is dependent on the chosen plant and the used method.
Therefore, it is important to have a valid transformation protocol for each individual plant.
Here we present the transformation of several genera of carnivorous plants with the marker protein GFP using agrobacterium-mediated transformation or PEG-mediated protoplast transformation.

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Poster 41

Multi-Target Drug Discovery: Development of Dual Histone Deacetylase-Proteasome Inhibitors for Potential Cancer Treatment

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Inhibitors of histone deacetylases (HDACs) are an emerging therapeutic agents in cancer treatment, with by now four compounds approved by the Food and Drug Administration rendering them prosperous members of the therapeutic arsenal against cancers. In the case of multiple myeloma, HDAC inhibitors were found to inhibit tumor cell growth and induce apoptosis in the target cells as a single agent but additionally showed strong synergistic activity in combination therapy with proteasome inhibitors (PIs).
Despite the highly significant relevance of combination therapies, we wondered if also a single multi-target drug acting through two independent modes of action would do the job, thereby harnessing the advantages of polypharmacology. These include a more predictable pharmacokinetic profile, the statistically lower probability of developing target-based resistance, the guaranteed simultaneous presence of both modes of action in the target tissue and lower risks of drug–drug interactions.
On the basis of thorough analysis of the topology of the binding pockets of the chymotrypsin-like yeast proteasome 20S core particle a first-in-class dual target drug (RTS-V5) was designed and synthesized. The compound was successfully shown to selectively inhibit the clinically preferred HDAC isoform 6 as well as proteasome activity.
With this proof of principle at hand, we set out to further finetune the activity by iteratively resizing and rearranging the side chains and capping groups of the dipeptide structure to optimize the affinity for both targets. So far, all of the follow-up compounds exhibited promising inhibitory activity paving the way for further optimization studies towards dual HDAC-proteasom inhibitors.

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Poster 42

The STAT5b linker domain mediates the selectivity of catechol bisphosphates for STAT5b over STAT5a

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Signal transducers and activators of transcription (STATs) mediate signals from cell surface receptors to the nucleus and represent therapeutic targets for the treatment of human diseases. Most STAT inhibitors developed to date are designed to target the protein-protein interaction domain, the SH2 domain, and possess only limited selectivity for a single STAT protein. We recently described catechol bisphosphates (CBPs) as the first inhibitors of the STAT5b SH2 domain which display selectivity over the close homologue STAT5a. Here, we show that Arg566 in the STAT5b linker domain is the determining factor for the selectivity of CBPs. Arg566 in STAT5b can engage in electrostatic interactions with one of the phosphate groups of CBPs, while Trp566 in STAT5a cannot. Arg566 also determines the affinity of a phosphotyrosine-containing peptide derived from the EPO receptor, which is a natural occurring interaction partner of STAT5a/b. Our data provide the first demonstration that an amino acid in the linker domain of a STAT protein can determine the affinity of a small-molecule inhibitor for a STAT SH2 domain, and contribute to the understanding of the divergent biological functions of the highly homologous STAT5a and STAT5b proteins. In addition, our data suggest targeting the interface between the SH2 domain and the linker domain as a new design approach for the development of potent and selective STAT inhibitors.

Poster 43

The dithiolane X10056 inhibits TRPV2 channels endogenously expressed in primary macrophages

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The superfamily of transient receptor potential channels (TRP) consists of about 30 mammalian members, forming mainly nonselective cation channels. TRP channels are involved in a multitude of physiological and pathophysiological processes such as nociception or thermosensation and are regulated by various chemical and physical stimuli. TRPV2 is a Ca^{2+}-permeable ion channel, which is highly expressed in cells of the immune system like mast cells or macrophages. However, the role of TRPV2 in such cells is not very well understood partially due to a lack of potent and selective pharmacological tools to investigate its function in native cells. Therefore, we performed a fluo-4-assisted functional screen of a compound library (4562 compounds) on HEK293 cells heterologously expressing murine TRPV2 (HEK_{TRPV2}). We identified a dithiolane (X10056) as a novel and potent TRPV2 inhibitor. X10056 blocked TRPV2-mediated Ca^{2+} influx with an IC_{50} of 7.0 µM. Further Ca^{2+} assays with 27 derivatives and 39 chemically related compounds were performed. The inhibitory properties of X10056 were confirmed by using fura-2-mediated single-cell Ca^{2+} assays and electrophysiological whole cell recordings in HEK_{TRPV2} cells and in the mouse RBL mast cell line, endogenously expressing TRPV2. TRPV2 is believed to play a role in controlling macrophage function such as phagocytosis and migration. Therefore we isolated and cultured primary bone marrow-derived macrophages (BMDM) from mice. Quantitative PCR revealed the expression of TRPV2 in BMDM. 2-APB elicited a Ca^{2+} influx in BMDM that could be inhibited by X10056, confirming the functional expression of TRPV2 in BMDM, which makes X10056 a useful tool for further investigating TRPV2 function Ca^{2+} assays in primary macrophages.

Poster 44

A Universal RNA Regulation System – Synthetic Riboswitches to Control tRNA Processing

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RNA plays an important role in many cellular processes besides its classic function as messenger in gene expression. Riboswitches, regulatory RNA elements mostly located upstream of a coding region in bacteria, are a useful tool in synthetic biology to control gene expression in a ligand-dependent manner. The regulation depends on RNA secondary structure, which usually influences transcription or translation.

Here, we describe a synthetic riboswitch element, whose functionality is based on an unusual, new regulatory principle. Designed *in silico*, this theophylline-dependent riboswitch controls RNase P-catalyzed tRNA 5'-processing by masking or presenting the single-stranded 5'-leader region of a tRNA precursor. In addition to this novel orthogonal regulation principle, this synthetic regulatory RNA allowed us to study RNase P catalysis *in vivo*. Thus, we were able to show for the first time, that RNase P-catalysis is influenced by the secondary structure of the substrate 5'-leader. Finally, our data from *Escherichia coli* and human embryonic kidney cells demonstrate that *in silico* predictions can be used to design an RNA-dependent regulation which can be applied in different domains of life.

Poster 45

Flow diversion beyond the circle of Willis: endovascular aneurysm treatment in peripheral cerebral arteries employing a novel low-profile flow diverting stent

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Background:
Flow diversion (FD) has emerged as superior minimally invasive therapy for cerebral aneurysms. However, aneurysms of small peripheral vessel segments have not yet been adequately treatable. Currently established devices necessitate large microcatheters which impede atraumatic maneuvering. We want to show our experience with the novel low-profile FD Silk Vista Baby (SVB), offering the as yet unique feature of deliverability via a 0.017 inch microcatheter.

Materials and methods:
25 patients (27 aneurysms) were prospectively included. A total of 30 SVBs were employed, predominantly targeting demanding aneurysms of the anterior communicating artery complex. The efficacy of the FD was assessed using two- dimensional vector-based perfusion and conventional digital subtraction angiography (DSA) after implantation and at the first follow-up at 3 months. The first follow-up was available in 22 patients.

Results:
All devices were implanted without technical or clinical complications. Eleven treatments were performed using the recommended Headway 17. In 14 interventions the even more maneuverable Excelsior SL10 was used as an alternative delivery system. Aneurysmal influx was strongly reduced after implantation. All parent vessels remained patent. 17/27 aneurysms were completely occluded at first follow-up (~2.7 months), 6/27 aneurysms showed decreased influx or delayed washout and one remained unchanged. In three cases follow-up DSAs are remaining.

Conclusion:
SVB provides enhanced controllability in vulnerable segments beyond the circle of Willis. Smaller variants (2.25 mm and 2.75 mm) can safely be implanted via the superiorly navigable Excelsior SL10. Hence, the SVB represents the next evolutionary step in minimally invasive treatment of cerebral aneurysms.

Poster 46

Analyzing the time-to-treatment of patients with obsessive-compulsive disorder

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With a 12-month prevalence of 3.8%, obsessive-compulsive disorder (OCD) is one of the 4 most common psychiatric diseases in Germany. The time period from symptom development to the beginning of an adequate therapy was reported to be 17 years. However, some of the corresponding studies are older than 10 years. Especially with regard to the digital change of the last few years, there have been many new possibilities for patients to inform themselves about their symptoms independently and to search for therapy options. Thus, it remains unclear to what extent these developments affect the period from the beginning of symptoms to the beginning of treatment.

In this prospective systematic survey, we record the time elapsed between the onset of disease-related symptoms and the start of treatment in the patients surveyed. In addition, we assess how patients inform themselves about their symptoms at the beginning of their illness. The survey was conducted on 100 patients who are undergoing outpatient psychiatric treatment due to an OCD at the Department of Psychiatry and Psychotherapy at the University of Leipzig Medical Center. The average duration from the beginning of the first symptoms to the beginning of treatment was 14 years. 36% of the patients informed themselves independently at the beginning of their illness. With 28%, a search engine was most frequently used. In conclusion, almost two-third of the patients do not inform themselves about the symptoms of the OCD independently. Although the time to start of treatment was 14 years on average and therefore lower than in previous studies, it is still very long. We further plan to investigate subgroups, in particular the group of *digital natives* born after 1980 since they tend to be more attached to the internet.

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Poster 47

The influence of trimethylamine N-oxide (TMAO) on endothelial cell function

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TMAO itself but more importantly its precursors are incorporated from food uptake of animal-based products. Increased serum concentrations of TMAO have been associated with atherosclerosis, myocardial infarction, heart failure, stroke and thrombosis. However, the exact underlying mechanisms are incompletely understood. Atherogenesis is characterized by endothelial-to-mesenchymal transition (EndMT), a process where endothelial cells lose their phenotype and gain a mesenchymal character producing components of the extracellular matrix found in atherosclerotic plaques such as versican. The objective of the study was to evaluate the influence of TMAO on physiological endothelial cell function and transition into mesenchymal cells and reveal the underlying mechanism.

While exposure to TMAO showed no increased apoptosis rate of primary human endothelial cells (ECs) in concentrations comparable to the serum levels of patients, it reduced the number of endothelial cells in the S-Phase of the cell cycle by 53% ($p<0.05$). The capacity to form angiogenic sprouts was significantly reduced (50%) under treatment of ECs with TMAO, as measured with the *in vitro* network formation assay ($p<0.05$). In line, trans-differentiation of ECs into mesenchymal cells was by 6.8-fold increased under TMAO. To identify potential regulatory cues underlying the enhanced effect of TMAO on EndMT, gene expression of ECs treated with or without TMAO was analyzed using NGS. Most importantly, we found the metabolic immune cell receptor MIR1 significantly upregulated under TMAO treatment, known to enhance infiltration of lymphocytes and uptake of LDL. The results show that TMAO has the potential to interfere with endothelial identity, function and proliferation.

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Poster 48

Practical demonstrations of glucagon administration in parents of paediatric patients with type I diabetes mellitus

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Background:
Severe hypoglycaemia is the most prevalent emergency situation for diabetic patients requiring the administration of glucagon. We investigated the practical skills in glucagon administration in parents of paediatric patients with type I diabetes (T1D).

Methods:
We performed a placebo demonstration with parents of paediatric patients with T1D to assess their practical skills in the administration of glucagon. Occurring administration errors were documented. An interview was used to identify further errors associated with glucagon administration. Afterwards, parents' questions and all identified errors were addressed. Both before the demonstration and after the discussion of the errors, the parents were asked to rate their own skills in administering glucagon on a scale ranging from 1 (very good) to 6 (very poor).

Results:
58 parents took part in the study. In 9% (5/58) glucagon was not present at home and in 21% (11/53) it exceeded the expiry date. 14% (8/58) tried to insert the needle into the glucagon vial without removing its cap. 16% (9/58) did not add any solvent. 69% (40/58) did not check if the placebo powder simulating the glucagon was completely solved. 0% (0/58) of the parents named an incorrect injection site (visceral, gluteal, femoral).
The parents' self-reported confidence in their ability to administer glucagon rose from a median grade of 3 (Q25/Q75 2/4) before the demonstration to 1 (1/2) after the discussion of the errors.

Conclusion:
In a simulated glucagon administration, we found that parents of children with T1D committed severe administration errors. Potentially, those errors have a negative impact on the rescue of the patient from the life-threatening situation associated with severe hypoglycaemia.

Poster 49

The Leipzig Health Atlas – A Repository for Research Data and Models

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The publication of research results is part of good scientific practice and is increasingly expected and demanded. The FAIR data principles of data sharing are an important guideline - even if medical data sharing makes it necessary to define access restrictions.
The Leipzig Health Atlas (LHA) is a project to support presentation and secure sharing of publication results from a wide range of medical topics, (bio)medical data (e.g., clinical, epidemiological and molecular data sets), as well as models and tools, e.g. for risk assessment of breast cancer. In order to meet the goals, a repository for sharing research data and models was set-up aiming to make data FAIR (**f**indable, **a**ccessible, **i**nteroperable, and **r**eusable).
The LHA repository uses the research data sharing platform SEEK as a foundation and provides some additional functionalities. To improve findability, contributors can annotate their uploaded content with concepts from the Human Disease Ontology. Upon request, clinical study data are accessible via the study data querying tool i2b2 for feasibility studies. Moreover, contributors can deploy their uploaded models into a continuous integration and delivery platform, where models are enhanced with a web interface (e.g. R-Shiny apps) as live demo.
The target audience of the LHA consists in particular of clinicians, epidemiologists, molecular and human geneticists, pathologists, biostatisticians and modellers and is publically available at www.health-atlas.de.
The project is funded by the Federal Ministry of Education and Research (i:DSem, 031L0026) in Germany.

Poster 50

Musical Attention Control Training for patients with acquired brain injury – a feasibility study

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Music-based therapy has been studied in motor and speech rehabilitation of neurological diseases, but there are only few studies on the use of music-based therapy for the rehabilitation of attention. This study aimed at implementing and evaluating a music-based group therapy for patients with neurological diseases presenting attention deficits at the Clinic for Cognitive Neurology of the University Hospital Leipzig. 20 neurologic patients with acquired brain injury who suffered from attention deficits revealed by the initial standardized neuropsychological assessment were included. All patients were tested again for attention abilities, interference control and mood at the end of their therapy. Participants received a music-supported group therapy (5-13 sessions over 3-7 weeks) as add-on to the standard therapy. Before and after each session patients evaluated several subjective parameters (e.g. mood, attention) and the quality of the training session. Each training session on specific attention control functions included structured rhythm exercises, free and melodic tasks and rhythmical exercises to participants' favorite songs.
The implementation of the music-based training in the therapy routine was successful. Subjective evaluations of patients showed improvements of mood and attention after training sessions and patients enjoyed the training although it was perceived as exhausting. Results showed an enhancement of attention functions of the patients and significantly better interference control and mood. Because the training was an add-on to the standard therapy we cannot conclude that these findings were related solely to our training. Therefore we assess a control group that only receives the standard therapy and plan a randomized-control trail study.

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Poster 51

Serum BDNF levels correlate with structural brain measures in minor depression

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Depressive disorders represent a large variety of clinical phenotypes. Diversity in symptoms and biological signatures complicates patients' stratification in research and clinical management. Thus identification of the biological subtypes of depression is a crucial step in further research.

In this study, we aimed to disentangle biological correlates of minor depression - a subclinical depressive disorder, where two to four depressive symptoms disturb a patient for at least two weeks. We investigated the correlation between serum levels of Brain-Derived Neurotrophic Factor (BDNF) and structural Magnetic Resonance Imaging (MRI) parameters in 20 subjects with minor depression and 40 healthy controls.

We observed a positive correlation between serum BDNF and cortical thickness and volume along the midline structures and medial prefrontal cortex in subjects with minor depression, but not healthy controls. These regions are well known for their relevance to mood disorders. The correlations were significantly different between minor depression and the healthy control group as shown in an interaction analysis. Interestingly, the correlations with cortical thickness were driven by subjects with first-episode depression.

We conclude that serum BDNF and imaging parameters are specifically associated with minor depression in a region- and condition-dependent manner. A positive correlation between serum BDNF and structural grey matter estimates was most consistently observed for cortical thickness. We discuss why cortical thickness should be preferred to volumetric estimates for such analyses in future studies.

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Poster 52

Magnetic Resonance Imaging guided Focused Ultrasound treatment *in vivo* in 7 Tesla preclinical MRI

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Magnetic resonance imaging guided focused ultrasound (MRgFUS) allows precise and non-invasive tumor heating at moderate temperatures 41-46°C. Thus, a sensitization of tumor tissue could be achieved before radiation therapy. The purpose of this study was the implementation of a new preclinical FUS system and MRI based temperature control in a preclinical MRI with tumor-bearing mice.

A novel MRI conditional FUS phased-array transducer has been developed (11x11 elements, copper shielding, aperture 1.0 cm^2, frequency 2.0 MHz) and installed at 7 T MRI (Bruker). The MR compatibility of the transducer was tested with a agar-CuSO4 phantom. For *in vivo* MRgFUS, a mouse was anesthetized with 2% isoflurane in air and oxygen.

The sonication was started manually for 55 s at 4.8 W/cm^2 followed by MR thermometry [FLASH: TE=4.5ms, TR=80ms, FOV=8x5cm^2, slices=6 (2mm), matrix=64^2; acq. time=17s]. The sonication power was adjusted to hold the temperature at 45°C for 30 min. Real-time temperature monitoring at the skin was performed with fiber optics (Luxtron). Proton resonance frequency shift MR thermometry was visualized offline in MATLAB from the k-space data.

MR images of the phantom showed 2.4 fold reduction of the signal-to-noise (SNR) and 0.7 mm thick zipper artefact through the center of the phantom along the phase-encoded direction in presence of the transducer. FLASH images, measured for MR thermometry have SNR 11. The target temperature (45°C) varied ±1°C. Thermometry calculations showed max. temp. discrepancy of ≤1°C between the temperatures measured by fiber optics (45.4°C) and thermometry (44.4°C).

This study showed the feasibility of targeted FUS heating and MRI based temperature control at 7 T. The measured SNR ensures minimum background noise for MR thermometry calculations.

Poster 53

Delayed Stroke after Aneurysm Treatment with Flow Diverters in Small Cerebral Vessels: A Potentially Critical Complication Caused by Subacute Vasospasm

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Background:
Flow diversion (FD) is a novel endovascular technique based on the profound alteration of cerebrovascular hemodynamics, which emerged as a promising minimally invasive therapy for intracranial aneurysms. However, delayed post-procedural stroke remains an unexplained concern. A consistent follow-up-regimen has not yet been defined, but is required urgently to clarify the underlying cause of delayed ischemia.

Materials and Methods:
In the last two years, 223 patients were treated with six different FD devices in our center. We identified subacute, FD-induced segmental vasospasm (SV) in 36 patients as a yet unknown, delayed-type reaction potentially compromising brain perfusion to a critical level.

Results:
Furthermore, 86% of all patients revealed significant SV approximately four weeks after treatment. In addition, 56% had SV with 25% stenosis, and 80% had additional neointimal hyperplasia. Only 13% exhibited SV-related high-grade stenosis. One of those suffered stroke due to prolonged SV, requiring neurocritical care and repeated intra-arterial (i.a.) biochemical angioplasty for seven days to prevent territorial infarction. Five patients suffered newly manifested, transient hemicrania accompanying a compensatorily increased ipsilateral leptomeningeal perfusion. One treated vessel obliterated permanently.

Conclusion:
FD-induced SV is a frequent vascular reaction after FD treatment, potentially causing symptomatic ischemia or even stroke, approximately one month post procedure. A specifically early follow-up-strategy must be applied to identify patients at risk for ischemia, requiring intensified monitoring and potentially anti-vasospastic treatment.

Poster 54

Direct inhibition of coagulation factor Xa and not fIIa (thrombin) allow aPC mediated anti-inflammatory functions

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Thrombin is the key protease in regard to thrombus formation. However, in regard to protease dependent signaling other coagulation proteases, including fXa, likewise convey cellular effects. We postulate that inhibition of fXa or fIIa convey different effects in regard to inflammation despite comparable anticoagulant efficacy. Using *in vivo* assays we determined doses of rivaroxaban and dabigatran conveying comparable effects in regard to bleeding and thrombosis. Using – in regard to hemostasis – equally potent dosages of fIIa and fXa inhibitors we analyzed the impact of direct fIIa and fXa inhibition on myocardial infarction. Direct fIIa and fXa inhibition resulted in comparable infarct size. However, while an anti-inflammatory was observed following direct fXa inhibition, this was not apparent following direct fIIa inhibition. Furthermore, fXa inhibition, but not fIIa inhibition, reduced expression of proinflammatory cytokines (IL-6, TNF-alpha), NF-κB activation, and cardic fibrosis in infarcted heart tissue. Mechanistically, fIIa inhibition, but not fXa inhibition, resulted in lower endogenous protein C (PC) activation. Importantly, the protective effects following fXa inhibition were lost following inhibition of endogenous aPC (mAb MPC1609). Here, we show a new function of the coagulation system inhibition of fIIa and fXa can convey distinct anti-inflammatory effects despite equal anticoagulant efficacy. Following direct fXa inhibition sufficient thrombin to promote protein C activation appears to be available, resulting in preserved thrombin-dependent protein C activation and cytoprotection.

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Poster 55

Daten für die Medizinische Forschung - das Datenintegrationszentrum des Universitätsklinikums Leipzig

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Hintergrund:
In der Medizininformatik-Initiative des Bundesministeriums für Bildung und Forschung werden universitätsmedizinische Standorte gefördert, darunter auch das Konsortium SMITH mit Beteiligung des Universitätsklinikums Leipzig und der Universität Leipzig. Ziel ist es, eine innovative Struktur zur einrichtungsübergreifenden Vernetzung und für den Austausch von Forschungs- und Versorgungsdaten zu entwickeln.

Methoden:
Die Bereitstellung von Daten oder Analyseergebnissen erfolgt über standardisierte Schnittstellen auf der Basis von HL7 FHIR, HL7 CDA und IHE. Die Verfahren und zugehörigen Unterlagen zur Beantragung der Nutzung von Daten werden im Konsortium SMITH abgestimmt und in den teilnehmenden Einrichtungen ausgeprägt, unter Berücksichtigung der datenschutzrechtlichen und medizinethischen Vorschriften. Der Nachweis der Funktionsfähigkeit von Datenintegrationszentren erfolgt im Rahmen von Audits.

Resultate:
Das Datenintegrationszentrum wurde als eine zentrale Einrichtung des Universitätsklinikums etabliert. Erste Forschungsprojekte konnten bereits in 2018 und 2019 unterstützt werden. Dazu gehören u. a. die Projekte IFB Adipositas und INDEED (Notfallmedizin). Im 1. Quartal 2020 werden erste technische Lösungen zur regelhaften Bereitstellung von Daten für die medizinische Forschung zur Verfügung stehen. Dazu werden Schnittstellen für Machbarkeitsanalysen sowie für die Bereitstellung verschiedener medizinischer Daten – auch an externe Partner – implementiert.

Ausblick:
Die Förderphase der Medizininformatik-Initiative dauert noch bis Ende 2021 an. Schwerpunkte der sich anschließenden Weiterentwicklung der Dienste für die Datennutzung werden dann u. a. in der Bereitstellung spezialisierter Auswertungsdienste und in der Integration weiterer Datenquellen liegen.

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Poster 56

Human milk fatty acid composition and maternal lifestyle related time trends

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Introduction:
This study is one of the first to investigate the impact of lifestyle-related time trends on human milk fatty acid composition in two different cohorts. These cohorts were recruited from the general population a decade apart in Ulm, Germany, using comparable methodology.

Methods:
Human milk samples from lactating women collected 6 weeks post-partum were analysed [Ulm Birth Cohort Study (UBCS), n=585; Ulm SPATZ Health Study (SPATZ), n=520)]. Centred log ratio transformation was applied to fatty acid data. Principal Component analysis (PCA) was used to determine study-dependent fatty acid profiles. The effect of the study on the fatty acid profiles was determined using a general linear model.

Results:
Two principal components were retained. Scores from the first principal component were positively associated with saturated fatty acids (SFAs) and trans-fatty acids (TFAs), and negatively with monounsaturated fatty acids (MUFAs), n-6 and n-3 polyunsaturated fatty acids (PUFAs). The inverse was true for the second component. The least square (LS) means of the first principal component were positively associated with the UBCS study, and negatively with the SPATZ study. These associations remained significant even after adjustments for maternal lifestyle-related factors.

Conclusions:
None of the lifestyle-related factors we examined in both cohorts explained the time trend differences in the fatty acid profiles between these two studies. However the differences in fatty acid profiles may reflect the changes in dietary habits in the more recent cohort, which may comprise fewer intakes of dietary TFAs, SFAs and slightly higher intakes of vegetable oils. Some of these differences may also indicate variations in mammary gland biosynthetic capacity within populations.

Poster 57

Enhanced Radiation Effects by combined Treatment with Decitabine and Abacavir in a murine Model of human pediatric Medulloblastoma

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Medulloblastoma (MB) is the most common malignant pediatric brain tumor. Standard therapy consists of surgical excision followed by radio-chemotherapy. The 5-year-overall-survival for children is between 45 (Group 3) and 95% (WNT) depending on molecular genetic subgroup. Our previous *in vitro* studies showed a significant combinatorial enhancement of IR, DNA-demethylating agent decitabine, and telomerase inhibitor abacavir on clonogenic MB cell death without enhanced neurotoxicity. Here, we translate those results in an orthotopic mouse model using a human PDX cell line from the Group 3 medulloblastoma. Tumour-bearing mice were treated with 0.1 mg/kg decitabine and/or 50 mg/kg abacavir daily for 14 days and/or with 2 Gy single dose irradiation at day 8. Mice were euthanized as soon as defined humane endpoints occurred (= survival time). Brain tissue was cryo-preserved for immunostaining (CD31, Ki-67). Kaplan-Meier analyses for overall survival showed mice receiving triple treatment had a significantly longer survival time (median 66 ± 9d) compared to mice receiving IR only (50 ± 2d, $p=0.03$; n=10). Analyses of CD31 staining showed a significantly lower amount of tumour blood vessels (14 % reduction, $p=0.05$) and significantly less tumour cell proliferation (Ki-67; 15 % reduction, $p\leq0.05$; n=10) in the triple-treated compared to the untreated group.Using an orthotopic group 3 MB mouse model, we show for the first time that the multimodal therapy with decitabine, abacavir, and IR has the clinical relevant potential to prolong overall survival. In further studies, we will evaluate if the treatment is also effective in another high-risk MB subgroup using a SHH/p53-mutated PDX mouse model.

Poster 58

Differences of centile curves of refraction between Germany and China

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Background:
It has been shown that the prevalence of myopia increases with increasing age during childhood. The form of myopia that starts around and after start in school is called school-myopia.
The prevalence of myopia and of pathologic myopia with more than 6 dioptes is larger in China than in Germany. Genetics as well as differences between the school systems may contribute to the different prevalence.

Purpose:
Centile curves of refraction for a German Cohort of Children were generated and compared to data from China. This allows for comparison of refractive development and to elicit differences in the development after school start in both ethnicities.

Methods:
As part of the LIFE Child study the eyes of 1046 boys and 953 girls, aged 3 to 18 years, were measured with the ZEISS i.Profiler plus (Carl Zeiss Vision GmbH, Germany) without cycloplegia. Reference curves were calculated with the R-package GAMLSS as continuous function of age.

Results:
At the age of 5 there was only little difference for both boys and girls between the centile curves of both study groups. Both ethnicities showed a myopic shift with increasing age. In China the myopic shift is higher for all centiles compared to Germany. The difference of the myopic shift is highest for the lower centiles and lower for the higher centiles and can be seen in both genders. The difference of the median at age 15 between Germany and China is 1.41 D for boys and 2.21 D for girls.

