UNIVERSITÄT
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Medizinische Fakultät

15th

Leipzig Research Festival for Life Sciences

2019

ABSTRACT BOOK

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(Hrsg.)

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15th Leipzig Research Festival for Life Sciences

18. Januar 2019

Veranstalter

Medizinische Fakultät der Universität Leipzig
Fakultät für Lebenswissenschaften der Universität Leipzig

Impressum

Herausgeber

Die Universität Leipzig ist eine Körperschaft des öffentlichen Rechts. Sie wird durch die Rektorin Prof. Dr. med. Beate A. Schücking gesetzlich vertreten. Weitere Informationen insbesondere zur Aufsichtsbehörde finden sich im Impressum der Universität Leipzig.

Inhaltlich Verantwortlicher gemäß § 55 Abs. 2 RStV:
Medizinische Fakultät der Universität Leipzig
Verwaltungsdirektor Oliver Gotthold
Liebigstraße 27 b
04103 Leipzig

Die Deutsche Nationalbibliothek verzeichnet diese Publikation in der Deutschen Nationalbiografie; detaillierte bibliografische Daten sind im Internet über: http://dnb.dnb.de abrufbar.

Redaktion

Cornelia Dolling
Hartmut Stollberg

Konzeption / Organisation

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ISBN: 978-3-00-061805-5

http://resfest.uniklinikum-leipzig.de/

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Vorwort

Liebe Kolleginnen und Kollegen, liebe Gäste,
wir begrüßen Sie sehr herzlich zu unserem

15. Leipziger Research Festival of Life Sciences der Universität Leipzig.

Auch im Jahr 2019 freuen sich die Medizinische Fakultät und die Fakultät für Lebenswissenschaften über die wieder sehr gute Beteiligung am Leipziger Research Festival of Life Sciences.

Das wissenschaftliche Forum gibt allen jungen »Life Science« WissenschaftlerInnen und ÄrztInnen aus der Universitätsregion die Möglichkeit, ihre neuesten Forschungsergebnisse in einer öffentlichen »Wissenschaftswerkstatt« zu präsentieren. Auch dieses Festival hat eine hohe Zahl von Abstracteinsendungen erreicht und unterstreicht damit die Attraktivität dieser Fächergrenzen-überspannenden wissenschaftlichen Kommunikationsplattform. Der vorliegende Abstractband soll ebenso der interessierten Öffentlichkeit, der Politik und Industrieunternehmen dienen, die facettenreiche Aktivität und die Erfolge der Leipziger Wissenschaftslandschaft gerade im Bereich Lebenswissenschaften und der gesamten Medizin kennenzulernen. Der Band ist mit Stichpunkten zur Forschungskompetenz zugleich ein wissenschaftliches »who is who« des Forschungsstandortes Leipzig, um schnelle Problemlösungen durch direkte Zusammenarbeit zu erleichtern.

Mit besonderer Wertschätzung des wissenschaftlichen Nachwuchses werden wieder die besten Posterpräsentationen mit den renommierten Forschungspreisen des Research Festivals Leipzig ausgezeichnet. Nach den Erfolgen und dem großen Interesse in den vergangenen Jahren freuen wir uns auch in diesem Jahr, dass wir durch die Forschungsverbünde und wissenschaftlichen Partner in den Lebenswissenschaften – dazu gehören das Biotechnologisch-Biomedizinische Zentrum (BBZ), das Fraunhofer Institut für Zelltherapie und Immunologie in Leipzig, das Innovation Center Computer Assisted Surgery (ICAAS), das Integrierte Forschungs- und Behandlungszentrum AdipositasErkrankungen (IFB), das Max-Planck-Institut für Kognitions- und Neurowissenschaften in Leipzig, die Research Academy Leipzig, der Sonderforschungsbereich 1052 »Mechanismen der Adipositas« und das Universitätsklinikum Leipzig - wieder eine großzügige Unterstützung erhalten haben.

Wir hoffen, dass unser Research Festival in seiner 15. Auflage wieder seinen doppelten Zweck der Präsentation eigener innovativer Forschungsergebnisse und des Kontaktforums von jungen und älteren Wissenschaftlern und Ärzten über Fach- und Hierarchiegrenzen hinaus erfüllen wird. Das Research Festival begleitet und stärkt somit die zukunftsweisende Entwicklung des biomedizinischen und biotechnologischen Standorts der Universität Leipzig. Für die engagierte Mitarbeit, ohne die dieses Festival nicht zustande gekommen wäre, danken wir allen Unterstützern sehr.

Prof. Dr. Thomas Arendt
Prof. Dr. Michael Schaefer
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Prof. Dr. Michaela Schulz-Siegmund
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Foto: Christian Hüller

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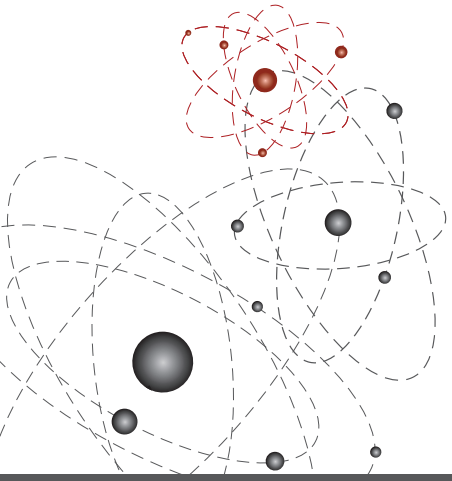

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Optimization and acceleration of technology transfer processes in life science research

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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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It's Leipzig Researcher Development Programme is aimed at guiding young postdoc researchers on their path to professional independence in their scientific field. The Leibniz Programme promotes international, interdisciplinary and intergenerational exchange between junior and experienced international scholars.

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UNIVERSITÄT LEIPZIG
Medizinische Fakultät

Sonderforschungsbereich 1052
„Mechanismen der Adipositas“

SFB 1052
Obesity Mechanisms

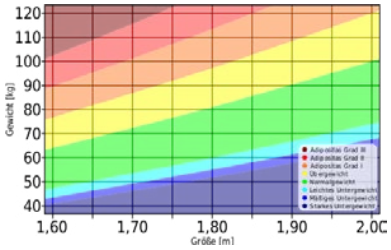
DURCH DICK UND DÜNN – EIN BLICK HINTER DIE KULISSEN DER ADIPOSITASFORSCHUNG

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/m^2 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.

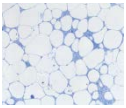
Der Sonderforschungsbereich konzentriert sich dabei auf drei Schwerpunkte: **Überernährung, Fetteinlagerung und Entzündung sowie Adipokine** (Hormone im Fettgewebe).

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.

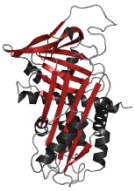

Weißes Fettgewebe.

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 (visceral 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

Abstracts Research Festivals 2019

Poster 1

Weigh more, pay more? Public's opinion on varying health insurance contributions among divergent weight groups

Bernard M.

Integriertes Forschungs- und Behandlungszentrum (IFB) Adipositas-Erkrankungen, Universität Leipzig

In Germany, the costs for obesity increased with its prevalence over time and can be annually estimated in the billion ranges. These costs are merely covered by statuary health insurance, a solidary system that is equally financed by employers and employees. Within this system no differences of health insurance contributions are made between people with or without health issues. In this study we aimed at investigating public's opinion on the national solidary system with regard to health insurance contributions made by people with and without obesity. Therefore, data of 179 non-obese German participants were assessed (51.40% female; age M=32.46, SD=5.74) by digital questionnaires. Paired t-test revealed that participants suggest a significantly higher proportional contribution for health insurance for people with obesity (M=18.58, SD=16.6) compared to people with normal weight (M=16.43, SD=13.53). Moreover, multivariate analysis revealed determinants of increased disparity between health insurance contributions between weight groups. Overall, around three quarters of participants suggested an equal contribution rate between both weight groups. However, we found significantly differences in suggested contributions rates for people with obesity among participants with stronger explicit stigma and higher BMI, whereas disparities decreased with higher income. Furthermore, participants suggested significantly higher contributions for both weight groups compared to the current contribution rate of 14.6%, indicating that participants are not thoroughly familiar with the local health care system or rather its conditions.