Conclusion:
Around school start myopia progression is much higher in China compared to Germany. The increase of short-sightedness is highest for the most myopic children, whereby Chinese children develop higher degrees of short-sightedness throughout school time.

Poster 59

Reasons for magnesium intake during pregnancy – The Life Child pregnancy cohort

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A diet rich in micronutrients is recommended by nutritional guidelines for pregnant women in industrial countries. Even if magnesium is an essential mineral for which the need increases during pregnancy, those guidelines do not include magnesium supplementation. Still, many pregnant women take oral magnesium. To find socioeconomic predictors for oral magnesium intake in pregnant women, the data from the LIFE Child pregnancy cohort were analysed.

The LIFE Child-study (NCT02550236) is a population-based longitudinal cohort study conducted at the Research Center for Civilization Diseases in Leipzig. Records were taken during 24th and 36th week of pregnancy. Those included questionnaires about socioeconomic characteristics, medication, and dietary supplement intake. To find socioeconomic predictors, statistical analyses were done with SPSS.

Magnesium was taken by 48.3% (375/777) of pregnant women in the 24th week and by 51.6% (389/753) in the 36th week. 78.4% (24th week: 171/218) and 80.6% (36th week: 199/247) of the preparations, for which detailed information was provided (24th week: 218/411, 36th week: 247/427), were recommended or prescribed by a physician. 79.3% (142/179) of women in 36th week of gestation began magnesium supplementation during pregnancy. 20.7% started magnesium intake before the pregnancy. Number of pregnancies, family income, graduation and profession of the mother were not correlated to magnesium intake. A positive correlation for age with low effect size has been shown.

About half of the pregnant women took magnesium. The start of magnesium intake during pregnancy suggests that supplementation is pregnancy-related. Physicians had a great impact on the decision of oral magnesium supplementation. Strong socioeconomic predictors were not found.

Poster 60

Can OCT complement established detection methods for approximal carious lesions?

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Aim:
Intraoral detection of approximal carious lesions with optical coherence tomography (OCT) and established diagnostic methods.

Materials and Methods:
64 approximal surfaces of premolars and molars of four probands were examined by visual-tactile assessment (ICDAS ll), digital radiography, fiber optic transillumination (FOTI, Lercher GmbH&Co.KG) and by an intraoral OCT probe (IOP [1], SD-OCT Telesto). Surfaces with ICDAS ll-code 0 were scored as 0, surfaces with code 1–4 as 1. Similarly, in digital radiographs no visible signs of radiolucency were scored as 0, D1–D4 as 1. For FOTI and OCT, surfaces evaluated as 'sound' (no shadow and no bright signal zone) were scored as 0, otherwise as 1. Statistical analysis was performed using contingency tables, Friedman- and McNemar-test (α=0.05).

Results:
For all methods, individual intraoral circumstances result in a wide range of statistical differences. OCT significantly differed from visual inspection ($p_i \leq 0.03$) in 2 out of 4 probands. Radiography or FOTI were different from OCT in 3 out of 4 probands ($p_i \leq 0.02$). In 1 out of 4 probands visual inspection vs. radiography or FOTI and radiography vs. FOTI were significantly different ($p_i \leq 0.02$). For all probands the agreement between OCT and visual inspection was 36.4–84.6%, between OCT and radiography 21.1–62.5% and between OCT and FOTI 15.8–66.7%. In contrast the agreements between introduced methods were: radiogr.-FOTI 52.4–94.7%, visual inspection-radiogr. 37.5–81% and visual inspection-FOTI 31.3–76.9%.

Conclusion:
The intraoral OCT probe provides additional information on approximal carious lesions and could be a valuable supplement to established diagnostic methods.

References:
[1] Medical Laser Center Lübeck; orangedental GmbH&Co.KG; Dep. of Cariology, Endodontology and Periodontology Leipzig

Poster 61

Impact of simulator-based training on acquisition of transthoracic echocardiography skills in medical students

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Introduction:
Due to the expanding role of ultrasound as a diagnostic tool in modern medicine, medical schools rapidly include ultrasound training into their curriculum. The objective of this study was to compare simulator-based training with classical teaching, using human models, to teach focused transthoracic echocardiography examination.

Methods:
A total of 22 medical students with no former transthoracic echocardiography training undertook a 90-minute e-learning module dealing with focused echocardiography and important echocardiographic pathologies. Subsequently, they had to complete a multiple-choice-questioner, followed by a 120-minute practical training session on the Heartworks, (Cardiff, UK) and the CAE Vimedix, (Québec, Canada) simulator (n=10) or on a live human model (n=12). Finally, both groups had to complete a post-test consisting of 10 video-based multiple-choice-questions and a timed, focused echocardiography examination on another human model. Two blinded expert observers scored each acquired loop, that recorded 2 seconds of each standard view. Statistical analyses were performed with SPPS 24 (SPSS™ 24, IBM, USA) using the Mann-Whitney-Test to compare both groups.

Results:
Analysis of measurable outcome skills showed no significant difference between transthoracic echocardiography training on human models and high-fidelity simulators for undergraduate medical students.

Key Messages:
This study showed that both human-model and simulator-based transthoracic echocardiography training show benefits for training undergraduate medical students. Due to various advantages of simulators a potential integration of these learning methods into the medical curriculum has to be considered.

Poster 62

Evaluating GPR56 antibodies for immunohistology

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GPR56 (ADGRG1), belonging to the family of adhesion GPCRs (ADGRs), has pleiotropic functions in tissue development and regulation. RNA-sequencing data suggest a broad, non-lineage specific expression of GPR56 protein in many human tissues, although it has only been investigated in a few. Partly, this is caused by the lack of GPR56 antibodies evaluated to detect the protein in tissue specimen. To overcome this issue, we screened numerous antibodies for GPR56 specificity in immunohistology. First, several human adherent cell lines were quantified for GPR56 surface expression using the monoclonal GPR56 CG4 antibody (Peng YM et al. J Leuk Biol 2011;90:735), well-established to work in flow cytometry. Next, stable GPR56 knockout (KO) clones of a strongly $GPR56^+$ cell line were generated. The cell line was transfected with two *GPR56* CRISPR/Cas9-GFP-constructs, $GPR56^-/GFP^+$ cells were sorted and grown as monoclones. Established stable clones of each construct were analyzed for the underlying *GPR56* mutation as well as quantified for GPR56 mRNA and protein expression. Afterwards, we examined all GPR56 antibodies thoroughly by comparing wild-type cells with the GPR56KO clones including paraffin embedding and immunostaining, flow cytometry and Western blotting. Eventually, one antibody was found to detect GPR56 specifically in each method.

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Poster 63

The central role of iron and macrophages in chronic wounds: Investigating strategy to improve wound healing

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In CVI patients accumulation of erythrocytes in the tissue and consequently iron overload, have been reported. Iron has been found in wound edge and wound bed of chronic venous ulcers (CVU). These and other findings suggest that iron is an important factor in the establishment and development of ulcers in the skin, although, the molecular mechanisms behind ulcer formation are still unclear. As in the body, macrophages (Ma) play an important role in iron recycling and respond to dysregulated iron homeostasis in the skin, in this project we aim to investigate the role of iron in the pathogenesis of CVU; mimicking *in vitro* erythrocytes-overload macrophages and establishing a skin iron-overload model in mouse. To dissect the response of M1 and M2 Ma to erythrocyte overload we mimicked erythrocyte accumulation in the skin *in vitro* by co-culture of primary macrophages (M1 and M2) generated from human blood monocytes with autologous erythrocytes or Fe(II). Cytokine analysis revealed that M1-like Ma released significant fewer amounts of pro-inflammatory TNF and IL12, suggesting a down-regulation of the inflammatory response in M1-like Ma by erythrocytes and Fe(II). Interestingly, M2-like Ma showed a clear pro-inflammatory response with an increase of TNF and IL-6 and a decrease of IL-10 in presence of erythrocytes and Fe(II). Hence, gene expression data suggests a complex iron-regulation is needed when iron homeostasis is dysregulated. In addition, we establish iron-overload murine model to uncover iron-induced dysregulation of Ma and its consequence for homeostatic and wounded skin. Moreover, we currently establish an iron-chelating approach using nanoparticles to modulate iron effect on Ma *in vitro*.

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Poster 64

Chronotype in association with relationship satisfaction in German parent dyads

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Introduction:
Understanding modifiable factors impacting relationship satisfaction among parents is important to develop interventions to increase relationship satisfaction.

Methods:
Sleeping characteristics and relationship satisfaction were assessed at three time points between 2016 and 2018 in the Ulm SPATZ Health Study. The Actor-Partner Interdependence Model was used and Structural Equation Modelling was applied to test the association between sleeping features and relationship satisfaction scores. The mediating roles of parity, sociodemographic features, and child and parent age were evaluated.

Results:
Our study is based on 162 couples. Median maternal and paternal ages were 32.3 years and 35.0 years, respectively. Within couple median age difference was 1.9 years. Most participants had a high school degree (70%). Sixty nine couples had more than one child. Sleeping characteristics had a moderate agreement between free and working days. In men, higher values for time of getting out of the bed, sleep duration and midpoint of sleep were observed during free days. Sleeping characteristics and relationship satisfaction scores were moderately correlated within couples with Spearman correlation coefficients ranging from 0.10 to 0.52. The partner's sleeping characteristics and within couple differences affected relationship satisfaction scores in women more than in men. Our results point to a significant mediation role of parity and child age in the association of sleeping characteristics with relationship satisfaction.

Conclusions:
Our work shows that sleeping characteristics affect relationship satisfaction with a significant partner and actor effects in women but not in men. Child age and parity play a mediating role in the relation between sleeping and partner relationship.

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Poster 65

Does prolonged time to irradiation influence survival in IDH-wildetype glioblastoma patients with large residual tumor mass?

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Introduction:
IDH-wildtype glioblastoma (GBM) is the most common brain-derived malignancy. Treatment includes tumor resection followed by adjuvant radio(-chemo)therapy (Rx). There is evidence that patient who received subtotal resection might benefit from shorter time to irradiation (TRT, time from surgical resection to the beginning of Rx). We therefore investigated the influence of volumetrically determined residual tumor burden (RV, remaining tumor volume after first neurosurgical tumor resection) and TRT in GBM patients on survival.

Methods:
All patients diagnosed with GBM between 2014 and 2017 at our department, aged over 18 years, with proven IDH-wildtype, post-operative cranial MRI within 72 hours after surgery and admission to adjuvant Rx were included. Pre- and post-operative volumetric analysis of tumors and statistical analysis (survival analysis via Cox regression) were performed.

Results:
89 of 154 GBM patients were included into the study. Regimen of adjuvant therapy (p=0.006) and RV (p=0.003) were significant prognostic factors in univariate analysis. TRT (≤28 days vs. > 28 days), on the other hand, was statistically non-significant. A co-dependency analysis between TRT (≤28 days vs. > 28 days) and RV (<4 ml vs. ≥ 4ml) presented a tendency for patients with greater RV to benefit from shorter TRT but statistical significance was not reached (p=0.157). Moreover, no other RV threshold benefitting patients with shorter TRT could be revealed with statistical significance by further analysis.

Conclusion:
The presented data indicates that it is safe for all GBM patients, including those with large residual tumor mass, to be admitted to radiotherapy more than 28 days after surgery but also that adjuvant therapy should not be delayed.

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Poster 66

Development of a personalized *ex vivo* drug screening test for patients with ovarian cancer

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Background:
The standard therapy of patients with ovarian cancer consists of debulking followed by chemotherapy. Initial response rates are very high, but recurrence occurs in 85% of the cases. Personalized *ex vivo* analyses of various anti-tumor compounds in a standardized tissue slice culture system (Sönnichsen et al) might be a promising approach for individualized therapeutic decisions. In comparison to cell culture, tumor slice cultures maintain the direct tumor microenvironment which plays a role in resistance mechanisms and thus therapy response.

Methodology:
Patient's tumor samples were collected during surgery, cut into standardized slices and cultivated in triplicates for 2, 4, 7 and 14 days. A baseline control was prepared at day 0. The cultured tissue was PFA-fixated and paraffin embedded. Hematoxylin eosin staining was performed for microscopic evaluation of morphologic structures. Subsequently, immunohistochemical staining against CD3 was applied to examine the immune setting of the tumor and its environment.

Results:
Ovarian tumor tissues (n=3) were viable over a period of 14 days. Histological and immunohistochemical staining showed that morphology and parameters like cellular formation, proliferation and heterogeneity were adequately represented in the slice cultures. HE staining demonstrated the characteristic features of the tumor microenvironment. Staining against CD3 revealed T-cells in ovarian tumor tissue slices up to 14 days *ex vivo*.

Conclusion & Outlook:
To investigate apoptosis and proliferation, staining against Ki-67, cleaved-PARP1 and Hif1a is ongoing. Next we are planning *ex vivo* efficacy testing of various agents like Carboplatin, Olaparib and Durvalumab to develop a pre-test for identification of responders and non-responders.

Poster 67

Detection of disseminated tumor cells (DTCs) might improve prognosis of breast cancer patients

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Background:
Despite successful treatment of the primary tumor recurrence occurs in about 30% of breast cancer patients. One reason might be hematogenous spread during early disease stages. Disseminated breast cancer cells preferentially migrate into the bone marrow (BM) where they become dormant. Due to low proliferation in this "steady state" DTCs are persistent against systemic chemotherapy and may cause metastatic relapse at a later stage. DTCs may serve as independent prognostic markers that are associated with impaired survival.

Methodology & Results:
BM aspirates were collected from the anterior iliac crest during surgery. After density gradient centrifugation cell suspensions were transferred onto glass slides and subjected to immunocytochemical staining against pan-cytokeratin. DTCs were visualized in pink using alkaline phosphatase and short counterstaining with hematoxylin which colored the nuclei light blue. DTCs were semi-automatically detected and enumerated using the Aperio Versa microscope-based scanning system with rare events software that selected DTC candidates according to color, shape, intensity and size. Reference slides with a mix of bone marrow cells and a defined number of HCT116 cells were used as a positive control. Between February and November 2019 BM aspirates from 79 breast cancer patients were collected. Per patient about 4 million BM cells were analyzed. DTC analysis revealed a positivity rate of 30%.

Conclusion:
A very promising approach to eradicate DTCs is the use of bisphosphonates (BP). Breast cancer patients that were tested positive for DTCs could benefit from BP intake and hence better prognosis even years after first diagnosis. Based on DTC status, patients with high risk for relapse can be identified and treated accordingly.

Poster 68

Endothelial-mesenchymal transition in esophagogastric cancer progression and metastasis

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Objectives:
Peritoneal dissemination (PD) is one of the most common causes of cancer-related mortality in esophagogastric cancer (EGC). Although Epithelial-Mesenchymal Transition (EMT) is an established molecular process, the role of Endothelial-Mesenchymal Transition (EndoMT) in tumor progression and peritoneal dissemination of EGC is not defined yet. We investigated Endo-MT associated changes in EGC.

Methods:
EGC tissues from primary tumors and peritoneal metastatic sites were double-immunostained for endothelial (CD31, VE-Cadherin) and mesenchymal markers (SFP1, Vimentin). Human umbilical vein endothelial cells (HUVEC) and primary human esophageal and intestinal microvascular endothelial cells (HEMEC, HIMEC) were treated either with tumor-derived chemokines (IL-1β, TGF-β2, TNFa, IL-6) or with EGC-tumor cells conditioned-media and analyzed for EndoMT-associated changes by real-time PCR, western blotting and immunofluorescence.

Results:
Expressions patterns consistent with EndoMT were evident in primary tumors and in sites of peritoneal dissemination *in vivo*. Tumor conditioned-media, IL-1b and TGF-b 2 induced spindle-like cell morphology, increased the expression of mesenchymal markers (FSP-1, Vimentin, Snail) and decreased the expression of endothelial markers (CD31, VE-cadherin) *in vitro*. EndoMT-cells demonstrated increased migration and proliferation along with increased VEGF-expression.

Conclusions:
We demonstrated alterations in expression patterns and endothelial cellular characteristics consistent with EndoMT, indicating its role in the setting of metastasis of esophagogastric cancer.

Poster 69

The Wnt-Antagonist, Dickkopf-1 (DKK1), as serological Biomarker in the Barrett-Metaplasia-Dysplasia-Carcinoma Sequence

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Background:
Esophageal adenocarcinoma (EAC), even after curative surgical resection, is associated with poor prognosis, due to high rates of local recurrence and early lymph node or systemic micrometastases. Dickkopf-1 (DKK1) gene encodes a secreted protein, which inhibits the canonical Wnt signaling pathway and its involvement in EAC-Pathogenesis has been already reported from our group. The usefulness of DKK1 as a serological marker in EAC has not been sufficiently investigated.

Materials & Methods:
DKK1 tissue expression and levels of serum concertation were evaluated in healthy controls and patients with Barrett-Metaplasia,-Dysplasia or EAC by immunohistochemistry and ELISA respectively. In EAC patients, the serological concertation of DKK1 was determined before neoadjuvant therapy, before and after the esophagectomy.

Results:
DKK1 tissue expression and serum concertation were found elevated along the neoplastic progression of the Barrett-metaplasia-dysplasia-carcinoma sequence. Immunohistochemistry demonstrated strong DKK1 staining in the neoplastic cells of EAC tissue comparing with a weak staining of the basal layer of the corresponding healthy esophageal mucosa. DKK1 serum levels correlated with tumor stadium and were markedly decreased following tumor resection.

Conclusion:
DKK1 expression increases along the neoplastic progression of Barrett-metaplasia and correlates with the tumor stadium in EAC-Patients. High DKK1 serum levels are significantly decreased following surgical removal of the tumor. Thus, DKK1 could represent a good biomarker for EAC-Patients.

Poster 70

TGF-beta1 and TGF-beta2 mediated Epithelial-mesenchymal transition in esophageal adenocarcinoma cells

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The esophageal adenocarcinoma (EAC) is characterized by an early lymphogenic dissemination and a poor prognosis. The tumor biology and the impact of autocrine, paracrine and endocrine mediators are involved in these mechanisms. For dissemination, the tumor cells need to escape the solid tumor and invade into new target structures. This mechanism is described as epitheliale-mesenchymal transition (EMT), which could be initiated by TGF-beta. Two proliferation and motility of the esophageal adenocarcinoma cell lines (OE33, OE19) were analyzed after TGF-beta1 and TGF-beta2 treatment. EMT marker gene expressions (e.g. vimentin) were assessed by qRT-PCR. TGF-beta2 led to a deceased proliferation rate compared to untreated and TGF-beta1 treated cells in OE33 cells. In OE19 cells both, TGF-beta1 and TGF-beta2 treatment resulted in an increased proliferation compared to untreated cells. In OE33 cells the motility was affected by TGF-beta1 only, while in OE19 cells the motility was increased by TGF-beta1 and TGF-beta2 compared to untreated cells. The vimentin mRNA-expression in OE33 cells was increased by TGF-beta1 and TGF-beta2 (14.7-fold and 25.9-fold). However TGF-beta1 and TGF-beta2 only led to a moderate increase in the vimentin mRNA-expression (4.0-fold and 1.8-fold) in OE19 cells. TGF-beta1 and TGF-beta2 induce EMT and cellular motility in a cell line specific pattern. The responsible intracellular signaling cascades addressed by TGF-beta1 and TGF-beta2 and their contribution for dissemination in EAC patients need to be investigated with full details.

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Poster 71

Comparison of HER2, estrogen and progesterone receptor expression profiles of primary tumor and synchronous axillary lymph node metastases in 149 breast cancer patients - indicating tumoral heterogeneity

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Background:
Comparisons of receptor expression profiles (ER, PR and HER2) between primary tumor and synchronous lymph node metastasis are rare. Primary aim of this trial is to present data on the epidemiologic aspect of tumor heterogeneity with synchronous lymph node metastases (LNM) in breast cancer patients.

Methods:
We retrospectively analyzed 149 consecutive patients with breast cancer and synchronous LNM who underwent oncologic surgery between 2008 and 2018 at the university hospital Leipzig, Germany.
Formalin-fixed and paraffin-embedded (FFPE-material) were routinely examined immunohistochemically according to the ASCO/CAP guidelines using Ventana-platform. The results for ER, PR and HER2 were analyzed case-by-case comparing results from the CNB of the primary tumor within the breast and axillary LNM. The tumors were grouped into the different intrinsic subtypes as luminal A and B, HER2-enriched and triple-negative by the different immunohistochemical staining results.

Results:
Overall there were 61 (40,1%) patients who had at least one receptor change, with 16 patients with two receptor changes. The discordance rates between primary tumors and axillary LNM were 13,4% for HER2, 10,1% for ER and 28,2% for PR. In total there was a receptor loss in 69 cases and a receptor gain in in 8 cases.

Conclusions:
Our results imply the high frequency of subtype differences between primary tumor and LNM. This could be explained by intra-tumor heterogeneity. Subtype changes should be taken into account for an optimal and individual treatment. Larger studies are necessary to validate these data and gain further information.

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Poster 72

Nrf2 as molecular target in esophageal adenocarcinoma cells *in vitro*

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Despite improved treatment regimens the overall survival of the esophageal adenocarcinoma (EAC) is still poor. Additionally the incidence of the EAC is increasing (approx. 600%) in the western population during the last 4 decades. Nrf2, which is responsible for the cellular stress defense by inducing proteins and enzymes to maintain cellular integrity, will be evaluated as a potential therapeutic target in EAC.

Four EAC cells lines (OE19, OE33, SK-GT-4, FLO-1) were used, to investigate Nrf2-ctivation by qRT-PCR and Westernblot analysis and the responsiveness of EAC cells to 5-fluorouracil (5-FU) and cisplatin in a Nrf2 dependent manner.

NRF2 is highly expressed in the investigated EAC cell lines and is also increased in EAC patient specimens compared to metaplasia specimens. The EAC cell line OE33 is highly receptive for 5-FU with an IC_{50} of 0.58µM, no proliferation inhibitory effect was seen in OE19 cells. Cisplatin treatment (10µM) resulted in an anctivation of Nrf2 by increased phosphorylation in OE19 and FLO-1 cells. Furthermore Nrf2-siRNA knockdown resulted in a decreased motility of OE19 cells and decreases the expression of central Nrf2 downstream targets (NQO1, GCLC, IDH1 and ME1).

Further target validation of Nrf2 revealed a downregulation of enzymes responsible for NADPH and thioredoxin production and regeneration, quinone detoxification and GSH utilization. Taken together, targeting Nrf2 could be a vulnerable molecule to increase chemosensitivity in the esophageal adenocarcinoma.

Poster 73

Characterization and functional analysis of T-lymphocytes in patient-derived slice cultures (PDSC) of esophago-gastric-junction (EGJC) and gastric cancer (GC) as an ex vivo model to study individual response of immunotherapy.

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Objectives:

Novel treatment strategies in cancer are targeting successfully the immune system, however the response rates in EGJC and GC are limited. Predictive markers and *ex vivo* models are urgently needed for better patient stratification. The model of patient-derived slice cultures of EGJC/GC maintains the different cellular components of the natural cancer environment and is suitable to test tissue susceptibilities. Here, we analyse the preservation of T-cells in patient-derived tissue *ex vivo*.

Methods:

PDSC were freshly prepared from surgical EGJC/GC specimens and cultured over four days *ex vivo*. In different conditions the tissue was treated with CD3/CD28 T-cell stimulator and Nivolumab in combination and in single treatment. Tissue morphology, proliferation and apoptosis of tumor cells were investigated by H&E and immunofluorescence staining (panCK, Ki67, cPARP). T-cells were further characterized by immunohistochemistry (CD3, CD4, CD8, FoxP3, PD-L1).

Results:

T-cells remained preserved over four days of cultivation in PDSC *ex vivo* and are distributed in several layers of the slice. After treatment with a combination of Nivolumab and CD3/CD28 T-cell stimulator the apoptosis rate of tumor cells increased and the proliferation rate of tumor cells decreased compared to the negative control.

Conclusion:

T-lymphocytes can be retained over four days *ex vivo* in PDSC of EGJC/GC. First experiments responding to T-cell stimulating treatment indicate the functionality of the T-cell population in PDSC of EGJC/GC *ex vivo* and potential tumor response. Further analysis and quantification is needed.

Poster 74

Head and neck cancer therapy with CAR-NK cells

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Head and neck cancer (HNC) is the sixth most common cancer in the world and represents a group of malignancies of the upper aero-digestive tract with high incidence among heavy smokers and drinkers. More than 90% of the cases are head and neck squamous cell carcinomas (HNSCC) diagnosed in locally advanced stages that despite therapy, will lead to locoregional recurrence or distant metastases. Treatment frequently requires multimodality therapy which has high toxic effects and does not improve prognosis, especially for advanced HNSCC. There is an urgent need for the development of novel therapeutic modalities for HNC. While HNSCC employs different mechanism of evading immune cell attack, using chimeric antigen receptors (CARs) to redirect natural killer (NK) cells towards specific tumor surface antigens will allow improved cytotoxicity. CD44v6, an oncogenic splice variant of CD44, was chosen as surface target as it was described to be overexpressed on primary and metastatic HNSCC. Preliminary *in vitro* data showed improved cytotoxicity, higher degranulation and granzyme A levels in CD44v6-CAR bearing NK cells compared to a mock control. Fluorescence microscopy illustrated targeted killing of HNSCC by CD44v6-CAR-NK cells. These results will be further tested *in vivo* using HNSCC models established in immunodeficient NSG mice by subcutaneous or orthotopic xenografts of tumor cell lines or primary tumors. We aim to determine CAR-NK therapy efficacy in reducing primary tumor growth, infiltrating tumors and limiting metastasis, as well as to evaluate CAR-NK cell homing in the host.

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Poster 75

Mechanisms of Keratinocyte-Melanoma Cell Interaction

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The transformation from a normal melanocyte to a melanoma cell is a stepwise process and the heterogeneous mechanisms of tumor development and progression remain incompletely understood. Based on several studies, we hypothesize that keratinocytes affect early melanoma development through direct interactions or via indirect mechanisms involving cell-cell contacts, cytoskeletal proteins and by secretion of mediators. The aim of this project is to characterize underlying mechanisms by which mutations in keratinocyte cytoskeletal proteins affect proliferation, cell-cell-contacts, adhesion and migration of melanoma cells.
Epidermal keratinocytes from regions bordering the tumor were collected from human malignant melanoma samples using laser capture microdissection, followed by whole-exome sequencing to identify novel keratinocyte genes triggering melanoma cell proliferation. Preliminary data of 10 patients suggest a significant enrichment of somatic mutations in different keratinocyte genes belonging to pathways of biological processes like cell adhesion and epidermis development, e.g. Wnt-, cadherin- and integrin-signaling. We hypothesize that several mutated genes of one biological pathway or of different pathways in melanoma patients trigger the hyper-proliferative and metastatic character of melanoma cells. Preliminary data suggest a reduced relative count of SK-Mel5 melanoma cells co-cultured with FAK-inhibitor treated KCs compared to wildtype.
In future experiments, we determine the influence of an inhibited or activated form of every identified pathway in keratinocytes on melanoma cell/ melanocyte proliferation, followed by generating the identified mutations in keratinocytes to identify the mechanism responsible for the initial step for melanoma cell progression.