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Zivilisationserkrankungen

Molekulare Onkologie

Klinisches Imaging

Poster 2

Characterization of the adipose progenitor cell marker MSCA1 in normal weight and obese children

Hanschkow M.[1,2], Bouloumié A.[3], Dietrich A.[4], Kiess W.[1], Körner A., Landgraf K.[1,2]

1 Integriertes Forschungs- und Behandlungszentrum (IFB) AdipositasErkrankungen, Universität Leipzig
2 Klinik und Poliklinik für Kinder und Jugendmedizin, Universität Leipzig
3 Inserm, UMR1048, Team 1, I2MC, Institute of Metabolic and Cardiovascular Diseases, Université de Toulouse, Toulouse, France
4 Klinik und Poliklinik für Viszeral-, Transplantations-, Thorax- und Gefäßchirurgie, Universität Leipzig

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Obesity is characterized by an increase in fat mass caused by an increase in adipocyte number and/or adipocyte size and is often associated with adipose tissue (AT) dysfunction and metabolic impairment. It is suspected that adipocyte progenitor cells play an important role during healthy and obesity-related AT expansion and represent therefore a potential target for obesity treatment strategies.

The percentage of adipocyte progenitor cells within the stroma-vascular fraction (SVF) is determined by flow cytometry using the specific surface marker MSCA1. In addition, a possible association between MSCA1 expression in AT and serum levels of MSCA1 in children is investigated.

For method establishment we investigated the percentage of adipocyte progenitor cells in SVF in visceralAT of adult women and detected 2-4% MSCA1 positive cells. AT MSCA1 expression as well as serum levels were measured in lean (n=35) and obese (n=30) children. The expression of MSCA1 showed no gender-specific differences. Interestingly and in accordance with adult studies, adipocyte MSCA1 expression was significantly higher in obese compared to lean children. Moreover, our data show no association between MSCA1 expression in AT and circulating MSCA1 in the serum. The serum levels show no significant difference between obese and lean children.

In conclusion adipocyte MSCA1 Expression but not MSCA1 serum levels are related to obesity in children. Currently we are investigating whether AT MSCA1 expression and/or serum levels are suitable as a surrogate marker for the number of MSCA1 positive progenitor cells in AT of children.

Poster 3

The effect of acute dopamine depletion on reinforcement learning and working memory in relation to self-reported diet

Hartmann H.

Max Planck Institut für Kognitions- und Neurowissenschaften

The neurotransmitter dopamine (DA) is important for cognitive control and feedback learning. Those processes are altered in humans with obesity, which is influenced by high fat and sugar diet (HFS). In animals HFS leads to alterations within the DA system and changes signal transmission in cognition-related brain regions. We investigate the influence of low fat/sugar diet (LFS) and HFS on the DA system and DA-mediated cognition in humans.

Healthy, female participants were assigned to LFS or HFS group (n_{LFS}=49, n_{HSF}=31) using the Dietary Fat and Free Sugar Questionnaire. Amino acids, metabolic hormones and parameters of fat and sugar metabolism were analyzed from blood. Participants performed cognitive tasks on each of two test days. Test days differed in dietary DA manipulation based on acute DA precursor depletion (ADPD) prior testing, to investigate brain DA levels.

LFS and HFS differed significantly in cholesterol and glycated hemoglobin. The HFS group had a higher Phe+Tyr to large neutral amino acid ratio, reflecting higher central DA. Decreased central DA after ADPD impaired working memory performance in the LFS (n_{LFS}=22), but not in the HFS group (n_{HSF}=16). Performance on the reinforcement learning task was not affected by the intervention (n_{LFS}=13, n_{HSF}=13).

Our results show that the two diet groups are distinct in parameters of fat and sugar metabolism and the amino acid ratio suggests differences in central DA transmission, due to higher DA in the HFS group. Decreasing DA reduced working memory performance only in the LFS group, suggesting different properties of the DA system due to fat and sugar consumption.