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Poster 76

Replacement of miR-24-3p exerts tumor inhibitory effects in pancreatic cancer cell lines by downregulating c-myc and survivin, and by inducing apoptosis

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Pancreatic cancer (pancreatic ductal adenocarcinoma, PDAC) remains as a cancer entity with poor prognosis for the patients, with an overall 5-year survival rate of only around 5%. Attempts to improve the treatment of pancreatic cancer have still been largely unsuccessful. Thus, the identification of novel targets or therapy options is urgently needed to increase survival rates of PDAC patients in closer future. MicroRNAs (mRNAs) are small non-coding RNAs which can regulate physiological and pathological processes in cancer cells. Their pathological downregulation in cancer provides the basis for miRNA replacement therapy.
In the present study, we directly compare various tumor-inhibitory effects of hsa-miR-24-3p replacement in different pancreatic cancer cell lines *in vitro* and *in vivo*. Transfection of miR-24-3p leads to reduced cell proliferation measured by WST-1, reduction of colony formation, altered cell morphology and decreased viability as determined by cell density, propidium iodide and Hoechst staining using a Celigo Imaging Cytometer. Most prominent was the increased activation of apoptosis seen in flow cytometry via annexin-V, by luminescence-based caspase-3/7 activation assay and survivin/c-myc protein level reduction in Western blots *in vitro*. Systemic treatment of PDAC xenograft-bearing mice with polymeric nanoparticles for siRNA delivery exhibited tumor growth inhibition, accompanied by downregulation of c-myc and survivin on the protein level. The human miRNA-24-3p has been described as pro- and anti-tumorigenic, depending on the cancer entity. We show that replacement of miRNA-24-3p in pancreatic cancer cells leads to several anti-tumorigenic effects *in vitro* and *in vivo*. In conclusion, miRNA-24-3p replacement is a promising strategy for PDAC-treatment.

Poster 77

A Melanoma Mutation Panel for Individualized Treatment of Melanoma Cultures

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Melanoma is the most aggressive form of skin cancer. Its standard of care is treatment by surgery, chemotherapy, radiation and more recently immunotherapy and targeted therapy. However, response rates to single-agent immunotherapies are low and severe side effects often impair the treatment success of combined immunotherapies. For BRAF (~50 %) and NRAS (~30 %) mutated tumors, targeted therapies directed against the RAS-RAF-MEK-ERK pathway may be used. Relevant treatment responses are currently only observed for BRAF-mutant patients that reach response rates of up to 80%. However, the vast majority of patients show drug resistance months after beginning the treatment. Interestingly, most of these patients harbor activating mutations in other druggable pathways. Therefore, an individualized combinatorial treatment approach might help to overcome many of the current treatment failures. In this project we aim to identify treatment combinations based on individual mutational patterns. A pre-clinical *in vitro* model was set up using melanoma cultures and tumor microfragments. To select individual treatment combinations, a panel of 83 target genes was sequenced on a NextSeq high-throughput sequencing instrument (Illumina). Depending on the mutational profile, the biological effects of different drug combinations were tested to examine the optimal treatment strategy. We analyzed cell proliferation using the IncuCyte® system and cell viability based on an ATP assay. In summary, our results show that the standard therapy of vemurafenib and cobimetinib in BRAF-mutant cells appears to be less effective than a combination of vemurafenib and apitolisib (PI3K inhibitor). The results of this project may lead in future to a more individualized treatment for metastatic melanoma patients.

Poster 78

Histopathological and molecular Reclassification of Cervical Adenocarcinoma using pattern-based infiltration and Endocervical Adenocarcinoma Criteria and Classification (IECC)

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Background:
The updated WHO Classification of Tumours of Female Reproductive Organs published in 2014 is used to classify endocervical adenocarcinoma (AC) into different histologic subtypes. Recently, two additional classification systems have been presented. A pattern-based system introduced in 2015 categorizes AC based on histomorphologic appearance, clinical features and depth of invasion. In 2018 the International Endocervical Adenocarcinoma Criteria and Classification (IECC) was published as an alternative to the WHO classification. The IECC classifies carcinoma based on etiology and HPV-association and includes the newly discovered tumor entity of the invasive stratified mucin-producing carcinoma (ISMC).

Methods:
This study aims to evaluate the new classification system in comparison to the WHO system. To achieve this, all cases of AC that were treated with upfront surgery between 1997 and 2019 at UoL were reevaluated and reclassified based on WHO 2014, pattern-based system 2015 and IECC 2018. In unclear cases p16 immunhistochemistry and PCR representing HPV 18 were used for reclassification.

Results:
53 cases were reevaluated. 53.8% (n=28) were classified as pattern C tumors, 32.7% (n=17) as pattern B and 13.5% (n=7) as pattern A. 39.6% (n=21) were identified as endocervical AC, not otherwise specified (NOS), 22.6% (n=12) as mucinous AC, 17.0% (n=9) as endometriod AC and 15.1% (n=8) as carcinoma with mixed histology including one case of IMSC. One mesonephric carcinoma and one serous AC were identified.

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Conclusion:
Most cases were reclassified as NOS type which matches data from literature. ISMC may appear more often in tumors with mixed histology. The majority of cases were identified as pattern C tumors which generally correspond with a poor prognosis.

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Poster 79

Preoperative Evaluation of the Parametrium in Uterine Cervical Carcinoma

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Research question:
Local tumor spread to the parametrium (≥ stage IIB) in uterine cervical cancer is associated with an unfavorable prognosis and usually indicates treatment by primary chemoradiotherapy. Recently, the international federation of gynecologists and obstetricians (FIGO) has updated its staging recommendations and specifically calls for the usage of magnetic resonance imaging (MRI). However, the performance of MRI in detecting parametrial involvement is still unclear. The aim of this retrospective analysis was to compare the diagnostic value of MRI and clinical examination (CE) with respect to parametrial invasion (PMI).

Methods:
By means of database research we identified 452 treatment-naive patients who underwent primary operative treatment for cervical cancer between 1999 and 2018 and for whom radiological reports were accessible. Patients received MRI as well as CE under general anesthesia. For each examination method we calculated sensitivity and specificity, in addition to positive and negative predictive values (PPV; NPV,) for the detection of parametrial invasion using postoperative histology reports as a reference.

Results:
165 patients had PMI. In 157 cases, PMI was suspected in CE. Diagnosis was correct in 127 (81%) of them, in 38 patients PMI was missed. These data yield a sensitivity of 76.9% and a specificity of 87.2%. The PPV was 81% and NPV was 84%.
In MRI, PMI was suspected in 157 patients. This finding was correct in 113 cases (68%). In 52 cases (32%), MRI did not detect PMI. Therefore, sensitivity was 68.4% and specificity was 81.2%. PPV was 72% and NPV was 79%. These differences were not statistically significant.

Conclusion:
In this study, MRI was not superior to CE in assessing the parametrium for cervical cancer invasion.

Poster 80

Analysis of central versus local deviating HER2 test results in gastric cancer in the multicenter VARIANZ study

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Purpose:
VARIANZ is a non-interventional study funded by BMBF (01ZX1610E) recruiting patients (pts) receiving treatment for stage IV gastric cancer. The primary objective of VARIANZ is to investigate resistance factors of HER2 target therapy. Locally assessed HER2 status was re-assessed centrally using immunohistochemistry (IHC) and in situ hybridization. In 22.2% of all pts HER2 status was not confirmed. Only pts with confirmed HER2+ status seem to benefit from trastuzumab. Here, we aimed to investigate causes of HER2 discrepancies between local and central pathologies.

Methods:
Information about HER2 test procedures was collected from participating pathologies. Tumor samples with central and local HER2 tests (n=375) were grouped: central HER2+ concordant to local HER2 status (HER2+/HER2+) and central HER2- deviating from local HER2 status (HER2-/HER2+).

Results:
Type of antibody used locally and participation in round robin tests did not influence HER2 deviation rate. In central testing, cytoplasmatic HER2 staining of tumor cells was detected in 60.3% of HER2-/HER2+ probes compared to 40.6% in HER2+/HER2+ ($p<0.05$). Concordant to this result the percentage of HER2 membrane stained tumor cells was low in HER2-/

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HER2+ (13.97±21.87%) vs. HER2+/HER2+ (61.19±31.31%; p< 0.001). 32% of tumor samples originated from surgical resection specimens in HER2-/HER2+ vs. 9% in HER2+/HER2+ (p< 0.001). The majority of pts undergoing surgery received neoadjuvant chemotherapy.

Conclusions:
Identification of pts who benefit from HER2 targeting therapy remains challenging. The extent of cytoplasmatic HER2 staining may influence test results. Beyond that, the use of surgical resection specimens for assessment of HER2 seems to lead to less robust results compared to the use of biopsy material.

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Preservation of the mesureter to reduce urinary complications: analysis of data from the observational Leipzig School MMR study

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Objective:
The mesureter is a thin tissue structure ensheathing the ureter and connecting it to the posterior abdominal wall. The effect of mesureteral preservation on urinary complications is currently unclear. We hypothesized that mesureteral preservation would lead to a reduction in such complications.

Methods:
We retrospectively analyzed 100 consecutive TMMR procedures which were performed for cancer of the uterine cervix and in which the mesureter was preserved (intervention group, 01/2014 – 06/2017). We compared this group to the previous 100 consecutive TMMRs which were performed before the introduction of mesureteral preservation (control group, 09/2010-01/2014). We analyzed and compared urological and specifically ureteral complication rates in both groups. All patients were treated within the prospective observational monocentric mesometrial resection (MMR) trial.

Results:
Mesureteral preservation was feasible and was associated with a significant decrease in ureteral complications (11% without mesureteral preservation vs. 3% with mesureteral preservation, p=0.049). Furthermore, we found a significant decrease in the number of postoperative percutaneous nephrostomies and re-operations (7% vs. none, p=0.014). There was also a trend towards a decrease in other urinary complications such as postoperative bladder atony and uretero-vaginal fistulas.

Conclusion:
The mesureter constitutes a convenient dissection plane enabling the preservation of lateral ureteral blood supply during TMMR. In our study, maintenance of mesureteral integrity was associated with a significant reduction in ureteral complications. Mesureteral preservation might also be useful in other types of pelvic surgeries with a high risk of ureteral damage.

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Anti tumor effects of histone deacetylase (HDAC) inhibitors in gastric cancer

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Objective:
Histone acetylation regulated via histone deacetylases (HDACs) plays a pivotal role in dysregulated oncogene expression in cancer. Thus, HDAC inhibitors (HDACi) have emerged as potential anticancer agents. In humans, 18 different HDAC subtypes exerting partially non-redundant functions have been described. Dysbalanced expression of HDACs has been implicated gastric cancer prognosis. Moreover, broad-spectrum HDACi have shown promising activity in gastric cancer cells. However, there is still a lack of studies in this tumor entity delineating the role of distinct HDAC subtypes and their anti-proliferative mechanisms.

Methods:
In a panel of gastric cancer cell lines expressing different levels of HDAC isoforms, we investigated the effect of HDAC inhibition on cellular proliferation and apoptosis. Furthermore, we studied the expression of receptor tyrosine kinases (RTKs) upon treatment with HDACi or siRNA-mediated knockdown of HDAC subtypes.

Results:
Inhibiting distinct isoforms with subtype specific HDAC inhibitors showed anti-proliferative effects. Of note, inhibition of class I HDAC subtypes was necessary and sufficient for antitumor effects in gastric cancer cells. Furthermore, HDAC inhibition caused a marked upregulation of growth factor receptors (e. g. HER1). This response in turn defined a rationale for combination therapies. In fact, dual inhibition of HDAC subtypes and RTKs led to additive effects.

Conclusion:
HDAC inhibition in gastric cancer shows effects on cellular growth. Due to the ability of epigenetic drugs to modify various pathways and oncogene expression, we further want to elucidate the potential of combined or sequential inhibition of HDAC and RTKs.

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The hyperspectral imaging patient data management and analysis framework HSIdb

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Hyperspectral imaging (HSI) is an emerging imaging system for medical applications, especially in disease diagnosis and image-guided surgery. HSI technology allows tissue observation beyond the limitations of the human eye. Moreover, many researchers are using HSI as a new diagnostic tool for tissue classification and tissue perfusion assessment. A hyperspectral imaging database (HSIdb) has been developed to easily manage a large number of HSI data of patients acquired at the University Hospital of Leipzig in the context of clinical studies. The HSIdb is currently dedicated to scientists and physicians of the University of Leipzig involved in research projects. It provides viable approaches to properly organize, manage, and store, both imaging and associated non-imaging data types. It is first and foremost a data aggregation and management system with a focus on easy interactions with the researcher. The algorithm has been planned to assure data integrity, in future allow flexibility in data recoveries, produce user-friendly result format, and permit data access for users with a wide range of queries. The tool is written in Python so that it can leverage the rich natural language processing capabilities of the popular dynamic programming language. The interface allows the user to requests different queries to the search engine and gets a visual response with the results.
In future works, the HSIdb should be integrated into a web-based application to achieve a world-wide available open HSI database. Hence, researchers can use these data for e.g. artificial intelligence tissue-classification methods.

Keywords:
Clinical data, database, relational database, schema design, Hyperspectral imaging data

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Platform for data analysis and model supply for image reconstruction within Electrical Impedance Tomography

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Real-time monitoring of patients‘ vital state on emergency sites is crucial in order to assist physicians in taking decisions. Thorax electrical impedance tomography (EIT) offers an improvement to the lung auscultation that lacks precision, particularly in noisy environments. Recent research efforts empower the development of portable EIT devices, suitable for emergency cases. Onsite disturbances enforces the need for enhanced reconstruction results, which can be achieved by using patient specific models.The creation and usage of customized models for EIT reconstruction on portable devices require additional infrastructure for connectivity, computation and storage. We propose a dedicated platform for storing data, generating patient models and delivering them to EIT terminals. The current focus lies in the description of the system structure and communication processes needed to realize the connection between the modules of the mobile EIT system. The platform relies on a service based architecture and exposes standard, machine readable interfaces to clients, simplifying the communication between heterogeneous systems and allowing for a modular application. The communication workflow describes the necessary steps for acquiring parameters, selecting and providing models for image reconstruction in the scope of EIT. A first prototype of the base system shows the advantages and potential of such systems in the medical domains. In future work, additional components need to be developed to automate the model creation process for usage in EIT. Further, the resulting system shows potential for usage in different medical areas, where a universal access to a medical database is required and extended functionality through additional modules or external tools is needed.

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LIFE Metadata Repository – Mapping-based Integration of Study Data at the LIFE Research Centre

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Epidemiological studies are conducted at the LIFE Research Centre of the University of Leipzig investigating Leipzig inhabitants and patients from hospitals with dedicated diseases. Data about each person is captured during a examination process. Various input forms are used in selected information systems, each adapted to the collection situation and the individual abilities of the patient / test person. Hence, an input form are available in various forms and in several input systems. Note, examination program can be adapted over years, i.e., new questions and input fields can be added to an input form, while for others the question text and the assigned selectable answers (answer categories, code list) can be changed or completely removed. This typically results in multiple variations (implemented input forms) referring to the same conceptual input form and, thus, need to be summarized and harmonized before the recorded data can be analyzed. We address this data integration problem using a mapping-based approach. All data elements are managed by a metadata repository. They are mapped to an overwhelming virtual input form describing the data of the central research database. Transformations can be involved, e.g. conversion of data and data types on the way to the research database. An innovative algorithm automatically generates mappings, which are then available for review before they are productively used. This algorithm uses available metadata, e.g. question texts and parameter names, data types and value ranges as well as code lists to map input forms to each other with the goal to reuse knowledge from existing mappings. Both, metadata repository and mapping generation algorithm have been used since 2012. There are > 2000 mappings for > 650 input forms available.

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Classification of Barrett's carcinoma specimens by hyperspectral imaging (HSI)

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Purpose:
Hyperspectral imaging (HSI) technology combines imaging with spectroscopy and can be used for the classification of malignant and non-malignant cells. Thereby HSI combined with artificial intelligent algorithms can be used to predict tumor cells in in Barrett's carcinoma specimens.
Methods: HSI imaging records light between the visual and near-infrared light (500-1000nm). This technique was used to discriminate between squamous epithelium and esophageal adenocarcinoma and 45 specimens from Barrett's carcinoma patients were recorded. In 22 of the 45 investigated specimens contained also squamous epithelium. The specimens were stained by haematoxylin and eosin (HE). A non-parametric supervised classification learning algorithm (K-nearest neighbors (k-NN)) was used for discrimination.

Results:
Squamous epithelium and Barrett's adenocarcinoma cells displayed differences in the absorbance between the wave lengths of 500 to 700 nm. For both, the squamous epithelium and the Barrett's adenocarcinoma cells, the intra group variances of the investigated specimens were quite low. 333,275 and 74,000 spectra could be measured from Barrett's adenocarcinoma and from squamous epithelium, respectively. Specificity, sensitivity and precision with a k-NN (k=5) classifier were 0.74, 0.92 and 0.94 for the presence of Barrett's adenocarcinoma cells.

Conclusions:
HE-stained squamous epithelium and Barrett's adenocarcinoma cells showed specific spectral alterations, when measured by HSI. These characteristics could be used in the future to develop a computer-assisted algorithm to discriminate semi-automated for tumor cells Barrett's carcinoma specimens, which will help to foster decision-making support in histopathological diagnosis.

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Feasibility Studies with HL7 FHIR® and Clinical Quality Language

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In medical research, feasibility studies are an important tool to discover cohorts of interest. HL7 FHIR® is an emerging international interoperability standard in the medical domain. The Clinical Quality Language (CQL) is a high-level, domain-specific query language targeted at clinical quality measures. In the German Biobank Alliance, we use CQL to realize feasibility studies over biomaterial and data from more than 18 biobanks in Germany for biomaterial and data via our tool called "SampleLocator". We developed an FHIR server with internal fast CQL evaluation engine called Blaze, the first FHIR server able to execute CQL. Blaze is used in production in the German Biobank Alliance and is available open-source as part of the Samply suite cf. https://github.com/samply/blaze. First discussion with the German National Medical Informatics Initiative (MII), who has already adopted FHIR, has shown that CQL is suitable, not only for feasibility studies but also to specify data exports, in many use cases. Furthermore, major commercial FHIR server vendors have shown interest in implementing CQL in their products. In the future, CQL will be one cornerstone to leverage large sets of FHIR data.

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Towards a Comparison of National eHealth Portals

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National eHealth portals (NeHP) give patients access to medical records, exam results, and other services for citizens, like appointment scheduling, notification systems, and e-mail access to their doctors. Different countries use different approaches to design NeHPs. This causes the following problems: It is very difficult to compare the different approaches. Terminology, concept and structure of a NeHP of one country are not identical to those of other countries. If someone wants to build a NeHP for her/his country, she/he does not know which application systems are necessary to support all desired functionalities. NeHPs focus on providing access to features like scheduling citizens‘ appointments with physicians or managing a personal medication list or etc. NeHPs require having a patient-centered model that should be able to cover the activities related to health behavior of citizens. To describe the activities carried out by citizens to manage their health status we use the term ‘’citizen health function’’. As a basis for the comparison and analysis of different NeHP, 3LGM² meta model is chosen. With the help of 3LGM², health information systems are described on three layers. The domain layer consists of the information processing functions to be carried out, the other two layers describe technical components. In this work, we aim at describing a reference model for the domain layer of national health systems containing citizen health functions. It provides the basis of a comparison for different NeHPs. In the future, 3LGM² models which describe different NeHPs from different countries and which are based on that reference model, will be used to assess several structural quality characteristics.

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Improved Patient Safety with AMPEL – A Proof of Concept for Severe Hypokalemia

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Background:
Laboratory diagnostics are essential for diagnostics, therapy initiation and monitoring of patients. Physicians are aware of missed laboratory results, consequently adverse events for patients. At the University Hospital of Leipzig, a project of digital laboratory medicine (AMPEL) was introduced. We aim to establish a clinical decision support system (CDSS) based on scientific literature adapted to demands of clinicians. Severe hypokalemia is used as proof of concept.

Patients & Methods:
Both, potassium measurements in whole blood, serum and plasma and time lag between follow-up were investigated in 2018. Results were in accordance with literature reviews evaluated. Laboratory and clinical data were summarized. In 2019, the CDSS was introduced and prospectively evaluated in a randomized approach.

Results:
In 2018 414,988 potassium measurements (54,866 patients) were investigated. Median interval for follow-up was 5.6 h. Severe hypokalemia (< 2.5 mmol/L) was identified in 441 measurements and follow-up was faster (4.8 h). However, 159 follow-up measurements exceeded 6 h. Cut-offs for severe hypokalemia < 2.5 mmol/L and 6 h were viable. AMPEL computed 159 alarms for 131 patients. After AMPEL was introduced 2019, follow-up measurement was significantly faster after alerting.

Conclusions:
Severe hypokalemia is a critical medical diagnosis. Serious complications like ventricular fibrillation demand rapid therapy and follow-up measurement. AMPEL-CDSS is able to detect patients with absent medical consequences in real-time and support the physician.

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Development of a Laboratory Based Clinical Decision Support System (AMPEL) for the Management of Acute Kidney Injury

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Background:
Acute kidney injury (AKI) is defined as an increase in serum creatinine by ≥26.5 µmol/l within 48 hours or an ≥1.5 fold increase in serum creatinine within 7 days or an urine volume ≤0.5 ml/kg/h for 6 hours (KDIGO-criteria). AKI is associated with increased morbidity and mortality. It leads to chronic kidney disease (CKD) in up to 50 % of the cases.

Objective:
Aim of our study is to develop and evaluate a laboratory based clinical decision support system (CDSS) for AKI aiming for earlier detection, better management and better outcomes.

Methods:
We designed a framework for the automatic detection and staging of AKI based on serum creatinine measurements (according to the KDIGO criteria). First, we performed a retrospective analysis of all cases of 2018 at the University Hospital Leipzig (UKL) with at least one serum creatinine measurement (n = 89022).

Results:
In 6454 cases AKI would have been detected with help of the CDSS. 773 cases (12.0 %) were excluded from further analysis as dialysis was performed already before the detection of AKI. Regarding the remaining 5681 cases, AKI was staged as follows: AKIN 1 (n=4024, 70.8%), AKIN 2 (n=910, 16.0%), AKIN 3 (n=747, 13.2%). The diagnosis AKI (N17) was encoded in 25.5% of the cases (16.9%/40.0%/54.6% for AKIN 1/AKIN 2/AKIN 3, respectively). Dialysis was performed in 3.9% of the cases (1.0%/3.5%/20.0%). 8.9 % (504 patients) died during hospital stay (6.0%/14.3%/17.7%). Regarding the surviving patients, median GFR at discharge was 48 ml/min/1.73m² (49/57/16 ml/min/1.73m²).

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Conclusion:
AKI is common. The adverse outcomes, especially for AKIN 3 patients, as well as the low proportion with encoded AKI diagnosis indicate a high potential for our planned CDSS.

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Analysis and development of clinical workflow for minimally invasive magnetic resonance (MR) - guided interventions

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The importance of magnetic resonance (MR) guidance for minimally invasive interventions has increased in recent years due to well-known advantages in contrast to X-ray based imaging modalities. High soft tissue contrast, arbitrary slice orientation, absence of nephrotoxic contrast agents and ionizing radiation have to be mentioned. Several studies were conducted regarding visualization and tracking of MR conditional instruments, control of MR scanner, and communication systems [1]. At ICCAS current clinical procedures e.g. endomyocardial biopsy (EMB) were analyzed in order to develop a workflow model for the MR environment. To gather the required data literature review, expert interviews, and observations at Department of Cardiology of University of Leipzig Medical Center were conducted. Using the standardized Business and Process Modeling Notation (BPMN) high- and low-level models of the intervention's procedure were developed. Actions and their durations, anatomical structures, required medical staff, used instruments and materials were recorded. To guarantee an user-friendly, safe as well as time-efficient intervention under MR guidance, analyses of real-time imaging sequences, the development of emergency strategies, and the installation of an interaction system inside the MRI environment have been started successfully. To validate the developed workflow model comparative *in vitro* investigations between X-ray and MR guidance with clinical use-case EMB will be conducted using a silicone 3D printed arterial vessel model that was developed for this project.

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Characterization of Osx1:Cre Pten conditional knockout (Pten cKO) mice

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Background:

PTEN Hamartoma Tumor Syndrome (PHTS) comprises disorders caused by *PTEN* (*Phosphatase and Tensin homolog*) germline mutations. *Pten* is a tumor suppressor gene, which negatively regulates the growth promoting PIP-3(phosphoinositide 3-kinase)/AKT(proteinkinase B)/ mTORC1(mechanistic Target of Rapamycin complex 1) cascade. PHTS patients frequently develop lipomas, the mechanisms are unclear. We are using animal models with *Pten* insufficiency to identify factors that are potentially causal for lipoma development and evolvement of fatty tissue distribution disorders. We hypothesize that *Osx1(Osterix)*-expressing cells from *Pten cKO* mice are functionally different from wildtype (WT) *Osx1*-expressing cells and have an increased potential for adipocyte differentiation.

Methods:

We isolated bone marrow cells from mice with *Pten* conditional knockout in Osx1-expressing osteoprogenitor cells. Expression of *Pten* and adipocyte marker genes was determined by quantitative PCR. *Osx-Cre* expression was examined by PCR. Pten and protein S6 phosphorylation were shown by Western blot analysis.

Results:

Osx1:Cre Pten cKO mice developed lipomas at the age of 3-4 months. Pten protein in lipomas was not different from other adipose tissue depots in the same mouse or in control mice, while ribosomal protein S6 phosphorylation was upregulated in lipoma tissue. We could show *Osx-Cre* expression in bone cells from *Cre*-positive mice. *Pten* was downregulated to 60 per cent, while Adiponectin was upregulated to 340 per cent in *Pten cKO* compared to WT mice, indicating increased adipocytes in *Pten cKO* mice.

Outlook:

We will compare proliferative and adipocyte differentiation potential in addition to the amount of adipocytes in bones from *Pten cKO* mice and WT.

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Prevalence of amblyopia in a German cohort of children and adolescents

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Background:
Amblyopia results in absence of organic disease from insufficient visual experience during childhood and is a reduction of best-corrected visual acuity (BCVA) of usually one eye. Untreated or delayed treatment of amblyopia can cause a permanent loss of vision and therefore cannot be improved by spectacles. The present work investigated the prevalence of amblyopia and its treatment in a large cohort of German children and adolescents.

Methods:
Visual acuity (uncorrected and with habitual correction if worn), BCVA, non-cycloplegic autorefraction and covertest were determined in 1874 subjects, aged 3 to 16 years (mean = 9.2, SD = 3.9). Additional an interview containing information about pre-existing visits to ophthalmologists, eye diseases, eye surgeries and treatment with occlusion therapy was conducted.

Results:
Unilateral amblyopia (two-line interocular difference in BCVA with ≤ 20/32 in the worse eye and the presence of an amblyogenic factor) and bilateral amblyopia (subnormal BCVA < 20/40 and the presence of an amblyogenic factor) were found in 29 participants (1.5 %; 95% confidence interval: 1.0 % to 2.2 %) with no age or sex differences. The causes of unilateral amblyopia (27 participants) were anisometropia in 55.6 % of children, strabismus in 25.9 % and the combination of these factors in 18.5 %. Children with bilateral amblyopia showed all bilateral high ametropia. We observed 15 children with current amblyopia, who were treated with occlusion therapy in the past (62.2 %; 95 % confidence interval: 42.7 % to 83.6 %).

Conclusion:
The distribution of amblyopia in children and adolescents living in Germany is similar to previous European studies. Refractive errors were the major amblyogenic factors.

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A new human stromal vascular cell model from white adipose tissue exhibits enhanced adipogenesis

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Background:
Simpson Golabi Behmel syndrome (SGBS) cells [1] and immortalized [2] stromal vascular fraction (SVF) cells are currently used as *in vitro* models for human adipogenesis. The Beckwith-Wiedemann syndrome (BWS) is, similar to SGBS, an overgrowth syndrome of which a SVF cell line does not exist so far.

Aim and Methods:
In order to establish new human adipogenic cell models we characterized primary and immortalized subcutaneous SVF cells from an obese child with BWS as well as from 4 healthy children with obesity. Specifically, we investigated if the BWS cells differed in proliferation, differentiation, mitochondrial function and gene expression profile.

Results:
While primary cells entered senescence after 52 generations, immortalized cells continued to proliferate. We found that BWS and control cells were not different in doubling time or mitochondrial activity. Interestingly, adipogenic potential was 2.7-fold higher in BWS cells compared to healthy cells throughout a long-term cultivation and even after immortalization. In line with this, adipogenic gene (*PPARG*, *ADIPOQ* and *AP2*) expression was up to 6-fold increased in differentiated cells.
Since the BWS alone was unlikely to explain the enhanced differentiation, we aimed to decipher the underlying mechanisms promoting adipogenesis in those cells. Therefore, we performed genome-wide expression analyses and identified differentially expressed genes between the BWS and the control SVF cells, which might regulate adipogenesis.

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Conclusion:
Adipogenic potential is markedly increased in the BWS cells. In future studies we aim to clarify the relevance of the identified differentially expressed genes to human adipogenesis.

References:
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Sleep-Related Difficulties in Healthy Children and Adolescents

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Objective:
As sleep-related difficulties are a growing public health concern, it is important to gain an overview of those at special risk. The current descriptive study presents prevalence rates of sleep-related difficulties in healthy children and adolescents and outlines the effects of age, gender, and socioeconomic status (SES) on sleep-related difficulties.

Participants:
855 4–9 year-old children and 1,047 10–17 year-old adolescents participated 2011–2015 in the LIFE Child study, Germany.

Methods:
Parents of the child participants completed the Children's Sleep Habits Questionnaire (CSHQ), whereas adolescents self-administered the Sleep Self Report (SSR). Familial SES was determined by a composite score considering parental education, occupational status, and income. Multiple regression analyses were carried out to address the research questions.

Results:
Among 4–9 year-old children, the mean bedtime was reported to be 8 p.m., the mean wake-up time 7 a.m., and sleep duration decreased by 14 min/ year of age. Parents of 22.6% of the children and 20.0% of the adolescents reported problematic amounts of sleep-related difficulties. In childhood, bedtime resistance and difficulties sleeping through the night were reported most frequently. In adolescence, daytime sleepiness was most prominent. Sleep-related difficulties were more frequent among young boys and adolescent girls. Lower SES was associated with increased sleep-related difficulties in adolescents, but not in children.

Conclusion:
The present results confirm that sleep-related difficulties are common and appear in different sleep domains depending on age. Furthermore, gender differences can already be observed in early childhood, while effects of SES emerge only later in adolescence.

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PTEN in the context of adipogenesis – insights into lipoma development and treatment

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Background:
Germline mutations in the tumor suppressor gene PTEN cause PTEN Hamartoma Tumor Syndrome (PHTS). Loss of PTEN leads to an over activation of the PI3K/AKT/mTOR-pathway. Pediatric patients frequently develop lipomas, the mechanisms of lipoma development remain unclear. Treatment attempts with the mTORC1 inhibitor rapamycin could not reverse lipoma growth. Recently, lipomas associated with a related syndrome caused by activating PI3K mutations (PIK3CA-related overgrowth syndrome, PROS) were successfully treated with alpelisib, a novel PI3K inhibitor.

Methods:
We investigated the role of PTEN in preadipocyte function via knockdown in preadipocytes from healthy donors. We also tested whether alpelisib has growth-restrictive effects and inhibits differentiation in PTEN haploinsufficient lipoma cells (LipPD1) from a pediatric PHTS patient. We investigated proliferation, signaling, adipogenesis and senescence.

Results:
PTEN knockdown activated PI3K downstream targets AKT and ribosomal protein S6 via phosphorylation, while alpelisib inhibited their activation. Proliferation and differentiation into adipocytes was increased after PTEN knockdown, but decreased with alpelisib. PTEN levels increased during long term culture of preadipocytes and PTEN knockdown lead to decreased expression of the senescence marker p21. Alpelisib induced senescence in LipPD1 cells and reduced the expression of metabolic enzymes.

Conclusion:
Knockdown of PTEN activated downstream PI3K signaling, promoting proliferation and differentiation of preadipocytes and counteracting cellular aging. PI3K inhibition with alpelisib had opposite effects on proliferation, differentiation and senescence, suggesting a regulatory role of PTEN in these processes.

Poster 98

Motor skills in relation to physical activity, TV-watching, socioeconomic status and BMI in adolescents – results of a population-based cohort study in Leipzig

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The objective of this study was to collect prevalence data on motor skills of children and adolescents in the Leipzig area and to furthermore identify any relations with age and gender as well as with physical activity, socioeconomic status, BMI and TV-watching. Participants were 2,129 children (1087 boys, 1042 girls) from the ages of 4 to 17 years. They did five different motor tests for strength, coordination and flexibility, more sociodemographic and anthropometrical parameters were collected via questionnaires. Multiple linear regressions were performed to find relations.
Age was an important influence on strength and coordination with performance increasing with a higher age. Boys performed better than girls in locomotive strength tests after the onset of puberty, girls' results were better in flexibility and coordination during precision tasks. In terms of strength endurance and coordination under time constraint both genders produced similar results. BMI, physical activity and socioeconomic status are significantly related to four of the five tests results each. Of those three, physical activity showed the strongest relations followed by BMI. A lower BMI and higher physical activity related to better motor skills scores. TV-watching was not related significantly to either task. Prevalence data for motor skills in Leipzig's youth was created and now allows for future longitudinal inquires. Correlation of motor skills with sociodemographic parameters identified certain groups with low motor skills. As those groups supposedly have lower motivation to engage in physical activity measures of encouragement for them might be considered.

Poster 99

Genome-wide meta-analysis identifies novel loci of plaque burden in carotid artery

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Background:
Carotid artery plaque is an established marker of subclinical atherosclerosis and common pathomechanisms with coronary artery disease (CAD) are assumed. We aimed to identify genetic variants associated with carotid plaque burden (CPB) and to examine the potential shared genetic basis with CAD.

Methods:
We defined 8 types of CPB traits at the carotid arteries: plaque present (PP), plaque score (PS, number of affected segments), and 6 traits of plaque areas (PA). We performed (meta-)GWAS for PP and PS in two independent cohorts (LIFE-Adult & -Heart, n=7189) and for PA in LIFE-Adult only (n=1277). Further, we tested if previously reported CAD SNPs were associated with CBP. Attempting to identify causal genes, we analyzed candidate gene expression data (Illumina HT12 v4) for correlation with CPB traits.

Results:
We found 2 loci with genome-wide significance for PS. One locus was the known CAD-locus at 9p21 (p=8.73x10^{-12}), which was associated with PP (p=2.72x10^{-8}), but not PA (p=0.38). We also described a novel locus at 10q24 within *SFXN2* as the most probable candidate gene (p=1.97x10^{-8}). In addition, we detected a genome-wide hit at 5q31.1 for PA in men only, with *IL5* and *IRF1* being the most plausible candidates (p=5.35x10^{-9}). There was a significant enrichment of associated CAD SNPs in PP and PS (p=1.03x10-8), but not for any PA trait.

Conclusions:
We showed that CPBs are reliable traits to analyze genetics of subclinical atherosclerosis. The hit at 9p21 was not associated with plaque size, suggesting that this locus affects the onset of carotid plaques but not their growth. The observed non-random overlap of CAD and PS associations and their genetic correlation strengthens the hypothesis of a shared genetic background for these atherosclerotic manifestations.

Poster 100

Sweet smell of healthiness: How insulin resistance relates to chocolate odor sensitivity across a wide range of body weights

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The worldwide obesity epidemic is a major health problem driven by the modern food environment. Recently, it has been shown that smell perception plays a key role in unconscious decisions for foods and is thus closely related to eating behavior. Since smell perception seems to be altered in obesity, this fact might crucially contribute to weight gain. However, the underlying mechanisms of altered olfactory perception in obesity are not well understood yet. Since the olfactory system is closely linked to the endocrine system, we hypothesized that hormonal shifts in obesity might explain this relationship. In a within-subject, repeated-measures design, we investigated sensitivity to food and non-food odor in the hungry and sated state in 75 young healthy (26 normal weight, 25 overweight, 24 obese) participants (37 women). To determine metabolic health status and hormonal reactivity, we assessed pre- and postprandial levels of insulin, leptin, glucose and ghrelin. Odor sensitivity did not directly depend on body weight status/BMI or metabolic state (hungry vs. sated). However, we could show a strong negative mediating effect of insulin resistance assessed by HOMA-IR score on the relationship between BMI/WHR and olfactory sensitivity for the food odor. Post-hoc regression models revealed, that insulin resistance rather than obesity is responsible for this effect. Moreover, post-hoc analyses showed a positive relationship between BMI and olfactory sensitivity when controlling for insulin resistance.
These findings indicate a major impact of metabolic health status on sensitivity to food odors. Our results offer an explanation for controversial findings on smell sensitivity in obesity and contribute to a better understanding of the mechanisms behind this relationship.

Poster 101

Effects of obesity associated signals on astrocytic metabolism

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Regulation of food intake and energy balance is an essential process for the organism regulated mainly by neurons of the melanocortin system in the hypothalamus. However, also astrocytes respond to food-associated signals and contribute not only to brain metabolism but also to the metabolism of the entire organism. Here, we investigated whether and how hormones like insulin, leptin and other adipokines affect cellular metabolism of astrocytes, knowing that these changes in turn can influence the activity of neurons. Using primary astrocytic cultures from the mouse hypothalamus and cortex, the dynamics of metabolites were assessed using genetically encoded nanosensors for metabolites in combination with live cell imaging. Both insulin and leptin increase astrocytic NADH/NAD^+ redox ratio in a concentration dependent manner. Furthermore, the dynamics of the cytosolic concentrations of lactate, glucose and ATP in response were investigated. These preliminary experiments suggest that insulin and leptin modify astrocytic metabolism and pave the way for further analysis of the influence of nutritional hormones on cell type specific metabolism in the brain.

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Poster 102

Cell Homeostasis Or Cell Death – The Balancing Act Between Autophagy And Apoptosis Caused by Steatosis Induced ER Stress

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With increasing prevalence of the metabolic syndrome, the associated non-alcoholic fatty liver disease (NAFLD) is gaining in relevance. Mechanisms of genesis, maintaining and on-going development of NAFLD are not in detail understood. Our objective is to investigate steatosis induced endoplasmic reticulum (ER) stress over time and the subsequent effects of autophagy and apoptosis in an *in vitro* model.

The study was performed using *in vitro* cell culture models of HepG2 and Primary Human Hepatocytes (PHH). PHHs were isolated from human liver tissue and cultured in a classic 2D and a 3D sandwich culture. To induce steatosis, a mixture of free fatty acids containing 0.6 mM palmitate and oleate in a ratio 1:2 was used. Steatosis was characterized by measuring lipid accumulation qualitatively (Oil Red O Staining) and quantitatively (biochemical assays) normalized to protein (SRB staining). Proteins expressed during ER stress, apoptosis and autophagy are determined by Western Blot analysis. For ER stress, we will investigate three signaling pathways of the unfolded protein response including PERK, ATF6 and IRE1. PPARα will be measured as a marker for lipid stress, PARP, CHOP and JNK for apoptosis and MAP LC3 for autophagy.

We expect ER stress at an early stage to be balanced by autophagy with increasing activity of IRE1 expression. Later on, we anticipate a rise of ATF 6 as expression of an increasing lipid stress and consequently PPARα to enhance mitochondrial β-oxidation. Augmented lipid accumulation will increase ER stress response. The resulting decreased protein folding capacity leads to late ER stress which will likely ensue in apoptosis. All data will be measured time dependently in order to use them for validation of a mathematical model of ER stress response.

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Poster 103

High expression of the brite adipocyte progenitor marker MSCA1 indicates SVF cells with higher mitochondrial activity in adipose tissue of children

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Studies in adipose tissue (AT) of adults showed the existence of different progenitor cell subpopulations with different capacities to differentiate and proliferate. MSCA1+ adipocyte progenitor cells showed the highest adipogenic potential for development into brite adipocytes and had higher mitochondrial content after differentiation. Because of this, we aimed to investigate whether mitochondrial respiration increases with a higher *MSCA1* expression in cells of the stroma vascular fraction (SVF) of AT from children.

We measured *MSCA1* expression in isolated adipocytes and SVF cells in lean (n=35) and obese (n=30) children of our Leipzig Childhood AT cohort. For n=13 of these samples we specifically analyzed a possible relationship between high and low *MSCA1* expression in primary SVF cells and parameters of the mitochondrial respiratory chain using the Agilent Seahorse XF Cell Mito Stress Test Kit.

Both SVF and adipocytes *MSCA1* expression increases with increasing age of children. In accordance with adult studies, adipocyte *MSCA1* expression was higher in children with obesity compared to lean children. For the SVF *MSCA1* expression we did not observe a correlation between lean children and children with obesity. A higher *MSCA1* expression in SVF cells was associated with alterations in mitochondrial function, i.e. an increase in the mean oxygen consumption of more than 30% (p=0.038) of maximum respiration and more than 40% (p=0.032) in spare respiratory capacity.

In conclusion higher SVF *MSCA1* expression is related to the maximum respiration and spare respiratory capacity of the mitochondrial respiratory chain in children. The results suggest that mitochondria in SVF cells with higher *MSCA1* expression have a higher mitochondrial spare capacity for energy generation.

Poster 104

Identification of molecular factors that influence adipose tissue overgrowth/lipoma formation

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Background:
PTEN Hamartoma Tumor Syndrome (PHTS) comprises disorders caused by *PTEN* germline mutations. *PTEN* is a tumor suppressor gene, which negatively regulates the growth promoting PI3K/AKT/mTOR cascade. PHTS patients frequently develop lipomas, whereas the mechanisms are unclear. RNA sequencing of stromal vascular fraction (SVF) cells, with vs. without *PTEN* knockdown (KD), revealed 1379 differently expressed genes. We aim to characterize the role of these genes in adipogenesis, proliferation and migration of preadipocytes.

Methods:
We compared RNA-sequencing data from our model and from immortalized inguinal vs. epididymal mouse cell lines. We performed quantitative real-time PCRs (qPCR) to confirm RNA-sequencing results. To investigate if candidate genes were regulated during adipogenesis, we differentiated patient-derived *PTEN*-mutated lipoma cells and SVF cells from healthy donors into mature adipocytes and analyzed gene expression levels at day 0, 4, 8, 12 of differentiation.

Results:
Results from our model and mouse cell lines revealed six overlapping regulated genes (*SMIM10L1*, *NEGR1*, *CHIC1*, *GOLM1*, *ZBTB18*, *RMND5A*). We confirmed the RNA-sequencing results by qPCR. Most candidate genes were differentially expressed between undifferentiated vs. differentiated lipoma cells during adipogenesis. *SMIM10L1*, *CHIC1*, *GOLM1*, *ZBTB18 and RMND5A* were downregulated in PTEN KD cells and also showed lower expression levels in differentiated PHTS lipoma cells. *NEGR1* is upregulated in *PTEN KD* cells and also in differentiated lipoma cells.

Conclusion/outlook:
Six genes were differentially expressed in our *PTEN KD* model and also in inguinal vs. epididymal cell lines, suggesting a regulatory role in adipose tissue. We plan to characterize the function of these candidate genes.

Poster 105

Early retirement and depressive symptoms – Results from the population-based LIFE-Adult-Study

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Background:
Transition from employment to retirement is considered a crucial event. However, there is mixed evidence on associations between retirement and health, especially considering early retirement. In Germany, cases of early retirement due to ill health – particularly, mental ill health – are increasing. Hence, information on the health situation of workers and early retirees are urgently needed.

Methods:
Linear regression analysis using entropy balancing to achieve a balanced age- and sex-distribution between employed and retired persons. We analyzed data from 5,864 participants (656 retired, 5,208 employed; age: 18-66 years) with complete information on outcome and explanatory variables, controlling for sociodemographic information, social network, severe pre-existing conditions and duration of retirement. Depression was assessed using the Center for Epidemiological Studies Depression Scale.

Results (preliminary):
Overall, early retirees were at slightly lower risk for depression than employed persons (b = -1.29; 95% CI: -2.57; -0.01). However, early retirement due to ill health was linked to higher risk even after controlling for covariates (b = 3.27; 95% CI: 1.54; 4.99). Voluntary early retirees did not differ from employees regarding risk for depression. Duration of retirement did not change the association. Male gender, living in a partnership, high education and a larger social network were linked to lower depression risk.

Discussion:
Risk for depression among early retirees depends on reasons for retirement: Early retirement due to ill health is associated with increased risk for depressive symptoms. Employers and policy makers should focus on facilitating employment for workers with impaired health to increase the working population among older people.

Poster 106

The Heart and Gut Interplay – Examining the microbiome, intestinal permeability and TMAO in HFpEF in a ZSF1 rat animal model

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Background:
Elevated Trimethylamine-N-Oxide (TMAO) is associated with cardiovascular diseases, specifically Heart Failure with Preserved Ejection Fraction (HFpEF).
The precursor trimethylamine (TMA) is synthesized by the gut microbiome, passes into circulation and is metabolized to TMAO. Elevated plasma levels of TMAO therefore could be caused by a microbiotic shift and an increased intestinal permeability. Obese ZSF1 rats develop hypertension and metabolic syndrome, culminating in HFpEF. In this study we examined the gut microbiome and gut wall permeability in ZSF1 rats in an animal model of HFpEF with increased TMAO levels.

Methods:
TMAO was measured using Tandem-mass-spectroscopy in plasma samples of lean (n=12) and obese (n=11) rats.
Microbiome components were classified by identifying bacteria by DNA sequencing from stool samples.
Morphology of the intestinal barrier will be assessed by visualizing intercellular contacts through immune histochemistry while functionality will be determined via impedance based barrier tests on colon cells.

Results:
TMAO plasma levels were on average 86% higher in obese rats ($p<0.05$). The decrease in barrier function was significantly ($p<0.05$) smaller in obese rats. Using the relative changes in operational taxonomic units over time as a preliminary indicator, differences in phyla between obese and lean rats, deferribacteria (271% vs. -56%) and verrucomicrobia (25 % vs. -68%) were striking.

Conclusion:
Our data show a microbiome shift as well as an increase in plasma TMAO levels. Epithelial cells of obese rats appear to be less sensitive, which could be attributed to a decrease in cell reactivity.

Poster 107

A Biomathematical Model of Immune Response and Barrier Function in Mice with Pneumococcal Lung Infection

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Pneumonia is one of the leading causes of death worldwide. The course of the disease is often highly dynamic with unforeseen critical deterioration within hours in a relevant proportion of patients. Besides antibiotic treatment, novel adjunctive therapies are under development. Their additive value needs to be explored in clinical studies, and therapy schedules require optimization prior to introduction into clinical practice. Biomathematical modelling of disease and therapy might be a useful support. We propose a model of the murine immune response during infection with Streptococcus pneumoniae aiming at predicting the outcome of different treatment schedules. The model consists of ordinary differential equations describing the dynamics and interactions of bacteria, neutrophils, alveolar- and inflammatory macrophages, IL-6, IL-10, CCL2, CXCL1 and CXCL5, monocytes, and bacterial penetration through the epithelial barrier to cause blood stream infection. We impose therapy effects on this system by modelling antibiotic therapy and treatment with the novel C5a-inactivator NOX-D19. Equations were derived by translating known biological mechanisms and assuming certain response kinetics. Unknown parameters were determined by fitting the model predictions to time series data from experiments. Parameter fittings resulted in a good agreement of model and data. The model can be used to predict the performance of alternative schedules of combined antibiotic and NOX-D19 treatment. We conclude that we established a comprehensive model of pneumococcal lung infection, immune response and barrier function in mice allowing simulations of new treatment schedules. We plan the inclusion of further novel therapy principles and the translation of the model to the human situation.

Poster 108

Seroprevalence of West Nile virus in Sudan

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Background:
This study was initiated to investigate the seroprevalence of West Nile virus (WNV) in Sudan. Therefore serum samples were collected from patients with fever who represent the general Sudanese population and were tested for Dengue virus antibodies to avoid cross reactivity between WNV antibodies and Dengue virus (DV) antibodies. For analysis of WNV neutralizing antibodies (nAb) only DV nAb-negative samples were used.

Material and methods:
109 Dengue virus IgG-negative serum samples were analysed by microneutralization tests to detect WNV antibodies. 65 serum samples came from clinics in Kassala state, 38 from North Kordofan and 6 from Red Sea state. A first screening microneutralization test identified 31 nAb-positive samples. Neutralization was determined by microscopic analysis and enzyme-linked immunosorbent assays (ELISA). Positive screening results were confirmed in secondary microneutralization tests which determined the neutralizing antibody titres.

Results:
Out of 109 serum samples at least 41 (37.6%) neutralized WNV. The results show a seroprevalence of 32.3% (31 of 65) in Kassala state, 23.7% (9 of 38) in North Kordofan and 16.7% (1 of 6) in Red Sea state. The geometric mean of the titres is 76.08 in Kassala state and 36.29 in North Kordofan. On average WNV nAb-positive patients from Kassala state were 37.3 years old (nAb-negative: 25.7 years) and in North Kordofan 40.3 years old (nAb-negative: 38.4 years).

Conclusion:
More than a third of the analysed serum samples were positive for WNV neutralizing antibodies. The results demonstrate that a considerable part of the patients have had an infection with West Nile virus. In further tests these serum samples will be examined for other flavivirus neutralizing antibodies to test them on cross neutralization.

Poster 109

Surprisingly similar humoral immune response to *Cryptococcus neoformans* in patients with cryptococcal meningitis and in healthy people with presumed environmental exposure

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Cryptococcus neoformans (*Cn*), the main agent causing systemic cryptococcosis in immunocompromised patients, is known to be ubiquitously present in the environment. We aimed to further characterize the humoral immune response during cryptococcosis.

Methods:
We analyzed sera from Colombian cryptococcal meningitis patients, with or without HIV infection, and healthy control persons using flow cytometry, ELISA analysis, and 2D immunoproteomics. Additionally, we analyzed sera from susceptible wild-type Balb/c and resistant IL-4Rα-deficient mice pulmonary infected with *Cn*.

Results:
Surprisingly, sera of all human patient groups showed similar titers of anti-cryptococcal IgG and IgM directed against a) the whole organism, b) fungal proteins, and c) capsular polysaccharides. Therefore, we conclude that the level of antigenic burden and the nature of microbial encounter affects the anti-fungal humoral immune response only to a minor extent. This was further supported by the results of our murine model, where susceptible wild type Balb/c mice developed comparable titers of anti-cryptococcal antibodies as resistant IL-4Rα-deficient mice, despite greatly different fungal burden in the lung. We propose that exposure of humans to low doses of *Cn* is sufficient to trigger a long-lasting humoral immune response towards the fungus. Two-dimensional immunoblotting of sera from patients and healthy persons revealed that in total 230 immunoreactive protein spots out of a total of 311 cryptococcal protein spots detectable in the 2D gel were recognized by the human sera investigated in our study (n=40). Ongoing analysis is carried out on the nature of the immunoreactive antigens recognized by cryptococcosis patients and healthy control persons.

Poster 110

In-vitro anti-inflammatory activity of *Combretum collinum* leaves extract and its main phenolic compound myricetin-3-*O*-rhamnoside

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Combretum collinum is a deciduous shrub, which is commonly used in the northern region of Benin to treat inflammatory disorders and to promote wound healing processes. Phytochemical screenings could confirm myricetin-3-O-rhamnoside as the main phenolic compound for water and ethanolic extracts of the leaves. However, knowledge about the underlying pharmacological mechanisms of actions is still scarce. Therefore, the present study aims to assess the *in-vitro* anti-inflammatory effect of *Combretum collinum* aqueous leaf extract and its main phenolic compounds myricetin-3-O-rhamnoside and myricetin in immortalized human keratinocytes (HaCaT). To simulate an inflammatory process on skin, the cells were stimulated with tumor necrosis factor-alpha (TNFα) 20 ng/ml for 24 hours to overproduce interleukins 8 and 6. Thereafter, cytokine levels in supernatants were assayed by ELISA and the cell viability was determined using the MTT assay. *Combretum collinum* leaf extract and myricetin-3-O-rhamnoside, as well as its aglycone myricetin, inhibited the release of interleukin 8 after co-incubation with 20 ng/ml TNFα for 24 hours, resulting in IC_{50} – values of 142,5 µg/ml for *Combretum collinum* leaf extract, 121.9 µM for myricetin-3-*O*-rhamnoside and IC_{50} = 90,69 µM for myricetin. Furthermore, *Combretum collinum* aqueous leaf extract dose-dependently reduced the release of interleukin 6 in TNF-α-treated HaCaT cells, resulting in a decrease of IL-6 release by 29,3 % for the highest extract concentration of 200 µg/ml. The *in-vitro* anti-inflammatory activity of *Combretum collinum* aqueous leaf extract supports its ethnomedicinal usage in inflammatory diseases.

Poster 111

STAT5A phosphorylation as a predictive marker to detect T cell proliferation

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Background:
Immediate STAT5A phosphorylation (pSTAT5A) upon T cell receptor stimulation is critical event in T cells proliferation. Here we present a simple and sensitive flow cytometric – based assay to assess T cell proliferation. Given the critical role STAT5A phosphorylation in T cell proliferation, we decided to investigate a phosphorylation of STAT5A as an indicator of T cell proliferation.

Methods:
We determined pSTAT5A in T cell from 19 adult healthy donors stimulated with either CD3/CD28 or PHA.

Results:
After stimulation, T cells displayed a strong long-lasting phosphorylation of STAT5A, reaching a peak value after 24 hours. The median fluorescence intensity (MFI) of pSTAT5A increased from 112 ± 17 to 512 ± 278 (CD3/CD28) (24 h) and to 413 ± 123 (PHA) (24 h), the IL-2 receptor-α (CD25) expression was greatly enhanced and after 72 h T cell proliferation amounted to 52.3 ± 10.3 % (CD3/CD28) and to 48.4 ± 9.7 % (PHA). Treatment with specific STAT5 and JAK3 inhibitors resulted in a complete blockage of phosphorylation of STAT5A, CD25 expression and suppression of T cell proliferation.

Conclusions:
Compared with currently available methods, pSTAT5A is well suited to predict T cell proliferation. Moreover, due to its simplicity and robustness, the flow cytometric based pSTAT5 assay is especially appropriate to rapidly assess primary immune deficiencies (PIDs) associated with STAT5 defects including autoimmune diseases, CD25 deficiency and T cells proliferation defects.

Poster 112

Lower levels of HBV core antibodies are associated with poor treatment response during treatment with pegylated interferon in HBeAg positive patients

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Background and Aims:
Previous studies investigated the clinical relevance of quantitative antibody to hepatitis B core antigen (anti-HBc) levels. Nonetheless, the association of anti-HBc levels and viral antigens during treatment remains unclear. Our aim was to investigate this association to understand the immunological role of anti-HBc levels during treatment with pegylated interferon (PEG-IFN).

Methods:
135 HBeAg-(+) patients received 180 mg/week PEG-IFN (48 weeks). During treatment, 70/135 patients showed HBeAg seroconversion (SC) from whom two patients achieved HBsAg SC, whereas 65/135 patients showed no serological response. Anti-HBc was quantified using the WHO Anti-HBc Standard and the Anti-HBc II Abbot Architect system. Other HBV markers (HBV RNA, HBcrAg) were measured and correlated with anti-HBc levels.