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Poster 4

Reliance on model-free and model-based learning relates quadratically to severity of obesity

Janssen L.

Integriertes Forschungs- und Behandlungszentrum (IFB) Adipositas- Erkrankungen, Universität Leipzig

Obesity is the result of consuming more energy than is expended, and often of compulsive overeating despite negative consequences. Observed alterations in reinforcement learning in obesity have been suggested to underlie such failures of behavioural control. Behavioural control is thought to arise from a balance between two dissociable strategies of dopamine-mediated reinforcement learning: model-free and model-based. Previous studies investigating reinforcement learning in obesity either did not systematically disentangle between the two strategies, or found no differences when comparing lean and obese participants. A recent proposal suggests the existence of a quadratic relationship of the severity of obesity with tonic dopamine. We therefore hypothesized that weight status relates to the degree to which individuals rely on model-free vs. model-based learning and that it may do so in a linear or quadratic manner. We tested 91 healthy participants in a wide BMI range (lean (n=31): BMI=18.5-24.9 kg/m^2, overweight (n=30): BMI=25-29.9 kg/m^2, obese (n=30): BMI>30 kg/m^2) using a sequential decision-making task designed to dissociate model-free and model-based control. The weight groups differed significantly in their relative balance between model-free and model-based control, driven by increased model-based control in obese relative to lean and overweight participants. These findings suggest that obesity may be related to an imbalance in learning strategies driven by decreased model-based learning.

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Poster 5

Characterization of subcutaneous stromal vascular cells in order to establish new cell models for human adipogenesis

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Simpson Golabi Behmel syndrome (SGBS) cells and primary or immortalized stromal vascular fraction (SVF) cells are currently used as in vitro models for human adipogenesis. The Beckwith-Wiedemann syndrome (BWS) is another overgrowth syndrome of which a SVF cell line does not exist so far. In order to establish new adipogenic cell models we characterized primary and immortalized SVF cells from a child with BWS as well as from healthy children. We hypothesized that the BWS and the immortalized cells maintained an increased proliferative and adipogenic capacity over several generations compared to primary cells.

We analyzed primary and immortalized SVF cells from a girl with LIT1 hypomethylation (BWS) and 4 healthy children for proliferation, differentiation, mitochondrial function and gene expression profile throughout cultivation time.

Adipogenic potential was 2.7-fold higher in BWS cells compared to healthy cells throughout cultivation time. In line with this, adipogenic gene (PPARG, ADIPOQ and AP2) expression was up to 6-fold increased in differentiated cells. BWS and control cells were not different in doubling time or mitochondrial activity. While primary cells entered senescence after 52 generations, immortalized cells continued to proliferate. After immortalization procedure adipogenic potential was maintained, but it slightly declined with further cultivation time. Immortalized BWS cells still differentiated better than immortalized cells from control children.

Poster 6

PTEN Regulates differentiation, proliferation and cellular aging of preadipocytes

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Background:
The tumor suppressor PTEN antagonizes the PI3K/AKT/mTOR pathway, which promotes cell growth and proliferation. Germline mutations cause the PTEN hamartoma tumor syndrome, characterized by an tissue overgrowth, including lipomas. To understand these adipose tissue aberations we aim to assess PTEN function in the context of preadipocyte proliferation, differentiation and senescence.

Methods:
We used preadipocytes obtained from healthy individuals and reduced the PTEN levels either transiently by siRNA mediated PTEN knockdown or stable using the CRISPR/Cas9 system.