Results:
Patients were classified, corresponding to their anti-HBc levels before treatment into six ranges: anti-HBc levels were < 2.0 log (n=7); 2.0-2.5 log (n=10); 2.5-3.0 log (n=34); 3.0-3.5 log (n=34); 3.5-4.0 log (n=25) and >4.0 log U/mL (n=22). During treatment, all patient groups achieved median undetectable HBV RNA levels, whereas patients with anti-HBc levels <2.0 log U/mL showed no loss of HBV RNA levels and significantly higher levels of HBcrAg (U/mL) compared to all other groups. Depending on the anti-HBc levels at baseline, the probability of HBeAg SC and inactive carrier state was correlated to higher anti-HBc (0% for < 2.0 log; 35-45% for all five groups >2.0 log U/mL at week 24 during treatment).

Conclusion:
Anti-HBc levels strongly correlate with HBV RNA and HBcrAg levels during PEG-IFN treatment. Low levels (<2.0 log U/mL) of anti-HBc might be a marker for a low immune response and might be further investigated.

Poster 113

Neutrophil role in wound healing and modulation of their activity

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Chronic wound healing is a worldwide problem of vulnerable population, elderly people and people with diabetes. The failure of wound healing depends on several factors including the dysregulated interplay of immune and non-immune cells. Main problem of chronic wounds is a prolonged inflammatory state, high protease activity, constant pro-inflammatory cytokine and chemokine signaling and immune cells overreaction. Neutrophils contribute to it, but also they have sophisticated mechanisms of balancing inflammation, for instance, neutrophils have pro-resolution functions by inducing macrophage activation to be later phagocytized or formation of cytokine degrading aggregated Neutrophil Extracellular Traps (NETs) as shown in gout. We used full thickness wound healing model in wildtype and diabetic mice, analyzed appearance and localization of neutrophils, protease activity and inflammatory condition at different time. In diabetic mice protease and inflammatory mediators are high, delayed and persist longer, in accordance with delayed wound healing. All in all, unfavorable condition of diabetes leads to low pro-inflammatory factors, later appearance of PMN with inadequate protease activity, which hinders functions of PMN including resolution of inflammation and further wound healing. Further, we will monitor neutrophils *in vivo*, study role of aggNETs and analyze proteome/transcriptome at different healing stages. Overall, this will reveal unknown function of neutrophils and help to develop better wound healing strategies.

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Poster 114

Analysis of Porcine Pro- and Anti-inflammatory Cytokine Induction by *S. suis in vivo* and *in vitro*

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Weaning piglets are susceptible to invasive *Streptococcus (S.) suis* infection which can result in septicemia. The aim of this study was to investigate the cytokine profile induced upon *S. suis* infection of blood, to determine cellular sources of those cytokines, and to study potential effects of the induced cytokines on bacterial killing. We measured TNF α, IL 6 and IL 10 after an experimental intravenous infection with *S. suis* serotype 2 *in vivo*, and analyzed whole blood, PBMC and separated leukocytes to identify the cytokine-producing cell type(s). In addition, we used a reconstituted whole blood assay to investigate the effect of TNF α on bacterial killing in the presence of different *S. suis*-specific IgG levels. An increase of IL 6 and IL 10 was observed in two of three piglets with pronounced bacteremia 16 to 20 h after infection but not in piglets with controlled bacteremia. The data confirmed previous findings that *S. suis* induces TNF α and IL 6 and could demonstrate that TNF α is produced by monocytes *in vitro*. We further found that IL 10 induction resulted in reduced secretion of TNF α and IL 6. Rapid induction of TNF α was, however, not crucial for *in vitro* bacterial killing, even not in the absence of specific IgG.

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Poster 115

Comparison of B-cell epitope profiles among birch-related soy allergic patients before and after birch-specific immunotherapy

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Allergen immunotherapy (AIT) with birch pollen is expected to improve birch pollen-related food allergy. However, the efficacy of birch AIT is controversial. IgE- and IgG-binding epitope profiling before or after AIT might reveal prognostic- and/or therapeutic-relevant epitopes. In this study, we aim to study the allergen epitope recognition profiles of birch AIT patients using a peptide phage display approach.

We included 32 verum patients from the BASALIT trial (Birch Associated Soy Allergy and ImmunoTherapy, EudraCT-Nr.: 2009-011737-27). Patients were diagnosed with birch-related soy allergy. Subcutaneous injections of a recombinant hypoallergenic variant of the major birch allergen Bet v 1 were administered during one year. Sera collected at baseline and end of treatment were used in peptide phage display experiments. B-cell epitope profiles were constructed using data obtained from the selection experiments. We present preliminary results from IgE and IgG binding experiments using peptide microarrays. Selected peptides containing enriched allergen epitope motifs were tested. Results from the phage display data, peptide microarray data and the trial's primary outcomes are being compared.

Epitope maps reveal highly heterogenous binding patterns among patients. Peptide microarray experiments are ongoing. Preliminary data suggest a negative correlation between the number of IgE and IgG positive peptides at baseline with the patients' AIT outcome. The identification of clinically relevant IgE or IgG epitopes might improve patient selection and/or enable monitoring of patients' treatment response in future AIT.

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Poster 116

A time-resolved meta-analysis of consensus gene expression profiles during human naïve T-cell activation

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Background:
In order to predict the individual biological immune response, the research project "MyCellFight" is developing an automated immune chip enabling prediction of the specific immunological responses to a drug or chemical. Key events in the formation of an immunological synapse between APCs and T-cells for many individuals will be imaged simultaneously with this artificial immune system. To evaluate the detection of the initial immune response, a functional gene signature that reflects early events of the cellular activation and differentiation of T-cells is required.

Methods:
Based on an extensive literature research we performed a meta-analysis of CD3/CD28 induced T-cell activation kinetics with publicly available time-series RNA sequencing and microarray datasets. We used non-negative matrix factorization, an unsupervised deconvolution method that can infer changes in biological patterns over time when applied to time-series transcriptome data.

Results:
Here we present a kinetic view of gene expression changes in naïve CD4+ T-cells during antigen-independent activation with anti-CD3/CD28 beads and in T-cell polarization conditions. We developed a consensus gene expression profile from eight time points that includes central transcriptional regulators associated with T-cell activation.

Conclusion:
Our findings provide a consensus gene signature in T-cells during activation and contain a wealth of information to characterize gene expression changes in a coordinated and temporal fashion. The temporal characteristics of our markers help to understand the transcriptome landscape in activated and polarized CD4+ T-cells.

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Poster 117

Keratin-dependent mitochondrial dynamics

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Mitochondria maintain tissue homeostasis by dynamically switching between fusion and fission in response to endogenous and exogenous signals. Emerging evidence reveals that beside microtubules and actin, keratin cytoskeletal proteins control mitochondrial dynamics and activity, although underlying molecular mechanisms are incompletely understood.
Here, we identify a novel pathway through which keratins regulate mitochondrial fission in keratinocytes. We find that genetic deletion of keratins in mouse keratinocytes results in massively elongated mitochondria, in agreement with a strong reduction of the fission inducing GTPase Drp1. Of note, re-expression of keratins but not of Drp1 restored fission, indicating a regulatory mechanism in which keratins act upstream of Drp1. Given increased mitochondrial hyperfusion upon oxidative stress, a condition prevailing in patients suffering from keratin mutations, we investigated the levels of the antioxidant transcription factor Nrf2 and its relevance for mitochondrial hyperfusion. We found elevated Nrf2 levels in keratin-deficient keratinocytes. Most strikingly, stabilization of Nrf2 by electrophiles resulted in fused mitochondria in control keratinocytes. We are currently elucidating how Nrf2 regulates Drp1 localization in keratinocytes. Collectively, we have identified a novel regulatory mechanism by which mitochondrial dynamics is controlled in a keratin-dependent manner via theNrf2-Drp1 axis.

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Poster 118

The p21-mediated and senescence-associated hyperglycemic memory in diabetic nephropathy is therapeutically amendable

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Diabetic nephropathy (dNP), is the leading cause of end stage renal disease. A major therapeutic obstacle in dNP is the failure of renal recovery upon improved blood glucose level. The mechanisms underlying this phenomenon, known as the hyperglycemic memory, remain unknown. We aimed to identify therapeutic targets contributing to this memory in dNP. To achieve this, we conducted kidney mRNA-seq to evaluate pathways involved in hyperglycemic memory using mice models of type 1 and 2 diabetes. Blood glucose was reduced using an SGLT2-inhibitor, mimicking therapy in diabetic patients. *In vitro* and *in vivo* studies were conducted to determine mechanistic relevance. Despite a marked reduction of blood glucose levels using SGLT2 inhibition, albuminuria, histomorphological changes, and glucose-induced altered renal gene expression persisted. Sustained expression of p21, a senescence-associated cell cycle inhibitor, was among the top hits. Sustained tubular expression of p21 despite blood glucose lowering was confirmed in diabetic mice. Sustained p21 expression was linked with demethylation of its promoter. The nephroprotective zymogen protein C (PC) was among genes persistently repressed in dNP. Increased tubular senescence, interstitial fibrosis, and albuminuria were confirmed in diabetic mice with genetically impaired PC activation. Substituting the protease activated PC (aPC) or mimicking biased aPC-signaling (parmodulin-2) in addition to normalizing blood glucose levels reversed sustained tubular p21 expression, tubular senescence, and renal damage in diabetic mice. In conclusion, we showed that epigenetically sustained p21 expression and associated senescence contribute to the hyperglycemic memory in dNP. This pathogenic mechanism can be targeted by mimicking aPC-signaling.

Poster 119

Dictyostelium discoideum: Unusual occurrence of two active CCA-adding enzymes

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Dictyostelium discoideum is a slime mold belonging to the phyla of amoeba and is a widely used model organism for investigating cell differentiation, sociality and mobility. When starving, this organism is able to undergo a complex development to produce differentiated cells of spores and stalks while switching from a unicellular to a multicellular organism. Recent research gave rise to the occurrence of two genes coding for tRNA-nucleotidyltransferases in this organism. We cloned these genes and biochemically characterized the recombinantly expressed enzymes with different methods estimating the enzymes function, localization, substrate specificity and binding affinity. Surprisingly, our results show that both enzymes have the same activity and are fully active CCA-adding enzymes. This is the first discovery of an organism with two functional active CCA-adding enzymes. Our investigation showed that both use the same set of tRNAs and are localized equally. Knockout experiments showed that both enzymes are essential and phylogenetic analysis revealed a wide distribution of two tRNA-nucleotidyltransferase genes within the phylum of Dictyostelia. Further, we could show that both enzymes are regulated oppositely during the development and that both have different binding affinities.

Poster 120

Cardiopulmonary effects of the vasodilator relaxin on rats in normobaric hypoxia

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Hypoxia exposure for several hours leads to an impairment of left ventricular pump function and to a development of pulmonary edema. RLX is known to have positive effects on hemodynamic parameters in acute heart failure. Therefore, we expected that RLX might improve left ventricular pump function in hypoxia. Furthermore we hypothesized that RLX – as an effective vasodilator - might reduce pulmonary hypoxic vasoconstriction and thus could prevent pulmonary edema. Experiments were performed on 52 rats in normoxia or hypoxia (10% N_2 in O_2). 3 doses RLX (RLX D0=3µg/kg/d, RLX D1=15µg/kg/d, RLX D2=75µg/kg/d) were administered to hypoxia-exposed animals, RLX D1 also to normoxic rats. After 24 h, hemodynamic measurements were performed. Pleural fluid and lung tissue samples were obtained for further analyses. LV dP/dt max as a dimension of left ventricular contractility was increased by RLX D2, but remained significantly lower than in normoxic controls. In contrast, right ventricular contractility was re-increased to control level with RLX D1 and D2. All groups of RLX-infused rats showed moderate pulmonary edema while normoxic controls did not. In contrast to hypoxic controls, the edema in RLX-treated rats occurred predominantly in the upper lung lobe. Moreover, RLX-treated rats showed signs of lung congestion. In addition, we found an increased serum protein concentration in RLX-treated rats indicating dehydration. We suggest that RLX abrogated hypoxic pulmonary vasoconstriction resulting in pulmonary overperfusion. The following increase in pulmonary blood pressure may lead to liquid accumulation in the upper lung lobe due to gravity effects. In conclusion, the results show that RLX may improve hemodynamic function under hypoxic conditions but cannot prevent pulmonary edema.

Poster 121

A global analysis of self-cleaving ribozyme activity in *Schistosoma mansoni*

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RNAs, able to catalyze chemical reactions, are called ribozymes. Some ribozymes, so-called self-cleaving ribozymes, cut their own phosphate backbone at a specific position to enable their biological function. Ribozyme cleavage results in an RNA fragment with a 2', 3'-cyclic phosphate (2',3'-cP) and another fragment with a 5'-hydroxyl group (5'-OH). However, despite thousands of self-cleaving ribozyme examples, only a few selected representatives from some organisms have been linked to a biological role. To date, self-cleaving ribozymes have either been found by chance or by bioinformatics analysis. Here, we introduce a method with which we want to screen for novel self-cleaving ribozyme classes experimentally and which will enable us to study the *in vivo* activity of self-cleaving ribozymes on a genomic scale. Therefore, we are using deep sequencing with specific adapter-ligation methods to enrich ribozyme fragments. To capture the fragment with a 2',3'-cP, we established a procedure consisting of ligation using the *A. thaliana* tRNA ligase. As proof-of principle, we successfully used this strategy to capture self-cleaving ribozymes in *Schistosoma mansoni*, which has thousands of self-cleaving ribozymes in its genome. Furthermore, we also want to establish the capture of the fragment with the 5'-OH group using the RtcB ligase for the adapter-ligation. The discovery of additional self-cleaving ribozyme classes as well as further insight on self-cleaving ribozyme activity will allow us to decipher more biological functions of self-cleaving ribozymes in the future.

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Poster 122

RNA editing in the failing heart regulates formation of circular RNAs

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RNA editing is an essential process of life and is critically involved in human diseases. Circular RNAs (circRNAs) are generated by an alternative RNA splicing process called "back-splicing". Protein coding genes give rise to the majority of circRNAs. RNA editing events in flanking intronic regions of the circRNA encoded host gene mRNA were shown to regulate circRNA formation. This study aims to determine RNA editing in the failing heart and characterize its impact on the generation of circular RNAs. A next generation sequencing approach analyzing control (N=10) and heart failure patients (N=19) revealed 1211 genes to be differentially edited. We found 880 protein-coding RNAs differentially edited in HF, the most profound reduction in RNA editing were found in the cardiomyopathy-associated transcripts encoding for RYR2 and AKAP13. Among the >6600 expressed circRNAs, a total of 109 circRNAs, including a circular RNA encoded by the AKAP13 gene, were independently regulated from their host gene, indicating an alternative splicing mechanism contributing to circRNA formation. Significant changes in editing events in intronic ALU elements upstream and downstream of the back-splice site of circAKAP13 were identified. In contrast, no significant changes in RNA editing were observed in the 3'UTR, 5'UTR, and exons of the respective host gene AKAP13. Interestingly, the vascular-specific editing enzyme ADAR2 was reduced on protein level in failing hearts. Consistently, knockdown of ADAR2 resulted in an increase of circAKAP13 level. SiRNA-mediated knockdown of circAKAP13 in primary human endothelial cells significantly reduced the angiogenic capacity. This study proposes that the reduced RNA editing events in the failing heart lead to enhanced expression of circular RNAs.

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Poster 123

Elongation factor AFF4 regulates angiogenesis in primary endothelial cells

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Introduction:
Angiogenesis, the formation of blood vessels from preexisting ones, is crucial for regeneration after ischemic heart disease and during peripheral vascular diseases. This process relies on changes in the cells gene expression program, which is mediated by the RNA polymerase. Rapid expression changes upon stress stimuli are a result of the RNA polymerase II (Pol II) pause and release from the promoter. AFF4, as part of the super elongation complex, is regulating RNA-Pol II pause and release.

Methods and Results:
The expression of all AFF family members was characterized in primary human cell types of the cardiovascular system. AFF4 was the highest expressed family member in human umbilical vein endothelial cells (HUVEC) and in human coronary artery endothelial cells (HCAEC) compared to AFF1-3. The expression of AFF4 was reduced using siRNA-mediated knockdown, which was validated using specific primer in real-time qPCR and by immunoblot targeting AFF4. We then investigated the result of AFF4 knockdown on angiogenesis. An *in vitro* network formation assay, after a siRNA-mediated knockdown of AFF4, revealed a reduced capacity to form angiogenic sprouts (19,07% ± 1,33% reduction vs control siRNA).

Conclusion:
The RNA polymerase II elongation factor AFF4 is highly expressed in primary endothelial cells and regulates angiogenesis *in vitro*.

Poster 124

Large-scale identification of links between the human blood metabolome and transcriptome

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Integration of population-scale circulating human blood metabolite and gene-expression data can strengthen the knowledge of their reciprocal regulation and related disease phenotypes. Pre-processing and the preliminary investigating of sources of variation in multi-study metabolite data for use in a consensus covariate model can reduce bias in association (meta-) analyses. However, no consensus on the methodology for selection of covariates exists.
Metabolite data of three independent studies (LIFE Heart, LIFE Adult and the Sorb study) were pre-processed and strongly influencing factors for use as covariate were identified according to a previously developed and published workflow. Associations of 97 metabolites with 26,042 HT12v4 gene-expression probes from PBMCs and whole blood were calculated and individual study summary statistics were subsequently meta-analysed (N_{max}=7,706).
Age, sex, hours fasted, hematocrit, monocytes and neutrophils were identified as covariates for the association analyses. The meta-analysis revealed associations with 8,579 unique genes across the metabolome after correction for multiple testing. Most associations were described for the metabolite Acetylcarnitine (2,187 sig. genes). On gene level, *BCL11A*, zinc-finger protein coding gene, associated most widespread with 56 metabolites. Strong similarities between metabolite-gene association lists of metabolite pairs within and between metabolite groups were observed.

Principled pre-processing and inference of suitable covariates for multi-study metabolite data strengthens reliability of downstream analyses. The interconnectedness of the human blood metabolome and transcriptome and possible mediation effects on clinical endpoints such as Type II Diabetes will be studied in follow-up analyses.

Poster 125

Role of lncRNA Heat4 in the immune receptor locus IRL in heart failure

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This study aims to identify and characterize immunomodulatory lncRNAs in HF Using NGS, we identified the lncRNA Heat4 as upregulated in PBMCs of patients with HF compared to controls. Heat4 is located in the well-known immune receptor locus (IRL). The significant increase of Heat4 was validated in a larger cohort with HFrEF (n=64) compared to controls (n=39). Heat4 levels were negatively correlated to LVEF ($r=-0.45$, $p<0.001$) and associated with prevalence of HF (AUC=0.734, $p<0.001$) and death (AUC=0.789, $p<0.001$). Using MACS, we found Heat4 enriched in CD14+ monocytes and CD16+ cells. Monocytes can be differentiated in classical $CD14^{+}$ $CD16^{-}$ and non-classical $CD14^{-}$ $CD16^{+}$ populations that exert different immunomodulatory functions. Heat4 was enriched in non-classical monocytes, which have been reported to stay in the perivascular compartment and to release inflammatory cytokines. In contrast, ILRB was enriched in classical monocytes, which are known to be able to migrate through the endothelium into the tissue and differentiate to macrophages. Heat4 is located in the cytoplasm of monocytes consistent with a potential role as a RNA-binding molecule. The mRNA of the neighboring gene ILRB was upregulated after siRNA-mediated knockdown of Heat4 in monocytes. The lncRNA Heat4 is elevated in HF patients, being enriched in the cytoplasm of non-classical monocytes and regulates the mRNA of its neighboring gene that encode for the immune cell receptor ILRB.

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Poster 126

Evaluation of a luminometric cell counting system in context of Photodynamic inactivation

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Increasing antibiotic resistance of bacteria causes intensive research for alternative elimination methods against these pathogens. In addition to classical antibiotics, that inhibit bacterial growth by interference with specific bacterial structures, the photodynamic inactivation (PDI) constitutes a highly interesting alternative. Here, an in itself non-toxic often porphyrin-based photosensitizer binds to or is taken up by the bacteria. Upon illumination, these sensitizers induce the release of reactive oxygen species (ROS) especially singlet oxygen, that can inactivate bacteria independent from their antibiotic resistances. In this study, we analysed the effects of the photosensitizers TMPyP as blue light activated dye, on different bacterial strains of the ESKAPE pathogens by a luminescent based microbial cell viability assay that measures the amount of ATP in bacterial lysates as a correlate for bacterial number. We could show, that this method allowed the reliable quantification of bacterial concentrations solved in bacterial growth medium, comparable to that determined by established methods. Using this method, we could demonstrate that the PDI treatment susceptibility of different bacterial strains, including extensively drug-resistant pathogens (XDR, 4MRGN), is dependent on sensitizer concentration and illumination time. These results were confirmed by classical quantification of bacterial densities using culturing on agar plates. Furthermore, we could confirm the previously described blue light toxicity against MRSA even in the absence of photosensitizer. The evaluation of the assay in presence of dye and broth medium as a high throughput screening gives us a suitable instrument to detect previously limited information in photodynamic treatment.

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Poster 127

Isolation and cellular uptake of bovine milk derived extracellular vesicles

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Once considered as cell debris, *Extracellular vesicles* (EVs) have now gained substantial interest for their role in intercellular communication where they are known to deliver nucleic acids (e.g. miRNA) between cells, changing a cell's fate on a post-transcriptional level. Derived from cells, EVs are present in a variety of body fluids. We have chosen bovine raw milk as a source for EVs for both availability and functionality reasons. These have been shown to cross the intestinal membrane in nutritionally relevant doses making them interesting for drug delivery purposes [1]. Moreover, bovine milk is cost-efficient and available in large quantities, which are helpful conditions to shed light on the characteristics of these cell-released, membrane-enclosed structures and their detailed uptake mechanisms. Here we present a method to enrich bovine milk EVs via size-exclusion chromatography (SEC). The presence of EVs was confirmed by dot blot analysis of CD63 and transmission electron microscopy (TEM). According to the MISEV 2018 Guidelines from the International Society for EVs the isolation yield was estimated using a Bradford assay for total protein content, a sulfo-phospho-vanillin assay for the total lipid content and nanoparticle tracking analysis (NTA) for particle concentration. Further, we investigated the uptake of fluorescently labelled EVs in Saos-2 (human osteosarcoma) cells by CLSM. The uptake of bovine milk derived EVs in Saos-2 cells in these preliminary experiments makes them promising drug delivery systems, e.g. for local delivery in bone regeneration. Additionally, the variety of analytical methods applied creates a basis to further investigate their potential as drug carriers.

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Poster 128

The unfolded protein response in hypoxia/reoxygenation

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The unfolded protein response (UPR) plays a central role in actin cytoskeletal modulation (ACM) in hypoxia/reoxygenation associated stress. The UPR undergoes specific and ordered activation and de-activation during hypoxia-reoxygenation (H/R) and is tied to the actin cytoskeleton. The PERK arm of the UPR is active only during the hypoxic phase, while IRE1 activity is absent. Additionally, the actin cytoskeleton loses all definition within the cell resulting in severe disruption of the cellular monolayer and reduction of intercellular contact. During reoxygenation, PERK is quickly deactivated, and IRE1 signalling is strongly induced and regressively returns to basal six hours post reoxygenation. At this time, the cytoskeleton re-forms characteristic F-actin fibres. The use of an IRE1 inhibitor, Kira 6, prevents the recovery of the actin cytoskeleton. Using the PERK dimerizer GSK2606414 produces a similar effect. Furthermore, GSK2606414 prevents IRE1 activation during the reoxygenation phase. Thus, we show that the UPR plays an important role in the response and recovery of cells subject to H/R. We report that the activation of the UPR follows a pattern that is atypical to canonical ER stress and is tied to the actin cytoskeleton. Lastly, we report a novel relationship between PERK and IRE1 signalling during H/R.

Poster 129

ECV modified nanoparticles as a novel delivery system for small RNAs in cancer therapy

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Exosomes and extracellular vesicles (ECV) are actively taken up by target cells and may thus represent potential therapeutic drug delivery vehicles. Our study is dedicated to establishing a novel method for the introduction of therapeutic RNAs to human cancer cells using ECV-modified nanoparticles. ECVs were isolated from tumor cell culture for the delivery of small RNA molecules, i.e., siRNAs for the induction of RNA interference (RNAi) or antimiRs as efficient miRNA inhibitors, into tumor cells. We established an ECV purification protocol from cell culture supernatants. The ECVs were characterized by Nanoparticle Tracking Analysis (NTA) and Dynamic Light Scattering (DLS). Particle sizes and zeta potentials (surface charges) were measured, as well as particle concentrations, aggregation events and population distribution of ECVs in a liquid suspension. The siRNAs or antimiRs were complexed with low molecular weight polyethylenimine (PEI), and these PEI-based nanoparticles were then modified with the monodisperse ECV populations. ECV-modified PEI/siRNA or PEI/antimiR complexes were explored for the *in vitro* transfection of human tumor cell lines with siRNAs for gene knockdown (RNAi) or with antimiRs for miRNA inhibition. They revealed efficient knockdown of siRNA target genes or derepression of antimiR target genes, as determined in luciferase reporter assays or by RT-qPCR. Also, anti-proliferative effects were detected when targeting tumor-relevant genes like survivin. The analysis of the cellular uptake of ECV-modified PEI/siRNA complexes by FACS revealed differences when compared to their counterparts without ECV modification. All in all, our data demonstrate the usability of ECV-modified, PEI-based nanoparticles as efficient delivery system for small RNA molecules.

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Poster 130

Role of evolutionary conserved cold shock protein YB1 in unidirectional glomerular tubular communication in diabetic kidney disease

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Diabetic nephropathy (dNP) is a major cause of end stage renal disease, characterized by podocyte dysfunction and tubular dilation. A glomerular-tubular crosstalk as a driving pathomechanism in dNP has been suspected, but the paracrine signals remain largely unknown. As dNP is associated with inflammation and cold shock protein YB1 is known to modulate inflammation and renal disease, we speculated that YB1 contributes to dNP, potentially mediating glomerular-tubular interaction. The major goal of our study is to study the role of podocyte secreted YB1 in regulating inflammation in tubular cells in dNP. We used $YB1^{DPod}$ mice (podocyte specific YB1 knockout) and induced persistent hyperglycaemia using streptozotocin. As endpoints we analysed albuminuria as well as morphological and molecular changes associated with dNP.
$YB1^{DPod}$ diabetic (DM-$YB1^{DPod}$) mice displayed higher albuminuria and aggravated tubular dilation compared to DM-WT mice. Surprisingly, the mesangial area was reduced in DM-$YB1^{DPod}$ mice compared to DM-WT mice. These findings implied glomerular protection but enhanced tubular damage in DM-$YB1^{DPod}$ mice. The enhanced tubular damage was associated with increased expression of inflammasome activation markers in whole kidney extracts in DM-$YB1^{DPod}$ mice. We therefore hypothesized a protective paracrine effect of extracellular YB1 secreted from podocyte on tubular cells under hyperglycaemic condition. Mechanistically, pre-treatment of tubular cells with recombinant YB1 following LPS stimulation inhibits TLR4 mediated NF-κB and inflammasome activation *in vitro*, indicating that recombinant YB1 negatively modulates Toll-like receptor-4 (TLR4) signalling. These findings indicate that modified or recombinant YB-1 can be used as a potential therapeutic approach for dNP.

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Poster 131

Development of new antibody-based therapies against systemic amyloidoses

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It is increasingly recognized that post-translational modifications of amyloid proteins play a role in the formation and progression of human pathophysiological processes, such as Alzheimer‘s disease and systemic amyloidoses. The resulting proteins are particularly toxic because their proteolytic degradation is delayed and the proteins show a greater aggregation potential due to the increased hydrophobicity. In the past years, a special research focus of the Fraunhofer IZI-MWT has been the investigation of post-translational modifications such as the deamidation of asparagine or isomerization of aspartate to isoaspartate (isoD). This spontaneous and non-enzymatic reaction is considered to determine the half-life of proteins. Besides that, isoD-formation introduces an additional methylene group into the backbone of the protein or peptide, consequently altering its structure. This post-translational modification may also change the properties of proteins like solubility, conformation and function. We postulate that in analogy to the protein amyloid-β, the amyloid-forming proteins of the acquired or hereditary amyloidoses (i.a. transthyretin, serum amyloid A) could undergo post-translational modifications. The isoaspartate formation, which can remarkably be found in aged proteins, such as in deposits, is of particular interest. In addition, there are no therapies available that target organ damaging amyloid deposits. The goal of the scientific work is the production of therapeutic antibodies for the treatment of systemic amyloidoses or diseases associated with protein misfolding, deposition and fibril formation.

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Poster 132

The role of the RNA Splicing factor HRSP1 in Angiogenesis

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Alternative mRNA splicing is regulated by splicing factors which select introns and exons for the mature mRNA. Incorrect mRNA splicing is an important mechanism contributing to cardiovascular diseases. We created a coronary artery-specific expression score (CASS, arbitrary units) for a total of 680 RNA binding proteins (RBP). We used a large human transcriptome dataset of 53 different human tissues from a total of 11,467 human tissue samples, including 142 coronary arteries samples. A total of 82 RBP had a coronary artery-specific expression score ≥1.5. Among the RBP with the highest CASS, we found the myocardial splicing factor HRSP1 (CASS: 3.9). SiRNA-mediated knockdown of HRSP1 in human coronary endothelial cells reduced the formation of angiogenic sprouts in the network formation assay (38% ± 13% reduction vs control siRNA) as well as in the spheroid assay (64% ± 10% reduction vs control siRNA). To further characterize HRSP1 in angiogenesis *in vivo* we knocked down HRSP1 in a transgenic zebrafish line expressing GFP under the control of an endothelial-specific promoter, which marks the vasculature using injection of a Morpholino against HRSP1. Quantification of individual vessel phenotypes in Mo-HRSP1 treated zebrafish revealed significant reduction in vessel sprouting from the dorsal aorta (8% reduction), vessel crossing the ventral-dorsal midline (80% reduction) and in formation of dorsal longitudinal anastomotic vessels (19% reduction). In conclusion the myocardial splicing factor HRSP1 is enriched in human coronary arteries and has important functions for angiogenesis *in vitro* and *in vivo*.

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Poster 133

In vitro effects of cavitation induced by focused ultrasound in prostate cancer cells

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Introduction:
Focused ultrasound(FUS) is used for ablation of prostate tissue clinically, existing systems would profit from faster heating. Cavitation(C) is the rapid expansion, contraction and collapse of bubbles driven by cyclic change of the pressure in an acoustic field. The aim of this study is to characterize effects of FUS and C on prostate cancer(PCa).

Methods:
PCa cell line PC-3(ECACC) were cultured in FUS penetrable 96-well plates(Greiner bio one). FUS system was equipped with a 1.47MHz single FUS transducer. Cavitation dose was assessed with (i) terephthalic acid(Sigma) or (ii) hydrophone(Precision Acoustic). To investigate the synergistic effects of FUS with/without C to hyperthermia(HT) and radiation therapy(RT), cells were treated with FUS for 40s, water bath HT(45°C for 30min) and 10Gy X-ray irradiation(Gulmay).
Cell viability(WST-1 assay, Roche) and invasiveness (Transwell-Matrigel assay, Corning) were evaluated. Pore formation in cell membrane (Sonoporation) was detected with fluorescence staining by Propidium Iodide(PI, Sigma) and Cell Mask Stain(Thermo Fisher) during sonication.

Results:
C measurements showed in (i) and (ii) the occurrence of C at an acoustic intensity of 121W/cm2. C combined with HT or RT leads to reduced cell viability to 64%(C+HT) and 48%(C+RT) in comparison to C alone(86%). The potential of cells to invade was reduced to 41%(C+HT) and 33%(C+RT) compared to single treatment(C:77%; HT:68%; RT:54%) 48h after treatment. Cells in C group showed uptake of PI in 50% cells compared to 2% in untreated group.

Conclusion:
The study showed that C combined with RT or HT can remarkably inhibit PC-3 cell viability and invasiveness *in vitro*. The increased uptake of PI indicates sonoporation process what could be used in further studies for drug delivery.

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Poster 134

The adhesion GPCR GPR64/ADGRG2 is involved in the regulation of murine adipocyte differentiation and metabolism

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Expression and genome wide association studies have linked several adhesion GPCRs (aGPCR) to adipose tissue function and metabolic dysfunctions. Although RNAseq analysis of adipose tissue revealed high expression of numerous aGPCR, the physiological function in fat tissue still remains elusive. So far, only GPR116/ADGRF5 has been shown to modulate insulin sensitivity in adipocytes [1].
Previous work focused on the aGPCR expression during adipocyte differentiation using 3T3-L1 cells. Here, GPR64/ADGRG2 was found to be significantly upregulated, indicating potential functions of this aGPCR during differentiation. We showed that *Stachel*-derived peptide stimulation of GPR64/ADGRG2 activates the G_s protein/adenylyl cyclase pathway, which increases intracellular cAMP levels and stimulates lipolysis in both, the adipocyte model cell line 3T3-L1 and primary murine adipocytes. Furthermore, this activation of GPR64/ADGRG2 leads to a diminished adiponectin secretion as well as a lowered glucose uptake in mature 3T3-L1 cells.
Using a siRNA-mediated GPR64/ADGRG2 knock-down in 3T3-L1 cells we currently analyze the physiological function of GPR64/ADGRG2 in adipocytes. Thus, we are focusing on potential downstream effectors, which are related to lipolysis, glucose uptake, browning, and secretion of adipokines. Thereto, knock-down and wild-type 3T3-L1 cells are compared by using qPCR and Western Blot approaches. While our preliminary data highlight the previously unappreciated role of aGPCR in controlling the metabolic and endocrine functions of adipose tissues, current work will identify the specific physiological role of GPR64/ADGRG2 in adipocytes.

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Poster 135

Oligomer-Stabilized Calcium Phosphate Nanoparticles (CaP-NP) for Transfection of Brain Cancer Cells

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Introduction:
Convection-enhanced delivery (CED) is a minimal-invasive delivery concept for therapeutics through the narrow interstitial spaces of the brain via a pressure gradient needing stable NP <100 nm [1].

Aims & Objectives:
In this study, we investigated the ability of the amphiphilic oligomer O14PEGMA4410_NH_3 to stabilize NP and siRNA transfection of brain cancer cells.

Methods:
We prepared and loaded CaP-particles with siRNA by using nanoprecipitation. First, we analyzed the influence of different oligomer concentrations (2, 5, 10 µM) and siRNAs amounts (1, 10 µg) on size distribution using NTA and laser diffraction analysis. Transfection efficiency was investigated in rat glioblastoma cell line F98 by using survivin as a therapeutic target.

Results & Discussion:
We first analyzed the impact of different concentrations of oligomer and siRNA amounts on stability. We obtained NP below 100 nm using an oligomer concentration of 10 µM and 1 µg siRNA. The stabilization was not affected by serum proteins. We further analyzed stability in an artificial brain fluid. In this matrix, increased oligomer concentration of up to 40 µM were necessary to obtain stable CaP-NP <100 nm for at least 4 h. *In vitro* transfection efficiencies were analyzed for the F98 cell line. To this end, CaP-particles were loaded with survivin siRNA. CaP-particles showed satisfying *in vitro* transfection efficiencies as well as low cytotoxicity independent of oligomer concentration.

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Poster 136

Mononuclear cells release extracellular inflammasome complexes that induce pro-inflammatory signaling in endothelial cells

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Background and aims:
Inflammasomes are composed of a pattern recognition receptor, such as the NOD-like receptor pyrin-domain containing protein 3 (NLRP3), apoptosis-related speck-like protein (ASC), and the effector protease caspase-1. Here, we tested the hypothesis that NLRP3 inflammasomes can be released by circulating human monocytes into the extracellular space and induce inflammatory signaling in vascular cells.

Methods and results:
Stimulation of THP1 monocytes and of isolated primary human monocytes with lipopolysaccharide and nigericin activated the NLRP3 inflammasome and induced pyroptosis and the release of inflammasome complexes. Extracellular inflammasomes were isolated from cell-free supernatant and identified as inflammasome complexes by anti-ASC immunoblot. For functional characterization, isolated recombinant YFP-labeled NLRP3 inflammasome complexes were shown to be internalized by THP1 macrophages, endothelial cells and coronary smooth muscle cells (HCASMCs). Extracellular NLRP3 inflammasomes (eNLRP3) induced pro-inflammatory response in macrophages by increasing *IL-1ß* mRNA as well as IL-1β release. Treatment of HUVECs with isolated extracellular inflammasomes showed an increased expression of surface adhesion marker *Intercellular Adhesion Molecule 1* (*ICAM1*).

Conclusion:
Upon canonical NLRP3 Inflammasome activation, mononuclear cells undergo pyroptotic cell death and release inflammasome complexes into the extracellular space. Macrophages, endothelial cells and smooth muscle cells are able to internalize these extracellular inflammasome complexes that exert pro-inflammatory phenotypes. These findings support the concept that NLRP3 inflammasomes act as extracellular signal molecules triggering pro-atherogenic signaling mechanisms in vascular cells.

Poster 137

A novel TRPV3 blocker 26E01 inhibits TRPV3 channels functionally expressed in colonic epithelial cells

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The members of the transient receptor potential (TRP) channel family are crucially involved in the perception and processing of external stimuli like taste, olfaction and thermosensation. There is broad interest in identifying modulators of these channels, both to study their function and expression and to use these modulators to develop potential therapies for TRP-associated diseases. TRPV3 is a Ca^{2+}-permeable cation channel, which is prominently expressed in keratinocytes where it contributes to maintaining the skin barrier, skin regeneration, and keratinocyte differentiation but much less is known about its physiological function in other tissues. Therefore, we decided to explore the expression of TRPV3 in the gastrointestinal epithelium using the novel TRPV3-selective inhibitor 26E01. We identified 26E01 in a functional screen of the 16.671 drug-like compounds included in the ChemBioNet library. 26E01 blocks heterologous expressed mouse and human TRPV3 channels with an IC_{50} of 10 µM. We then evaluated TRPV3 expression in human colorectal carcinoma (CRC)-derived cell lines and in sections of the gastrointestinal epithelium via qPCR. The highest expression was observed in the distal colonic epithelium, followed by epithelia of the proximal colon, duodenum and stomach. We used electrophysiological patch clamp recordings and Ca^{2+} influx assays to demonstrate functional expression of TRPV3 in these cells. 26E01 did not show any toxic effects on CRC cells at concentrations of up to 100 µM, making it a useful tool to further study the physiological function of TRPV3 in the gastrointestinal tract.

Poster 138

Effect of Acidic pH on Wnt/ß-catenin signaling activation in esophageal epithelial cells

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Background:
Acid reflux is a major contributor in mucosal injury during gastroesophageal reflux disease (GERD). The molecular responses in GERD-injury, which result in Barrett's esophagus formation, are largely undefined. Wnt/β-catenin signaling is an important pathway for development and tissue homeostasis, while its dysregulation has been associated with tumorigenesis. We examined whether acid reflux activates the Wnt/β-catenin signaling in esophageal epithelial cells.

Methods:
Normal esophageal squamous cells (EPC1-, EPC2-hTERT) and a non-dysplastic Barrett's esophageal cell line (CP-A) were exposed to acidic media (pH 4.0) in a pulsive manner. Localization and levels of β-catenin were determined by Immunofluorescence staining and Western blot.
Wnt-activity was assessed by Luciferase assay. Immunofluorescence was used for β-catenin and E-Cadherin co-localization. Expression of β-catenin target genes was resolved by qRT-PCR.

Results:
Acid destabilized E-cadherin/β-catenin complexes in cell-cell junctions and resulted in β-catenin translocation to the nucleus. Wnt-activity correlated with nuclear translocation of β-catenin. Cytosolic shuttling of β-catenin occurred in a rapid and transient manner after acid withdrawal. Chronic pulsive acid exposure increased DKK1 gene expression in normal squamous cells but not in metaplastic columnar cells.

Conclusions:
These findings suggest that acid reflux induces β-catenin signaling in esophageal epithelial cells and that the DKK1-overexpression is the long-term response in the normal squamous esophageal tissue but not in the Barrett's esophagus. Our findings point out a homeostatic role of DKK1 during GERD injury, which may prevent the formation of Barrett's metaplasia.

Poster 139

New optogenetic tools in the fly: Characterization and application of next generation bPAC variants

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Optogenetics can be used to manipulate cellular processes with more precision and less invasively than by pharmacological means. This makes it the method of choice for many researchers in various scientific fields. Since the first report on channelrhodopsin-2 as a light gated cation channel, the optogenetic toolkit has now expanded to include ion pumps, anion channels, nucleotide cylcases, phosphodiestherases and voltage sensors.

Elevation of cyclic andenosine monopohosphate (cAMP) levels in cells or cellular compartments can be achieved using microbial photoactivated adenylate cyclases (PACs). Initially, a cyclase from *Euglena gracilis* was used until the focus shifted to the more powerful *Beggiatoa* photoactivated adenylate cyclase (bPAC). Still, many experiments require tighter control of cAMP production than bPAC can offer. Higher accuracy can be achieved by adjusting bPAC's activity in light or dark conditions or by enabling more precise subcellular localization, through mutations and fusions with membrane tags, respectively.

By making use of the experimental accessibility of *Drosophila melanogaster*, we present findings on newly engineered bPAC variants with improved localization and photostimulation properties for *in vivo* applications.

Poster 140

The flyPAD+ and the Panopticon - new behavioural assays to examine prandial signal action on Neuronal circuits

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The energetic state of an organism exerts its massive influence on behaviour on multiple levels, e.g. hunger reroutes energy expenditure to foraging activity; at the same time, food sensors are sensitized while bitter avoidance is lowered.

Neuropeptides play an integral part in relaying prandial signals, and many of them are evolutionarily conserved. To understand how these neuromodulators exert their pleiotropic effects will help to address feeding disorders more directly. A prandially relevant signal in fruit flies is the neuropeptide CCHa2, expressed in adipocytes, some midgut enteroendocrine cells and distinct brain neurons.

Previous reports have been contradictory in regard of the orexigenic or anorexigenic effect of CCHa2. We generated precise genetic knockouts of CCHa2 (CCHa2^{KO}) using CRISPR-Cas9 and tested them in a customized feeding assay to allow 24 h recordings (flyPAD+). Interestingly, starved CCHa2^{KO} flies consistently exhibited reduced initial feeding, followed by independent overeating later. This biphasic effect argues towards a higher-order role for CCHa2 in prandial motivation.

CCHa2 mutants were also reported to show reduced locomotion. To understand if the feeding phenotype of CCHa2^{KO} flies is consequence of their impaired activity as opposed to reduced feeding motivation we developed the Panopticon. An omnipresent food source allows to assess foraging-independent walking for >24 h, ruling out starvation-induced hyperactivity. Control flies were tested either on plain agarose or with spatially limited food patches for foraging-driven activity.

In summary, our suite of semi-automatic behavioral assays allows us to address where, when and how feeding quantity, quality and associated locomotion are influenced by internal state signals or subsets thereof.

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Poster 141

The influence of perineuronal nets on the aggregation and spreading of the Tau protein in Alzheimer´s disease

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Alzheimer´s disease (AD) is characterized by the formation of neurofibrillary tangles and senile plaques. The progression of these histopathological hallmarks follows a distinct spatio-temporal pattern. Interestingly, the distribution of pathological features is mainly restricted to specific brain regions and even types of neurons. Especially neurons ensheathed by perineuronal nets (PN) are protected against AD pathologies. PNs are matrix molecule assemblies mainly composed of chondroitin sulfate proteoglycans (CSPGs) which are supposed to mediate the neuroprotective properties of PN-ensheathed neurons. However, the underlying mechanisms remain elusive. Here, we aim at identifying the basic principles behind this selective neuronal vulnerability in AD.

First experiments in primary neuron cultures confirmed that PN-associated neurons are protected against internalization of recombinant, extracellular Tau-protein. In addition, treatment with the PP2A phosphatase inhibitor ocadaic aciddid not results in hyperphosphorylation or aggregation of Tau in PN-associated neurons. Still, immunohistochemical analysis of brains from CSPG mutant mice (aggrecan$^{+/-}$) crossbred with P301L mice (model for Tau pathology) revealed that the reduction of the aggrecan level has no effect on the vulnerability of PN bearing neurons for hyperphosphorylation of Tau.

These data indicate that CSPGs of PNs mediate their neuroprotective function on the extracellular level, potentially by inhibiting the internalization of extracellular Tau. Future experiments need to clarify whether the neuroprotective action of CSPGs can be transferred to neurons that are not naturally protected by PNs.

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Poster 142

Tau isoforms in the peripheral nervous system

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Alzheimer´s Disease is a progressive neurodegenerative disorder in the central nervous system. Histopathologically it is characterized by the presence of β amyloid plaques (β) and neurofibrillary tangles (NFTs). Thereby microtubule associated protein Tau (MAPT) is of great importance and main component of NFTs. In the healthy human brain, tau stabilizes the function and structure of microtubules. By contrast, in pathological form tau causes a depolymerisation of microtubules and induces a reduction of synaptic and axonal dynamics which ends in neuronal degradation. Tau aggregates and builds paired helical filaments (PHFs) which then assemble into NFTs. The aggregation of Tau is modulated by phosphorylation and the presence of specific tau isoforms.

In the adult human brain, tau has 6 isoforms which are alternatively spliced and occur to be found in different amounts. Exons 2,3, and 10 are spliced in different varieties.

The longest isoform counts 441 aminoacids and 14 exons. Every isoform carries either 3 or 4 microtubule binding repeats (3R/4R). These are said to play a big role in many tauopathies. 3R and 4R forms should always be in equation. If they come into an imbalance, for example, the grade of phosphorylation increases and causes dysfunction of tau. A lot of mutations in intronic splicing signals like in Frontotemporal Dementia and Parkinsonism linked to chromosome 17(FTDP-17) and in Pick's Disease (PiD) find their source in 3R and 4R imbalances.

Tau also has two more isoforms located in the peripheral nervous system. They show more heterogeneity by carrying exon 4a, 6 and 8 which are both very long. For this reason peripheral tau is named "Big Tau". Nothing much is examined on peripheral tau yet what leads us to give it more attention.

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Poster 143

Impact of high-fat high-sugar diet on dopaminergic gene expression and cognition in humans

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Obesity seems to be associated with dopamine (DA) signal transmission in the brain. In line, obese individuals show impairments in DA-dependent executive functions such as working memory and cognitive flexibility. Rodent literature suggests that a diet high in fat and sugar (HFS), even in the absence of obesity, induces alterations in DA signalling by affecting DA gene expression.
The open question addressed with this project is whether HFS has similar effects on gene expression and DA-related cognition in humans, independent of obesity. However, accessing human central DA is challenging. Hence, as literature indicated white blood cells as a promising proxy for analysing central gene expression, leukocytes were used as a surrogate tissue for the human brain.
We recruited male healthy participants aged 18 to 37 years following a diet high (HFS) or low (LFS) in fat and sugar as assessed by the Dietary Fat and free Sugar Questionnaire (DFS). The diet groups are matched for age, BMI and IQ. Blood samples were drawn to analyse the mRNA expression levels of genes within the DA signalling pathway: DA receptors 2, 3 and 5; dopamine-and-cAMP-regulated-neuronal-phosphoprotein-32 (DARPP-32); DA transporter and catechyl-O-methyltransferase (COMT).

Additionally, participants performed three cognitive tests assessing the executive functions working memory, attention, and cognitive speed and cognitive flexibility. With a sample size of 41 participants in the HFS and 34 in the LFS group we are cross-sectionally investigating the effect of diet on peripheral gene expression linked to DA-dependent cognitive performance. First preliminary results indicate a dietary effect on the expression levels of DA transporter and DA receptor D3 while differences in cognition could not be observed.

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Poster 144

Salt learning in Drosophila Larvae

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The ability to learn from past events and apply them to future situations can determine life and death of an organism. In 1985, Tully and Quinn showed that even an inconspicuous organism such as adult *Drosophila* is able to learn situational information and develop memory. Since then, much has been done in this field and *Drosophila* has been established as a generally valid model organism for learning and memory.
In particular, the *Drosophila* larva offers unexpected advantages: firstly, the availability and robustness of the larvae for behavioral experiments; secondly, the anatomical simplicity of the larval central nervous system, which consists of only about 10,000 neurons; furthermore, the almost unlimited variety of genetic tools which make it possible to activate or silence individual neurons.
All advantages - together with the latest publication of the connectome – make the larva a popular object of choice in neurogenetics. Above all, the insect mushroom body (MB) is a central unit when it comes to sensory input, processing, and behavioral output.
It has been shown that the MB consists of eleven compartments, all of which have a limited number of specific neuronal inputs (MBINs) and outputs (MBONs) - these MBINs can be either dopaminergic (DAN), octopaminergic (OAN), or of unknown identity.
Here, we analyzed different mushroom body input neurons to test their significance in salt-dependent aversive classical olfactory conditioning by using the Split-GAL4-UAS system to ablate MBINs at cellular resolution.

Our results reveal that an aversive salt-dependent memory is not formed by a single input neuron, rather presumably by an integral network of input neurons in the vertical lobe of the mushroom body.

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Poster 145

Comparison of SMA mouse models reveals proprioceptive synapses as a key component of motor circuit pathology

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Patients with Spinal muscular atrophy (SMA) suffer from muscle atrophy, motor neuron death and motor impairment. These impairments of the motor circuit are closely recapitulated in SMA mouse models. The most frequently used SMA model is the *SMA-Delta7* mouse which shows that proprioceptive synaptic loss leads to motor neuron dysfunction, whereas motor neuron death is mediated cell autonomously. The next step to identify the patient-relevant outcomes of the motor circuit pathology found in *SMA-Delta7* mice is their validation in other SMA mouse models.

Therefore, we investigated the motor circuit pathology in the commonly used SMA *Taiwanese* and *Smn2b*/- mice model. For morphological analysis of the motor circuit, we performed confocal analysis following immunohistochemistry on the differently affected spinal cord segments and muscles. Vulnerable spinal cord segments revealed ~50% motor neuron death in *SMA-Delta7* mouse, whereas the *Taiwanese* mice revealed ~20% and the *Smn2b*/- ~30% loss compared to controls.
Next, we investigated the degree of NMJ denervation in the proximal vulnerable muscles. NMJ denervation of *SMA-Delta7* mice was 50%, ~25% in the *Taiwanese* and *Smn2b*/- mouse models, while the resistant muscles are completely unaffected. Interestingly, in contrast to variable degrees of motor neuron death and NMJ denervation, 70% of proprioceptive synapses are consistently lost in all SMA mouse models compared to wild-type controls.

Here, we show that different SMA mouse models exhibit a variable degree of selective motor neuron death and NMJ denervation. In contrast, significant proprioceptive synaptic degeneration is constant among all mouse models, suggesting central synaptic loss as a key component for motor circuit pathology in SMA mice and patients.

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Poster 146

Correlation of the progression of tau pathology with the presence of selected tau modifying enzymes

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One common form of dementia is the frontotemporal dementia (FTD), which belongs to the subgroup of tauopathies. Subject of this work was the investigation of a mouse model of FTD.
In this model due to a pathogenic missense mutation in the microtubule-associated tau protein gene (MAPT gene) via a replacement of proline for leucine at site 301 (P301L mutation) deposition of aggregated and insoluble tau protein (TP) is occurring in the brain. In my work, the progression of TP pathology was studied at 2 different ages (2 months and 10-11 months) and in both sexes in 14 neuroanatomical regions. Transgenic mice (hTauP301L$^{+/+}$ / mTau$^{-/-}$), wild type mice (mTau$^{+/+}$) and knockout mice (mTau$^{-/-}$) were examined by immunohistochemistry, westernblot and ELISA. In order to observe the changes and the spreading of the TP, three forms of TP were determined: the total amount of TP, the amount of phosphorylated TP and the amount of aggregated TP.
Additionally, three proteins/ enzymes which may influence the spreading of the TP pathology in the brain have been investigated. The proteins studied were the proteoglycan aggrecan, the E3 ubiquitin ligase adapter protein gigaxonin and the AMP-related kinase-5. Colocalization with pathologically phosphorylated TP was investigated in all 3 proteins/ enzymes.

In this study we found a strong heterogeneity regarding the TP between the studied neuroanatomical areas as well as between the different transgenic mouse groups. It could also be shown that female mice are generally more affected by the TP pathology. For the investigated TP influencing proteins and enzymes no co-localization could be found.

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Poster 147

Deep Neural Network-Based Automated Segmentation of Synapses in Electron Microscopic Images

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Synaptic plasticity involves both activity-dependent and homeostatic changes in the strength of synaptic transmission. These changes can be caused by changes in the physiology as well as the morphology of the synapse. At glutamatergic synapses, morphological features include bouton morphology, the number and location of synaptic vesicles, the length of the active zone and of the postsynaptic density as well as the shape of the dendritic spine. Here we show how deep neural networks [1] can be used to automatically segment and quantify pre- and postsynaptic features in electron microscopy (EM) image stacks.

References:
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Poster 148

CG15744, a novel adhesion GPCR in *Drosophila melanogaster*

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Adhesion G-protein coupled receptors (aGPCRs) are a class of cell surface receptors involved in several physiological processes. Knowledge on the aGPCR GPR124 has gained relevance due to its role in angiogenesis and the formation of the blood-brain-barrier (BBB). The nervous system is made up of are two large classes of cells; neuronal and glial cells. Glial cells have a major role in the formation of the BBB in both vertebrates and *Drosophila melanogaster*. *Drosophila* has been used for many years as a model for genetic studies but, only two aGPCR have been thoroughly characterized so far. In the past few years three novel aGPCRs were discovered. This includes the protein encoded by the gene *CG15744*, a homologue of GPR124 located on the X-chromosome.

This study aims to focus on the physiological and molecular characterization of *CG15744* and to develop a new *Drosophila* model that can be used for future studies on aGPCRs. Expression and localization studies were conducted using flies expressing *13XLexAOp 2-6XmCherry* under the control of *CG15744-T2ALexA*. Preliminary data shows *CG15744* is expressed throughout the life cycle of the fly, specifically in the CNS and gonads of both sexes. In addition, the results also suggested a stronger expression of *CG15744* in the male CNS compared to females. Using the same flies, dissected adult brains were immunostained with Repo, a nuclear glial marker. The results suggest that *CG15744* appears to be expressed in the glial cells of the CNS and thus potentially have a role in the development of the BBB in *Drosophila*. Based on the preliminary data, it appears that *CG15744* may have an important role in the CNS of *Drosophila*.

Poster 149

The role of octopamine during reward processing in *Drosophila* larvae

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Octopamine (OA) is a biogenic amine which serves as neurotransmitter, neurohormone and neuromodulator among invertebrates and is functionally analogue to the vertebrate noradrenaline. OA acts as a neuromodulator in many different processes such as sleep, feeding, learning or other complex behaviours. Learning and memory in particular is based on past experience and enables an organism to adapt its behaviour to present circumstances which is crucial for any animal. Olfactory learning of *Drosophila* larvae takes place within the mushroom body (MB).
Initially, octopamine neurons (OANs) were thought to signal reward, whereas dopaminergic neurons (DANs) mediate punishment within the brain during conditioning. However, according to recent results, a distinct set of dopaminergic neurons are also involved in reward-signalling. Thus, the current assumption of a functionally separated model of OANs and DANs during reward-signalling has to be overturned, because of the limited function of OA.
Therefore, the following question arises: What does the octopaminergic system really do during reward processing? Employing microfluidics – a variant of calcium imaging – OANs could be identified responding to Arabinose and Fructose. These sugars are also used as a reward during conditioning. In combination with new available Trojan Gal4 lines for different OA receptors we characterized, our finding allows us to gain more insights into the signalling pathway upstream of the MBs, that is required to mediate reward information during memory acquisition.

Poster 150

Effect of Auranofin on TDP-43 self-interaction in pathogenesis of amyotrophic lateral sclerosis

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TDP-43 aggregation represents a critical step in the neurodegeneration of motor neurons in amyotrophic lateral sclerosis (ALS). Physiologically, TDP-43 is involved in regulation of RNA transcription in the cell nucleus. During stress, TDP-43 translocates from nucleus into the cytoplasm where it physically interacts with itself forming dimers prior to the development of so-called stress granules (SGs). Under chronic stress, SG formation serves as seed for pathologic cytoplasmic TDP-43 aggregation. We found that TDP-43 self-interaction is significantly reduced under treatment with the gold thiolate compound auranofin.

We aimed to understand how auranofin is able to inhibit TDP-43 self-interaction and to modulate the role of TDP-43 in SG formation. We used a NanoBit luciferase protein interaction assay, imaging analysis with EM-CCD-based microscopy and CFTR exon 9 splicing assay to evaluate the auranofin effect on TDP-43 self-interaction, intracellular localization, and splicing activity.

Auranofin treatment modifies formation of TDP-43 positive arsenite-induced SGs and results in formation of small partially TDP-43 positive cytoplasmic granules. It does not block physiological TDP-43 function on CFTR exon 9 splicing in contrast to the oxidative stressor arsenite. Thus, auranofin modifies TDP-43 mediated SG formation without interruption of physiological TDP-43 function, which makes it a potential drug for repurposing in ALS therapy.

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Poster 151

The Role of GlyT1 in Treatment of Chronic Pain

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Chronic pain is a disease, impairing severely quality of life of affected individuals. In Germany, approximately 6% of the population is suffering from neuropathic pain, a chronic pain isoform involving maladaptation of the somatosensory system that is currently difficult to treat. Thus, the identification of new treatment strategies is enormously urgent.

The amino acid glycine has important neurotransmitter functions in the CNS where it mediates synaptic inhibition. The glycine transporter 1 (GlyT1) has been shown to control the extracellular glycine concentration and constitutes a promising target for the modulation of neuronal inhibition in the context of chronic pain. A new pharmacological approach was successfully tested.

The specific and reversible GlyT1 inhibitor Bitopertin, originally developed for the treatment of schizophrenia, revealed an antihyperalgetic and antiallodynic effect in animal models for chronic pain both after single dose or long time application with osmotic minipumps, whereas no side effects were observed. To analyze the precise mechanism resulting in this effect, we are establishing an animal model allowing a cell type, regional and time specific knock out of the GlyT1 gene in the spinal cord by a viral based approach. In Cre reporter mice, stereotactic injection of adeno associated viruses for glia specific expression of Cre recombinase into the 4th lumbar vertebral segment of spinal cord resulted in efficient reporter expression. Similar experiment will be performed in mice carrying a floxed GlyT1 allele to analyze the consequences of GlyT1 loss on acute and chronic pain perception. Taken together these experiments will elucidate the mechanism how GlyT1 inhibition ameliorated the facilitated pain responses in the context of chronic pain.

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Poster 152

Analysis of tau protein levels in hibernating Syrian hamsters - an animal model of paired helical filament like phosphorylation

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Alzheimer‘s disease (AD) is a progressive neurodegenerative disorder. The establishment of clinical *in vivo* diagnosis of AD remains a challenge as the gold standard is the post-mortem histopathological evaluation of brain tissue. In the past years, the involvement of modern imaging techniques and the analysis of disease-related markers in the CSF have increased both the sensitivity and specificity of clinical AD diagnosis.

However, the application of these methods is limited by restricted access, high costs, its invasiveness and uncomfortable sample taking. There is the demand for the development of inexpensive and minimally invasive test platforms that can easily be incorporated in the clinical practice. Analysis of blood-based biomarkers fulfils these criteria and could potentially assist clinicians in the diagnosis of AD.

One of the major histological hallmarks of AD is neurofibrillary tangles, being constituted largely of hyperphosphorylated tau protein. AD-like hyperphosphorylated tau protein has been demonstrated in the brain of hibernating Syrian hamsters that were in torpid state. Therefore, we used hibernating hamsters as a model to evaluate the feasibility of the analysis of phosphorylated tau protein in peripheral blood samples. Serum samples were obtained from torpid state hibernators and non-hibernators euthermic state hamsters and analysed by tau- and phospho-tau-specific ELISA technique.

Poster 153

Construction of a 3D brain extracellular matrix model to study immune cell interactions in co-culture

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Neurodegenerative disorders are partly characterized by the activation of brain-resident microglia cells and by the infiltration of other immunocompetent cells such as T cells. However, their specific role and their interplay in disease are not clarified. 2D cell culture models do not resemble the soft 3D nature of brain tissues. Furthermore, it is difficult to investigate and manipulate complex cellular dynamics in living animals.
Therefore, we developed a biomimetic three-dimensional (3D) *in vitro* culture system for co-cultivation of microglia and T cells for the prospective study of their interaction under disease-related conditions. Since the activation and/or migration of immune cells in the brain might be affected by components of the extracellular matrix, defined 3D fibrillary collagen I-based matrices were constructed and modified with hyaluronan and/or chondroitin sulphate, resembling aspects of brain extracellular matrix.
Murine microglia and spleen-derived T cells were cultured alone or in co-culture on the constructed matrices. Microglia exhibited *in vivo*-like morphology and T cells showed enhanced survival when co-cultured with microglia. Both cell types invaded the 3D matrix to a different extent. The cells showed no changes in survival or behavior in dependence of the matrix modifications. Microglia could be activated on the matrices by lipopolysaccharide and responded with interleukin-6 and tumor necrosis factor-a expression and nitrite formation.
To our knowledge this is the first report on a 3D co-culture system of microglia and T cells. The findings herein indicate that cultivation on 3D matrices elicits *in vivo*-like behavior from both immune cell types as opposed to 2D culture and provides a useful tool to study their interaction *in vitro*.

Poster 154

Ethanol sensing in *Drosophila* larvae

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Drosophila melanogaster shows a remarkable tolerance to dietary ethanol as they feed on fermenting plant materials in which ethanol is the most abundant alcohol. The ingestion of ethanol has several benefits, such as improved mating success and fecundity in adult flies. Additionally, *Drosophila* larvae show an increase in weight and protection from natural parasites such as endoparasitoid wasps. However, the effect of ethanol on larval development, behaviour as well as the sensory processing is still unclear. Therefore, our aim is to answer the questions: (1) Do *Drosophila* larvae perceive ethanol? (2) Which sensory system is involved in the perception of it? (3) How is this system correlated to the brain function of the larvae?

To address these questions, we performed two-choice behaviour experiments to examine larval preferences for different concentrations of ethanol. For these experiments we used multiple strains of *D. melanogaster* (wildtype *CantonS*, *anosmic* mutants, *orco2* mutants) to identify putative ethanol receptors. Furthermore, we conducted learning experiments with ethanol-exposed and non-exposed *Drosophila CantonS* larvae to investigate the influence of ethanol on cognitive functions.

Our results of the two-choice behaviour test show a preference for ethanol with a strong peak at 8% ethanol for *CantonS* and *orco2*. In contrast, the *anosmic* mutants did not show a significant ethanol preference.

Furthermore, learning experiments indicate that *CantonS* perceive 8% ethanol as rewarding as it reinforces an appetitive association. Our results represent a fundament for the identification of the ethanol perception system in insects and may well radiate beyond the *Drosophila* and insect community given the evolutionary conserved function of ethanol throughout the animal kingdom.

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The Characterization of a GlyT1b/c Reporter *knock-in* Mouse

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Glycine acts as a neurotransmitter in the CNS. Its extracellular concentration is strictly regulated by high affinity glycine transporters (GlyTs). GlyT1 is expressed throughout the CNS, by glial and neuronal cells, presumably facilitating the clearance of glycine from the synaptic cleft at inhibitory synapses and acting as a modulator of the glycine concentration at NMDARs at excitatory synapses.

From human GlyT1 encephalopathy patients and a Glyt1 KO mouse model it is known that lack of GlyT1 function results in elevated CSF glycine concentrations and severe neonatal respiratory deficits. Additionally, conditional knock-out models revealed cell-type specific functions of GlyT1. Based on these results, it was presumed that different transporter subtypes (GlyT1a, b, and c), which are encoded by a single gene but controlled by different promoter elements, are expressed by different cell types and thus fulfill different functions. Here we introduce a GlyT1b/c reporter *knock-in* mouse, to elucidate the expression and function of these transporter subtypes *in vivo*.

Reporter analysis of GlyT1b/$c^{ki/ki}$ mice revealed highest expression in spinal cord, which could be corroborated on mRNA and protein level. Adult GlyT1b/$c^{ki/ki}$ mice showed a 80% reduction in GlyT1 expression and elevated CSF glycine levels similar to that seen in human patients.

GlyT1b/$c^{ki/ki}$ mice are smaller and lighter than their age-matched wildtype littermates and present hypoactivity, with intermittend spastic episodes including tremor. Analysis of the respiratory rhythm revealed slower and more regular breathing than that observed in control animals.

Taken together our data show that GlyT1 has important functions for the regulation of the extracellular glycine concentration also in adult animals.

Poster 156

Characterization of numerical chromosomal aberrations (copy number variations) in Alzheimer's disease brains using *in situ* hybridization.

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Alzheimer's disease (AD) is one of the most common neurodegenerative disorders worldwide. The neuropathology of this disease describes a progressive degeneration of neurons in human brain. The nerve cells degeneration is associated with formation and deposition of extra- and intracellular aggregates of β-amyloid-plaques as well as the hyperphosphorylation of microtubule-associated tau protein, thereby forming neurofibrillary tangles.
However, the primary cause of Alzheimer's disease is still unknown. New approaches assume, that the root of pathogenic cascades rest on higher incidences of aneuploidy states of neurons in AD-brains. Furthermore, large copy-numbers of certain DNA-fragments, (copy number variations; CNVs), have been observed in brain cells of AD-patients.
They might occur due to faults in the DNA replication process, or at least DNA repair. We hypothesize, that disturbances of cell-cycle protein regulation can lead to neuronal cell death. Thus, the project aims to investigate the occurrences and quantity of CNVs in different parts of the human brain. AD- and control brain section have been examined, qualitatively and quantitatively, with chromogenic and fluorescence *in situ* hybridization (CISH, FISH) using probes detecting parts of different chromosomes which had previously been identified by single cell DNA sequencing.
The examination also includes combinations of *in situ* hybridization and immunohistochemistry. Using these methods we are currently analyzing if aneuploid neurons are occurring in clusters, emerging more often in certain regions of the human brain or being localized nearby pathological protein deposits.

Alzheimer Forschung Initiative (AFI) is supporting this project (HippoGenAD, AFI/17021; 984000/222).

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Poster 157

Alzheimer's disease brain shows altered layer-specific gene expression pattern in temporal cortex

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RNA in healthy human brain is characterized by a strong heterogeneity and diversity, which both are at least partly caused by the interplay of a complex cellular composition and a mixture of universal and individual functional specificities including memory formation.
Recent data suggest that different neurodegenerative diseases, e.g. Alzheimer's disease (AD), show disturbances of RNA metabolism, which seems to have more impact on disease initiation and progression than initially assumed. Unfortunately, underlying RNA data only roughly describe differences between diseased and healthy human brain and did not provide layer-specific or even cellular resolution of RNA alterations. Moreover, published studies mainly focused on expression levels of mRNAs neglecting their 5' and 3' untranslated regions (UTR), which are known to be highly variable and especially divers in human brain.
Accordingly, we started to examine layer-specific RNA expression of human temporal cortex, a brain region very early involved in AD progression, and included 3' UTR in our bioinformatic analysis. For our approach we used high throughput sequencing of RNA (Illumina®) and direct RNA sequencing (Nanopore®). We established and performed laser-capture microdissection to specifically isolate brain tissue from external pyramidal layer III, internal pyramidal layer V+VI and white matter area of control and AD brains. After RNA preparation, ribosomal RNA depletion provided the basis for sequencing. We used a bioinformatic pipeline and UCSC genome browser to identify layer specific gene expression patterns. Our approach facilitates the evaluation of inter- and intraindividual changes of RNA metabolism in AD brain compared to age-matched controls.

The project was supported by SAB/EFRE (BBZ-011, RNABioDiag).

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Poster 159

Development of a neuronal *in vitro* ischemia model

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Under ischemic conditions, affected cells do not have enough oxygen and glucose available for metabolism. This deficiency leads to the activation of cellular signal cascades leading to cell death. The mechanisms of ischemia can be studied in cell culture under conditions of oxygen and glucose deprivation. Importantly, different cell types display specific vulnerability to ischemic conditions.

The aim the present study was to determine the ischemic period required to induce death of 50% of cultured cells. Therefore, the viability of differentiated mouse Neuro-2a (N2A) cells and of mouse primary neurons was analysed after ischemic periods for 0.5, 1, 2 and 4h and further cultivation for 24h under standard conditions. For quantitative analysis of viability and cell death, MTT and LDH assays were used. In addition, changes in number and length of neurites were quantified using immunocytochemical stainings.

An increase in extracellular LDH activity and a concurrent reduction in intracellular MTT conversion were observed with longer ischemic periods. N2A cells showed a 50% cell death after 2h of oxygen and glucose deprivation. After 4h of ischemia nearly 90% of the cells were dead. Similar results have been achieved in primary neurons, although there was a tendency for higher vulnerability compared to the N2A cell line. The number and length of neurites of differentiated N2A cells also decreased with longer period of ischemia. N2A neurites declined from 80% under normoxic conditions to 20% after 4h of ischemia.

Thus, we show that the duration of ischemia determines viability of N2A cells and primary neurons after further cultivation. A 2h oxygen/glycose deprivation period appears to be practical to study pharmacological/genetic interference with neuronal survival

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Poster 160

The Propacetamol metabolite N,N-diethylglycine and its influence on glycinergic neurotransmission as an allosteric modulator of GlyT1 in treating neuropathic pain

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Background:

Treating neuropathic pain is still challenging. Here, “classical” painkillers such as cyclooxygenase inhibitors or opioids are barely effective and come with severe side effects in higher dosage. Therefore, new pharmacological strategies are urgently required.

A novel approach is the enhancement of glycinergic neurotransmission by either facilitating glycine receptors (GlyR) or inhibiting glycine transporter (GlyT) function to increase extracellular glycine concentration, which has been shown to ameliorate pain symptoms in animal models for neuropathic pain. In this study, we analyzed, if the propacetamol metabolite N,N-diethylglycine (DEG) binds and influences GlyRs or GlyTs and thereby might be a suitable tool to influence glycine dependent neurotransmission *in vivo*.

Methods:

Substance induced currents were determined using the two-electrode-voltage-clamp (TEVC) technique on Xenopus laevis oocytes, expressing glycine transporters (1, 2) and glycine receptor subunits (α1-3) individually. Current responses of GlyTs and GlyRs after DEG application were compared to the maximal inducible amplitude after application of 1 mM glycine solution.

Results:

DEG did not show any effect on glycine receptor and GlyT 2 function, but seems to affect GlyT 1: Although single dose application in absence of glycine did not lead to reproducible current responses, coapplication of DEG with glycine resulted in a significant potentiation of the glycine induced amplitudes even exceeding the previously recorded and supposed V_{max} of the GlyT1.

Discussion:

Obtained Data suggest that DEG acts as an allosteric modulator on GlyT 1, but not as a substrate by itself. Future studies must address the effects of DEG on glycine dependent neurotransmission *in vivo*.

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Poster 161

Next generation candidates – deciphering the monogenetic causes of neurodevelopmental disorders

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With the help of exome sequencing (ES), the spectrum of monogenetic causes of neuro-developmental disorders (NDD) has been substantially advanced in the last decade but still countless pathomechanisms and pathogenic genetic variants are not yet described.

The goal of this study is to identify novel genes of NDD in 100 individuals, in whom no disease causing variants have been found in standard diagnostic settings. Using trio ES and comparing the patients with their parents, an evaluation of de novo variants as well as autosomal recessive and X-linked variants is possible. We then apply our in-house scoring system, considering variant and gene attributes, literature research, and inheritance, in order to set an objective parameter of the plausibility of the identified candidates. After sharing of candidate genes with the scientific community via platforms like GeneMatcher, we seek out collaborations to validate candidate genes, with the help of functional analyses or strong genotype-phenotype associations. Thus we aim to broaden the spectrum of known genetic causes of NDD and offer a genetic diagnosis for our patients.

Over the course of 2 months, 50 trio exomes have been evaluated and 23 families with candidate genes for NDD have been identified. The most noteworthy findings so far include (1) a *de novo* missense variant in *GNAI1*, which we already contributed to an ongoing international collaboration, (2) a *de novo* missense variant in *RHEB*, a promising candidate gene, where only two cases have been reported in the literature, and (3) a homozygous nonsense variant in *BDP1*, a strong candidate gene for autosomal recessive NDD.

Until the Leipzig research festival, we aim to expand our candidate gene list and will present the most promising results.

Poster 162

Child abuse and the Interpersonal Psychological Theory of Suicide: A Network Analysis

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Background:
While there is evidence for an association of child abuse with suicidal behavior, underlying mechanisms remain unclear. The Interpersonal Psychological Theory of Suicide (IPTS) states that the presence of feelings of social alienation (*thwarted belongingness*, TB) and the perceptions of being a burden for others (*perceived burdensomeness*, PB) lead to suicidal ideation. To enable an individual to act on these thoughts, capability for suicide (CS) is required. The current study intends to investigate the network of child abuse and suicidality in adulthood using the IPTS.

Methods:
145 psychiatric inpatients (M = 37.8 years, 62% female) with an acute suicidal crisis (n = 71) or a recent suicide attempt (n = 74) were included and examined at baseline, 6 months and 9 months later. We used the Childhood Trauma Questionnaire (CTQ), the German version of the self-injurious thoughts and behaviors interview (SITBIG), the German Capability for Suicide Questionnaire (GCSQ) and the Interpersonal Needs Questionnaire (INQ). Using the statistics program R, a network analysis was conducted.

Results:
Emotional abuse shows up as the central variable in the network. It is significantly related to sexual (r = .22) and physical abuse (r = .45), PB (r = .20) and suicidal behavior (r = .24). Physical and sexual abuse showed no significant relations with the different variables of the IPTS. CS was negatively related to suicidal behavior six months later (r = -.24).

Discussion:
The negative relationship between CS and suicidal behavior is not in line with the assumptions of the IPTS. Regarding child abuse, the results underline that emotional abuse plays a central role and may be important for suicide risk assessment.

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Retest Reliability of a Probabilistic Reversal Learning Task: Readouts from Raw Behaviour

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Dimensional psychiatry aims to improve psychiatric diagnoses by characterising psychopathology in terms of the functionality of core psychological constructs such as cognitive control and reward learning. However, while there are robust paradigms available from experimental psychology to probe those core domains, there is less knowledge on whether their readouts are reliable enough to be used as markers of individual differences.

Indeed, there seems to be an indication that some may be unreliable by design because they are specifically tailored to reduce between subject variability. In this study, we probed the retest-reliability of measures derived from a probabilistic reversal learning task designed to tap into flexible behavioural adaptation. 40 healthy participants (20 male) aged between 19 and 38 years (M=26.45, SD=3.88) completed the task twice with a 1-week gap between sessions.

Results suggest differential reliability of the behavioural readouts: it was poor for accuracy (ICC(A,1)=.48), moderate for switching after wins (ICC(A,1)=.67), and good for switching after losses (ICC(A,1)=.77). The analyses show that the readouts reliably index individual differences in behaviour in response to negative outcomes but, surprisingly, less so in response to positive outcomes.

We also discuss why reliability drops for accuracy and how to improve this as well as other aspects. Further, we are currently testing the reliability of process variables derived from computational modelling using a reinforcement learning algorithm to extend our findings.

Poster 164

Quality of life and associated factors after surgical treatment of vulvar cancer by vulvar field resection (VFR) with therapeutic lymphonode dissection and anatomical reconstruction (AR)

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Vulvar field resection (VFR) is a new surgical approach for vulvar cancer to improve local tumor control and to lower treatment-related morbidity. It is based on the embryologic origin of the vulva and the theory of ontogenetic cancer fields. VFR is completed by therapeutic lymphnode dissection and anatomical reconstruction (AR) of the vulva. In contrast to standard surgical treatment adjuvant radiation is not necessary. Survival of this new concept is superior compared to conventional treatment strategies. To examine whether patients quality of life (QoL) also benefits from VFR with AR we evaluated QoL in our patients.

Methods:
All patients alive treated with VFR in our prospective VFR study were interviewed with regard to long-term complications. Further, they were asked to complete the standardized QoL questionnaire EORTC QLQ-C30, the German Gynecologic Cancer Lymphedema Questionnaire GCLQ and a questionnaire evaluating sexual activity.

Results:
The mean global QoL of the 43 patients reached 66,1 (+/-25.5) points on a scale ranging from 0 to 100. Impairments through lymphedema were associated with a significant loss of QoL (Spearmans Rang Correlation **ρ**= -0,7; p<0,0001). Also preoperative co-morbidities as well as complicated wound healing were affected the QoL negatively (Wilcoxon test (p < 0,01).

Conclusions:
QoL of vulvar cancer patients treated with VFR is comparable to the QoL of a healthy German reference cohort. Lymphedema, impaired wound healing and preoperativ co-morbidities correlated significantly with a lower QoL.

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Adherence as a predictor of dropout in Internet-based guided self-help for adults with binge-eating disorder and overweight or obesity

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Objective:
Internet-based guided self-help (GSH-I) is an efficacious treatment for adults with binge-eating disorder (BED) and overweight or obesity. Although broadly accessible, high dropout from GSH-I has been reported. However, little is known about the factors explaining dropout from GSH-I, including patients' adherence to treatment.

Method:
Within a randomized trial on the treatment of BED, adherence to 4-month GSH-I was objectively assessed in $N = 89$ patients with BED and overweight or obesity. Objective adherence and subjective treatment evaluation were evaluated as predictors of dropout from GSH-I, defined as having accessed five or less of 11 modules. Cut-offs with optimal sensitivity and specificity were derived using Receiver Operating Characteristics curves analysis, and baseline sociodemographic and clinical correlates were determined.

Results:
According to our definition, $n = 22$ (24.7%) patients were defined as dropouts. Results of the full logistic regression model accounted for 72% of the variance in dropout and all objective adherence parameters (i.e., number of messages exchanged, days with a completed food diary, and days spent per module), but not patients' subjective GSH-I evaluation

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significantly predicted dropout. Specifically, not completing the food diary in week 7 had maximized sensitivity and specificity in predicting dropout. Patients' body mass index was positively associated with the number of messages exchanged between patients and coaches. No other associations between baseline variables and objective adherence were found.

Discussion:
Patients at risk for dropout from GSH-I can be reliably identified via monitoring of objective adherence and may be provided with additional interventions to prevent dropout.

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Peer2Me - A Peer-Support Program for adolescent and young adult cancer patients

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Background:
Past studies have shown that social support during cancer in young adulthood is of central importance. The exchange with other young patients who have already survived the disease is particularly desirable.

Design:
In the pilot study, started in January 2019, AYA cancer survivors (18-39 years) will act as peer mentors and support young adults with acute cancer for a period of three months in a personal one-to-one contact. The mentors are prepared in a 2-day training course which includes teaching of suitable conversation techniques, identification as a mentor as well as basics of Motivational Interviewing. The participation in monthly group supervisions is obligatory for the mentors. Using standardized questionnaires and qualitative interviews, first results on feasibility, satisfaction and psychosocial outcomes will be derived.

Results:
Mentors were recruited via social media (Facebook) and posters at the University Cancer Center in Leipzig. A total of 12 potential mentors were invited to a personal preliminary talk with the study director and finally 11 prospective mentors took part in the mentor training in April. Since the beginning, 17 tandems have formed between mentor and mentee. The first 8 tandems have so far been successfully completed. The mentees benefited the most from the exchange of information on side effects of the treatment and concrete assistance as well as questions on the desire to have children.

Discussion:
Peer2Me had a great response to those affected to be active as mentors or to accept mentor support. This study will provide initial results on the feasibility and implementation of a manualized peer mentoring program for AYAs and will serve as the basis for a planned clinical randomized peer support efficacy study.

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Predicting suicidal ideation in real time: An ecological momentary assessment study

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Aims:
To extend evidence on the short-term variability of suicidal ideation and the association with suggested proximal risk factors such as interpersonal variables (perceived burdensomeness, thwarted belongingness), hopelessness and depression in real-time.

Methods:
Ecological momentary assessment study (real-time data collection via smartphones) with psychiatric inpatients with unipolar depression and current or lifetime suicidal ideation. Over six days, n=74 participants rated their momentary level of suicidal ideation and the above-mentioned contextual variables up to 10 times per day on smartphones.

Results:
Descriptive evaluation of heat maps supported temporal instability for all variables. Multilevel analysis demonstrated significant positive associations between hopelessness, depressiveness, thwarted belongingness and perceived burdensomeness with suicidal ideation. Prospectively, hopelessness and perceived burdensomeness remained predictors for suicidal ideation.

Conclusion:
This study provides further evidence on the short-term variability of suicidal ideation in very short time frames implying the need of assessing it repeatedly in clinical and research settings. Furthermore we could show that the previously known risk factors depressiveness and hopelessness as well as interpersonal variables co-occur with suicidal ideation in real-time and that these are even partially able to predict changes in suicidal ideation prospectively.

Poster 168

BONEs but not CATs attract DOGs: Semantic context effects for picture naming after lesions to the language network

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In psycho- and neurolinguistic research the naming performance of healthy participants was reliably modulated in the picture-word interference paradigm (PWIP). If a categorically related distractor word is accompanying a target picture (CAT→[dog]^{picture}), the naming process is impeded comparable to characteristics of aphasic speech. In contrast, an associative relationship is facilitating it (BONE→[dog]^{picture}). Aim of this study was to replicate these semantic context effects to participants with a chronic left hemispheric brain lesion in order to (i) show the effectiveness of categorical inhibition and associative priming within the lesioned network and to (ii) draw conclusions on the neuroanatomical foundations of word production. For this purpose, we performed a PWIP contrasting categorical and associative contexts in a group of 32 aphasic patients, analysing reaction times and error rates followed by a voxel-based lesion-symptom mapping.

We find that also in the lesioned network categorical contexts impair speed and accuracy of the naming process, while an associative context only enhances accuracy. Interestingly, the strength of categorical inhibition and associative priming dissociates. We rediscover this dissociation on a neuroanatomical level. Confirming literature, lesions to the left MTG impair the overall naming performance. Lesions to the inferior frontal hub of the language network (lIFG) increase categorical inhibition. In contrast, lesions to the mid-to-posterior temporal hub (lMTG) increase associative priming.
The findings allow deeper insights into the functional and anatomical basis of word production. Moreover, they indicate adjustments in the material and strategies used in the rehabilitation of aphasia depending on lesion site.

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Semantic Interference in the Picture-Word Interference Task: Is there a Pre-Lexical, Conceptual Contribution to the Effect?

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Picture naming takes longer in the presence of a semantic-categorically related distractor word compared to an unrelated distractor word. This semantic interference effect in the picture-word interference (PWI) task is an empirical cornerstone in speech production research and of central importance in theory development and evaluation. Prominent models locate the effect at an abstract lexical level, yet only few studies have tested for a possible pre-lexical, conceptual contribution. Moreover, those studies that did are not conclusive.
We re-explored the locus of semantic interference by contrasting two task versions that were implemented as parallel as possible, but differed with respect to the processing stages involved: naming pictures (requiring conceptual processing and lexical processing) and deciding on their natural size (requiring conceptual processing only). We predicted semantic interference in naming, replicating the standard effect. If part of the effect is localized at the conceptual level, we predicted interference in size decision, too.
We found semantic effects in both tasks but with different polarity – interference in naming and facilitation in size decision. This pattern supports the view that semantic interference in PWI has its locus at the lexical level and its origin at the conceptual level.

Poster 170

Assessing changes in social functioning in the course of dementia: an instrument for research and clinical practice in German-speaking areas

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Background & Aims:
Dementia is one of the most common and most severe disorders in old age. In addition to cognitive decline and functional loss, changes in social functioning occur in the course of dementia. Currently, there is no valid instrument in German language for assessing social functioning in people with dementia. Therefore, we aim to adapt and psychometrically evaluate the English S*ocial Functioning in Dementia Scale* (SF-DEM).

Methods:
In a first step, the SF-DEM was translated from English into German according to the TRAPD model (*Translation*, *Review*, *Adjudication*, *Pretesting*, and *Documentation*). In a second step, we conduct a pilot study with 30 dyads comprising older individuals with mild dementia and a relative each. Study participants are visited and interviewed twice in their homes to collect relevant data, which are used to calculate psychometric test properties of the German version of the SF-DEM.

Results:
Different parameters of content validity and reliability will be provided. To assess reliability, the internal consistency of the scale will be determined using Cronbach‘s Alpha. In addition, the interrater and test retest reliability is estimated. In order to determine the construct validity, the results of the German version of the SF-DEM questionnaire are analyzed with the help of results of other suitable instruments using correlation methods.

Conclusion:
The German version of the SF-DEM will fill a gap in research and clinical practice, which currently lack an instrument to reliably assess social functioning in people with dementia. The overall study goal is to make the adapted German version available for free.

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Entwicklung eines Präventionsprogrammes für psychische Erkrankungen im Primarbereich
Umsetzbarkeit und praktische Implikationen

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Einführung:
Die Ergebnisse der BELLA-Studie zeigen, dass bei etwa jedem fünften Heranwachsenden zwischen 3 bis 17 Jahren ein Klärungsbedarf besteht in Bezug auf das Vorliegen einer psychischen Auffälligkeit. Ziel der Untersuchung soll es sein, einen ersten Entwurf eines Präventionsprogrammes hinsichtlich Umsetzbarkeit zu prüfen.

Methode:
Hierzu wurden vier Lehrkräfte und eine Schulbegleiterin telefonisch, leitfadengestützt befragt; kurz- und mittelfristig. In der Befragung wurden neben soziodemografischen Angaben bisherige Erfahrungen mit psychischen Krisen von Grundschülern und schließlich die Bewertung des Programms „Psychisch fit in der Grundschule“ erfasst. Es nahmen drei Schulen teil.

Ergebnisse:
Die Ergebnisse der Befragungsrunde 1 zeigen eine hohe Zufriedenheit der Lehrkräfte mit dem Modellprogramm. Die Lehrkräfte berichteten, dass das Programm kurzfristig präsent bei den SchülerInnen war. Weiterhin positiv erwähnt wurde die Offenheit der SchülerInnen an den Programmtagen. Änderungswünsche bezogen sich u.a. auf Aspekte wie: Gruppengröße (kleine Gruppen), zwei Moderatoren, stärkere Berücksichtigung kürzerer Aufmerksamkeitsspannen der Drittklässler.

Diskussion:
Das Programm „Psychisch fit in der Grundschule“ konnte bereits in seiner ersten Modellphase umgesetzt werden. Die SchülerInnen haben sich offen und beteiligt gezeigt; berichteten von eigenen Belastungen und Stärken. Die großen Klassenformate von zum Teil über 25 SchülerInnen haben die Erarbeitung individueller Themen erschwert; vor allem bei den Drittklässlern.

Schlussfolgerung:
Der Primarbereich bietet sich an, um bei den Kindern einen offenen Umgang mit belastenden Themen, Hilfesuchverhalten sowie einen ressourcenorientierten Blick auf die eigene Person zu stärken.

Poster 172

Diet-dependent effects of amisulpride on reinforcement learning and working memory in humans

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Alterations in dopamine-mediated cognition, e.g., reinforcement learning and working memory, have been observed in overweight and obesity, and may relate to the putative U-shaped relationship between markers of obesity and central dopamine. Recent rodent studies suggest that differences in dopamine transmission are due to a diet high in saturated fat and/or free sugar rather than obesity.
Whether or not this translates to humans is unknown. Moreover, the existence of a similar non-linear relationship between central dopamine and diet has not yet been assessed. We propose a double-blind, placebo-controlled, crossover study to investigate the causal effects of opposite pharmacological dopamine manipulations – a low (200mg) and high (400mg) dose of the D2-antagonist amisulpride – on reversal learning and working memory performance.
We will test 60 healthy women (BMI: 18.5-29.9 kg/m^2), who report either high or low dietary intake of fat and sugar (HFS vs. LFS). Participants are selected based on their score on the Dietary Fat and free Sugar questionnaire: those scoring in the lower or upper quartile are included. We hypothesize that a low and high dose of amisulpride have opposite effects on reversal learning and working memory performance due to its dose-dependent action on pre- and postsynaptic D2-receptors; a pattern that may be reversed for the groups if diet indeed relates to dopamine transmission in a U-shaped manner.
To assess the impact of repeated administration of the same cognitive task and improve our interpretation of the medication effects on performance, an independent behavioral retest study (n=28) was run without medication or diet groups. Together, these studies will enable us to detect diet-related dopamine anomalies in humans independent of obesity.

Poster 173

Läsions-Netzwerk-Symptom-Mapping bei Anososgnosie für Hemiplegie nach Hirninfarkt

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Die Anosognosie für Hemiparese (AHP) ist ein häufiges Phänomen nach rechtshemisphäriellen Hirninfarkten, welches durch eine variable Kombination motorischer Defizite mit kognitiven und sensiblen Störungen entsteht und durch Hirnläsionen in verschiedenen Lokalisationen verursacht wird, sodass man die AHP letztendlich a.e. als Netzwerkfunktionsstörung auffassen kann. Ziel dieser Reanalyse von Läsionsdaten aus zwei vorherigen Studien zur AHP ist es, mittels Läsions-Netzwerk-Symptom-Mapping Regionen zu identifizieren, die durch eine Netzwerkstörung indirekt am Auftreten der AHP beteiligt sind. Analysiert wurde 49 Patienten mit Hirninfarkt (25 Patienten mit AHP - definiert als fehlende Wahrnehmung der Störung trotz Konfrontation).
Beim LNSM wurde ausgehend von der individuellen Läsion der Patienten die mittlere funktionelle Resting-State-Konnektivität von 50 gesunden Probanden berechnet. Die so entstandenen Läsionsnetzwerkkarten spiegeln nun funktionell verbundene Regionen wider, in denen potentiell mit Diaschisiseffekten zu rechnen ist. Der Gruppenvergleich in VLSM und LNSM erfolgte mit der Statistical nonParametric Mapping Toolbox für SPM (Signifikanzniveau $p(FWE) < 0{,}05$).

VLSM zeigte eine signifikante Assoziation der AHP mit Läsionen im rechten Inselkortex (aus Vorstudien bekannt). Im LNSM zeigten sich signifikante Gruppenunterschiede im rechten Hippocampus. Hier war eine größere Läsionsnetzwerkkonnektivität mit dem Auftreten einer AHP assoziiert. Diese höhere Läsionsnetzwerkkonnektivität zum Hippocampus lässt sich so interpretieren, dass es möglicherweise zu einer Dysfunktion des Hippocampus kommt. Eine Gedächtnisstörung wiederum verhindert dann die stabile Encodierung des defizitären Funktionszustands und trägt dadurch zur Ausprägung einer AHP bei.

Poster 174

Grief and loss in elderly people: A qualitative study regarding the user acceptance of an internet-based self-help program from user and expert perspective

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Introduction:
The loss of a significant other is a stressful life event, especially for older people. The aim of this study is to investigate the user acceptance of an internet-based self-help program for mourners aged 60 years and above. Potential access paths as well as barriers of use will be identified from both the perspectives of users and experts.

Methods:
This study is following a qualitative design. Two focus groups consisting of elderly people (60+) with loss experience (N = 12) as well as experts from the medical care system (N = 8) were conducted using a discussion guide related to the model of the Unified Theory of Acceptance and Use of Technology (UTAUT). Qualitative content analysis according to Mayring (2015) was applied using MAXQDA.

Results:
From the user's perspective (mean age 64.5, 50 % female), an internet-based self-help program should comprise age group specific grief topics. Elderly participants felt confident to be able to use such a program. Potential access paths included e.g. general practitioners. A potential barrier was seen for people who prefer a personal relationship. From the perspective of health care experts (mean age 40.1, 87.5 % female), there was a high user acceptance regarding the target group of elders (60+). Access paths were seen across all specialist groups working with elderly people. A potential barrier was presumed in an insufficient guidance.

Discussion:
A key aspect for the use and the effectiveness of an internet-based self-help intervention for mourners is user acceptance. Judgments from potential users and experts showed a high user acceptance, but also the need to address age group-specific topics.
Conclusion: Internet-based self-help interventions can be a promising add-on treatment option for elderly bereaved people.

Poster 175

Approach or avoid? Pre-adult social experience determines behaviour towards conspecific adults

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Social experience, particularly aggression, is considered a major determinant of consistent inter-individual behavioural differences (*behavioural syndromes*), but the proximate cause is unclear. We investigate how pre-adult social experience affects future behaviour in adult male crickets. Using high-speed video analysis we first analysed the effect of a single fighting experience on the response of short-term socially isolated (48h: STI) males to touching one antenna. As in many animals, winning or losing leads to subsequently enhanced, respectively depressed aggression. STI-winners mainly turned towards the touch stimulus, whereas losers turned away. Considering that all known effects of social experience in crickets wanes after 3h, we were surprised to find that these differences were also evident before a fight. To test for effects of early, pre-adult social experience we next compared cohorts of adult crickets that were raised as larvae either with or without adult males and then isolated at their last larval stage for 14 days until adult (long-term isolates: LTI^+, LTI^-, respectively). When adult, LTI^+ males mostly turned away from the stimulus, just as STI-losers. In contrast, LTI^- adults turned towards the stimulus. However, 1h after a single defeat LTI^- losers now turned away from the stimulus, but this switch was not evident 24h later. We next subjected LTI^- adults to multiple (6x) consecutive wins or defeats. Multiple winners turned towards the stimulus, whereas losers turned away, this time the effect lasted for over 24h. This indicates that social subjugation during pre-adult life has long-term consequences for future adult behaviour. We are currently investigating the role of neurotransmitters in the acquisition of behavioural syndromes.

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Poster 176

Quantification of axon diameter, axon density, g-ratio, myelin thickness, and myelin density in human white matter tracts using light microscopy.

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Recent advances in magnetic resonance imaging (MRI)-based biophysical models facilitate the estimation of different white matter (WM) properties *in vivo*. However, the quantification of MRI-derived WM properties, such as axonal diameter and density, g-ratio (i.e. the ratio of the inner to outer fibre diameter) of individual axons, myelin thickness, and myelin density in human tissue requires validation. We use ultra-high resolution histology to characterise these microstructural properties in WM tracts in order to improve reference data for the interpretation of structural MRI findings.

MRI-scanned post-mortem tissue samples from a variety of WM structures, such as the optic chiasm, the corticospinal tract, and the corpus callosum are processed to obtain semi- (500nm) sections. Light microscopy of semi-thin sections is restricted by a very small field of view. To overcome this limitation, we optimised our pipeline for entire cross-sections of human WM tract samples. For a comprehensive description of tract properties we use high-resolution light microscopy images (resolution: 250nm) of cross-sections of entire tracts (~10mm²). Parts of these light microscopy images (111x111µm) were manually segmented by M.M. and T.T. into three structural compartments, i.e. axonal cytoplasm, myelin, and background to train a deep-learning algorithm. Axon density and diameter, g-ratio, myelin thickness, and myelin density can then be derived from these images.
Furthermore, using these segmented images a deep-learning algorithm is trained to compute the microstructural parameters of interest for the entire cross-sections of tracts.

Poster 177

Uremia-induced microglial activation promotes IL-1beta dependent neuronal dysfunction independent of the canonical caspase-1-dependent NLRP3-inflammasome

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Background:
Chronic kidney disease (CKD) causes cognitive impairment. The molecular mechanisms remain unknown. We observed high pro-IL-1beta and IL-1beta generation in uremia-induced microglia activation despite a lack of canonical caspase-1-NLPR3-inflammasome activation. We hypothesize that CKD causes microglial activation via caspase-8, contributing to inflammasome activation within the CNS.

Aim:
We aim to determine the relevance of inflammasome activation in CKD-induced cognitive dysfunction.

Methods and materials:
We used thallium-autometallography to monitor cellular K+-metabolism. CKD in mice was induced by 5/6 nephrectomy (5/6 NX). We conducted two-photon *intravital* microscopy (2-PM) in the brain. Knock-out mice ($NLRP3^{-/-}$, $Casp\text{-}1^{-/-}$, C57BL/6 background) were used to determine the relevance of inflammasome activation.

Results:
Mice with CKD revealed altered K^+-metabolism in the CNS and increased cytokine expression (IL-1beta). 2-PM revealed activation of microglia and neurons in CKD mice. Analyses of CKD- wild type C57BL/6 and CKD-$NLRP3^{-/-}$ mice revealed a comparable number of Tl-positive activated microglia, indicating that the uremia-induced reactive shift is independent of NLRP3 inflammasome activation.
However, in 5/6 NX $NLRP3^{-/-}$ mice the decrease of neuronal Tl-uptake was abolished, indicating that the NLRP3 inflammasome is indeed involved in CKD-induced K^+-dyshomeostasis of neurons. We further show that activation of microglial cells in CKD leads to secretion of Il1beta (alternate pathway of cleavage via Caspase8-RIPK1/3).

Conclusion:
These data suggest that uremia induces non-necroptotic Caspase 8 activation via RIPK1/3 in microglia cells (non-canonical inflammasome). These results may lay ground for new diagnostic approaches in CKD-associated neuronal dysfunction.

Poster 178

K_{ATP} channels modulate GABAergic drive in hippocampal area CA1

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ATP-dependent K^+ channels (K_{ATP} channels) are essential mediators between cell metabolism and electrical activity by coupling K^+ membrane fluxes to intracellular ATP levels. In pancreatic ß-cells rising levels of glucose and thus ATP leads to closure of K_{ATP} channels, membrane depolarisation and to exocytosis of insulin-filled vesicles. Gain-of-function mutations of $K_{ir}6.2$ K_{ATP} channels cause impaired release of insulin and in severe cases cognitive dysfunction and epilepsy, i.e., DEND syndrome (**D**elay and **E**pilepsy with **N**eonatal **D**iabetes).

While the development of diabetes mellitus in DEND syndrome patients is well understood, the pathophysiology of the neurological symptoms remains to be elucidated. It is well established that epilepsy and cognitive dysfunctions can result from an imbalance between excitation and inhibition. To determine the influence of K_{ATP} channels on GABAergic inhibition we performed patch-clamp recordings either from pyramidal cells (PC) or fast-spiking PV^+ interneurons (PV-IN) in acute hippocampal slices of wildtype mice. When opening KATP channels by bath applying their opener diazoxide to mimic DEND syndrome, spontaneous GABAergic release onto PCs and intrinsic activity of inhibitory PV-INs is significantly reduced. In contrast, the blocker tolbutamide shows little effect, indicating that under control conditions K_{ATP} channels are predominantly closed.

We further investigated the impact of K_{ATP} channels on network oscillations and recorded sharp wave ripples, which are thought to be important for memory consolidation. Disinhibition induced by diazoxide dramatically reduces the incidence of sharp wave ripples. In conclusion, ATP seems to be an important regulator of GABAergic drive and associated network oscillations in the hippocampal area CA1.

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Poster 179

Unraveling the human microstructural connectome using tissue clearing and fiber tracking

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The human brain is a huge network of connecting elements comprising the so-called connectome. Modern imaging techniques, i.e. MRI enable visualization of whole human brains *in/ex vivo*. One downside of MRI is still the limited resolution of at best 220µm. In contrast, classical histology paired with light microscopy reaches a resolution of ≥ 240nm. The goal is to overcome this limitation by validating existing and newly obtained MRI data. By reconstructing the same long range fiber tracts *en bloc* in MRI and with cutting-edge light microscopy techniques a foundation for microstructure-informed whole brain imaging is created.

Clearing techniques and light sheet microscopy are combined to bridge microscopy and MRI. In order for light to travel through tissue the sample needs to be thin enough or free of lipids. Lipids and differing refractive indices are the main reason for scattered light. Both issues are circumvent by using brain tissue blocks and making them transparent before or after applying immunofluorescence. After identifying two clearing approaches (CLARITY and iDISCO) various regions of interest have been processed. Those include *Medulla oblongata*, *Chiasma opticum* and *Corona radiata*. Also, three different microscopic setups are used for visualization: the Zeiss LSM 880 Fast Airyscan, the LaVision Ultramicroscope ll and the 3i Marianas LightSheet microscope. So far, each system can be used for imaging cleared human brain tissue and visualizing fiber tracks that have been found in an MRI scan. In a next step, image processing needs to be advanced as Big Data (single file size up to 1TB) is created and imaging, storing and analyzing of large cleared tissue data poses a challenge. Also, the re-alignment of found fiber tracks with MRI data is an exciting next step.

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Poster 180

Neurobiology in Major Depression: Investigation of cross-section area of the Vagus Nerve, Heart Rate Variability and inflammatory markers in Major Depression Starting study for 2020

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Background:
Major depression (MD) is a common affective disorder characterized by a low-grade inflammation as well as affections of the autonomous nervous system (ANS). The imbalance between the sympathetic and parasympathetic ANS may result in disruptions of the heart rate variability (HRV) as well as vegetative dysfunctions which are characterized by palpitations, impairment of sleep, appetite and gastrointestinal functioning. Affections of the vagus nerve (VN) could substantially participate in the pro-inflammatory state as well as the impairment of the ANS, as observed in Parkinson's Disease, in which the cross-section area of the VN is reduced.

Question:
To elucidate the role of the VN in MD, the research project focuses on the first-time ultrasonographic assessment of the VN in a cohort of depressed versus non-depressed subjects. Further, the association between the VN and the HRV, markers of inflammation and the presence of autonomous dysfunction and depressiveness shall be explored.

Methods:
This trial is a naturalistic cross-sectional study for which 120 subjects (MD = 60, controls= 60) shall be enrolled from 01/2020 on. The measurements include the high-resolution ultrasonography of the cross-section area of both VN, determination of serum levels of inflammatory markers (IL-1/6/10, INF-g, TNF-a, Indoleamine 2,3-Desoxygenase), HRV measures, as well as electrophysiological (ProSiCard) and questionnaire-based assessment of ANS dysfunction and symptom load of MD.

Discussion:
This study could participate in understanding the neurobiological pathogenesis of MD and could provide a link between inflammation, neurophysiological alterations and the clinical picture for which the VN could be a key mediator.

Poster 181

How do memory and attention influence food decisions and what are the underlying neuronal mechanisms?

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Escalating world-wide obesity prevalence urges the need to understand unhealthy eating behaviour and potential modifiers. Human behavioural studies suggest that besides the internal state (hungry or satiated) and external interaction (attention to food cues) also learning and memory play an important role in food preferences and decisions (Booth et al., 1982; Laney et al., 2007).

Namely, being hungry increases arousal and the susceptibility for food cues (Montagrin et al., 2019). This increased attention to food cues might explain that hunger leads to better memory performance for food versus non-food items (Morris & Dolan, 2001). However, little is known about the underlying neurobiological mechanisms, whether food memory is influenced by the individual's preferences or if the process is biased by attention deficits. We thus aim to determine the interplay of memory, attention and food desires and related underlying mechanisms in the context of food cue evaluation. Therefore, we are conducting a neuroimaging study on food wanting, memory and attention with overweight participants (n=60, BMI: 25-30kg/m²) featuring rather naive eating behaviour.

Measures of interest are hippocampus and amygdala activity during memory encoding and retrieval in two subsequent fMRI tasks (Thieleking et al., in prep), (food) wanting ratings, performance during retrieval, hunger ratings, brain microstructure (from diffusion-weighted imaging) and attention efficiency assessed by the Attention Network Test (Fan et al., 2002). Lastly, we study longitudinal changes in memory performance and attention efficiency after a two-week dietary intervention.

Findings of this dietary intervention could pave the way for new approaches to reduce unhealthy eating behaviour and eventually overweight and obesity.

Poster 182

Social experience influences learning and memory in crickets

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Social experiences, such as winning and losing an aggressive interaction, are considered a cause of individual differences in behaviour, even in insects. We aim to discover how aggressive experience influences learning capacity of individual crickets.

For pilot experiments we developed a simple appetitive olfactory learning paradigm using peppermint oil as a conditioned stimulus (CS) and water as an unconditioned stimulus (US). After training (3 x CS + US at 5 min intervals), a conditioned response to the CS (searching behaviour, head bobbing, antennal waving) was shown significantly more often by winners than losers (78 and 21% respectively; p = 0,0001), whereas naive crickets had an intermediate learn frequency (45%).

We are currently developing a differential learning paradigm, using automated video tracking analysis to capture the animal's responses and evaluate each individual's learning probability. Current data reveals significant differences in several behaviours between trained and non-trained crickets in response to the CS alone, including time-to-move after CS presentation, distance moved and time spent head bobbing. Modelling analysis (in progress) correctly identified animals that showed a conditioned response with a probability of 93%.

Further refinements should allow us to automatically calculate an individual's learning score. This tool will help us define the learning ability of single animals, and quantify how social experiences and the involved neurotransmitters influence learning and memory.

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Poster 183

Resolution of functional diaschisis contributes to early language recovery in patients with post-stroke aphasia

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Appriximately one third of all stroke patients initially suffer from aphasia. Various mechanisms have been discussed to play a role in loss and recovery of language functions. Neural dysfunction in structurally intact regions which are functionally connected to but distant from the lesion might contribute to the acute loss of language functions.

We combined lesion-network mapping and longitudinal (acute: day 0 - 3, subacute: day 4 - 22, chronic: day 84 - 696) task-based fMRI in 71 acute stroke patients with aphasia to test for relationships between early resolution of functional diaschisis effects and language recovery.

Lesion-network mapping was used to characterize (former) functional connections to the lesion site based on resting-state fMRI scans of demographically matched healthy subjects. We found that, in the early phase after stroke, regions which were more strongly connected to the lesion site showed a steeper increase in language specific fMRI activation than regions with weaker connections to the lesion site.

Additionally, resolution of diaschisis effect sizes over time was significantly correlated with improvement of language recovery scores. Our results suggest that regions functionally connected to but spatially separated from the lesion site become dysfunctional contributing to the early loss of language functions. Because these regions are structurally intact, resolution of neural dysfunction then contributes to language recovery within the early phase after stroke.

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Poster 184

First Application of Semi-Automated Algorithm for Hypothalamus Volumetry in 3 Tesla Magnetic Resonance Images on a Multicentre Study - A Pilot Study

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The aim of our research is to investigate structural neurobiological changes in the Diencephalon of persons with pedophilia and / or of persons who have committed sexual child abuse.

Therefore, we applied the method of semi-automated hypothalamus segmentation in 3 Tesla Magnetic Resonance Images (Wolff et al., 2018) for the first time on a multicentre study. The MRI-Scans of 308 men which were recorded in different Scanning Machines in five different locations in Germany were analyzed.

To assess the accuracy and consistency of the segmentation method within the application, a reliability test was performed. For this reason we created a sample of 20 subjects: Four participants from each of the five centers in which the scans were taken (Berlin, Essen, Hanover, Kiel and Magdeburg), and at the same time five participants from each study group (pedophilia and child sexual abuse, pedophilia without sexual abuse of children, child sexual abuse without pedophilia and control group) were chosen. In addition, the average age and the intracranial volume of the selection are representative of those of the total sample. Two raters independently measured the 40 hypothalami.

The main finding was the calculated intraclass correlation coefficient (ICC) of 0.945. Values over 0.9 are to be interpreted as excellent reliability (Koo & Li, 2016). Between the two ratters the mean difference was 0.37 % and the voxel overlap (Dice's coefficient) was 94.7 %.

In conclusion the method may be used to investigate the volume of the hypothalamus in 3 T MRI data in our multicentre study.

Poster 185

Comparative Microanatomy of the Auditory Cortex

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Molecular Neurobiology
Psychology and Cognition
Systemic Neurobiology

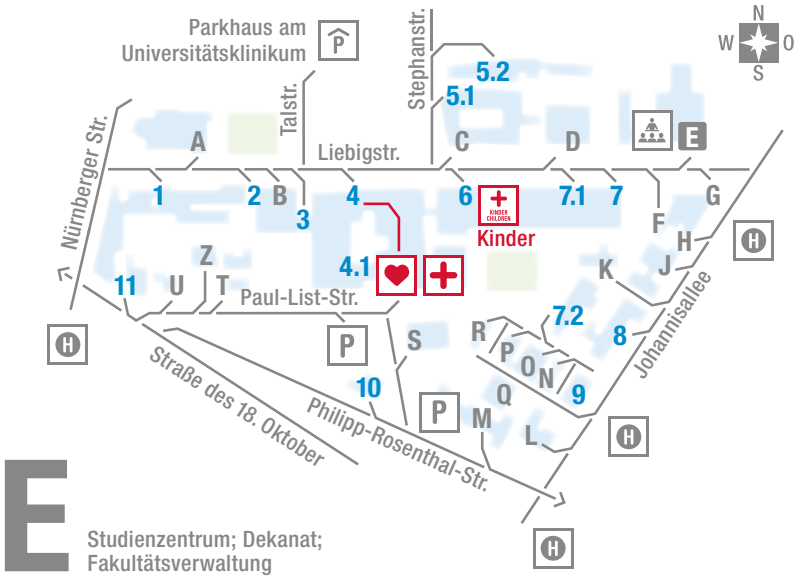
The neocortex facilitates a wide variety of cognitive functions such as sensory processing, motor output and associative capabilities serving as higher-order perceptual frameworks. While functional properties of different neocortical areas are distinguishable and have been investigated extensively in functional imaging, the microstructural properties and the resulting implications remain unclear in a number of areas.

In this study, we mapped microanatomical properties of the primary auditory cortex in the mouse brain using a variant of the IDISCO+ tissue clearing technique coupled with Light Sheet Microscopy for large-scale three-dimensional image acquisition. By employing a pattern recognition algorithm we termed Gabor Spherical Shell filtering, we managed to reliably identify cell soma positions and cell radii in a cleared whole-brain sample of mouse brain. Spatial analysis showed a distinct columnar pattern to the upper principal layers (1-3) of neocortical tissue.

In the future of this study, we want to investigate the lateralization of social communication in mice, marmoset monkeys and humans using the set of tools we previously established in order to investigate structures facilitating the specialization of the left auditory cortex hemisphere on social cues in different mammalian species.

Leipzig Research Festival for Life Sciences 2020

The 16th Leipzig Research Festival for Life Sciences 2020 is a platform to all young life science scientists and physicists from the Leipzig scientific landscape for the presentation of their research results and scientific exchange. The Research Festival shall also illustrate to the interested public, politics and as well as current and potential industrial partners how multifaceted the activities and the successes of the Leipzig scientists and doctors are in the field of life sciences and medicine.



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