Results:
The reduced PTEN levels (0.59 ± 0.03 fold) led to an increased proliferation of the preadipocytes as measured by nuclei counting (1.5 ± 0.2 fold after 7 days). Moreover, the adipocyte differentiation capacity could be restored in high passage presenescent cells that had already lost their ability to differentiate (1.41 ± 0.14 fold lipid accumulation). This corresponded with an increase in the adipocyte differentiation marker PPARy (1.8 ± 0.4 fold). We observed an activation of AKT signaling (enhanced AKT and ribosomal protein S6 phosphorylation) in PTEN knockdown cells, a decrease of the senescence marker p21 (0.4 ± 0.09 fold) and an increase in the NAD-synthesis enzyme NAMPT (1.28 ± 0.06 fold) suggesting a role of PTEN in regulating cellular lifespan. During long-term culture of preadipocytes the PTEN levels increased (3.7 ± 0.7 fold after 25 days). Levels of NAMPT decreased during long-term culture (0.04 ± 0.02 fold).

Conclusion:
Our results indicate that PTEN is involved in regulation of preadipocyte proliferation, differentiation and aging.

Poster 7

Genomweite mRNA-Expressionsprofile der in vitro-Adipozytendifferenzierung

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Adipositas entwickelt sich bereits in den ersten Lebensjahren und kann verschiedene metabolische und kardiovaskuläre Beeinträchtigungen nach sich ziehen. Welche Gene sind mit Adipositas und entsprechenden Parametern der Fettgewebsdysfunktion assoziiert und tragen zur Entwicklung klinischer Komorbiditäten bei? Diese Frage soll mittels differentieller Genexpressionsanalysen über den Zeitverlauf der Adipozytendifferenzierung beantwortet werden.

Datengrundlage bilden die Proben aus Simpson-Golabi-Behmel-Syndrom-Zellen (4 Experimente x 11 Zeitpunkte), isolierte Präadipozyten aus Erwachsenen (5 x 6 Zeitpunkte) und aus dem Fettgewebe von Kindern isolierte Adipozytenvorläuferzellen (8 x 2 Zeitpunkte). Gemessen wurde jeweils vom Stadium der Präadipozyten über verschiedene Stufen der Adipozytendifferenzierung bis hin zu reifen Adipozyten. Dazu wurden Illumina HumanHT-12 v4 Expression BeadChip-Arrays verwendet.

Die Analysen erfolgten nach der Durchführung diverser, standardisierter Präprozessierungsschritte und der Modellierung der Genexpression über den Zeitverlauf der Adipozytendifferenzierung. Sich anschließende Pathway-Analysen bezogen sich auf Gene Ontology und Kyoto Encyclopedia of Genes and Genomes. Damit sollen schließlich Aussagen zum Prozess der menschlichen Adipogenese getätigt werden.

Poster 8

Die Leipziger Schulernährungsstudie - erste Ergebnisse

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Hintergrund:
Elterliches Übergewicht und ein niedriger sozioökonomischer Status sind mit der Entstehung von kindlichem Übergewicht assoziiert und schwer mit Präventionsmaßnahmen zu erreichen. Zur Lebensumwelt von Kindern, zählen neben dem Elternhaus auch die Lebensmittelumwelt in (Schulverpflegung) und um Schulen. Diese sind daher mögliche Ansatzpunkte für Präventionsmaßnahmen.

Methodik:
Im Rahmen der Leipziger Schulernährungsstudie werden die direkte Schulumgebung der Kinder und das elternunabhängige Einkaufsverhalten der Schüler in den gegebenen Lebensmittelumwelten in Leipziger Stadtgebieten mit unterschiedlichem sozioökonomischen Status und unterschiedlicher Adipositasprävalenz untersucht. In die Studie werden Grundschüler der 4. Klasse und Schüler der weiterführenden Schulen der Klassen 6./7./8. eingeschlossen und u.a. Daten zur physischen Aktivität, Ernährungsverhalten, Soziodemografie und Anthropometrie erfasst.

Ergebnisse:
26 von 42 Schulen aus 13 Stadtteilen wurden bisher rekrutiert und 620 Schüler untersucht. Die Schüler sind im Durchschnitt 12,13 Jahre alt und 11,8% sind übergewichtig bzw. adipös. Bisherige Ergebnisse zeigen, dass 59,9% der Schüler an der Schulspeisung teilnehmen und 23,6% in der Schule nichts zum Mittag essen. 7,4% der Schüler essen kein Frühstück, weder zu Hause noch in der Schule. Dabei haben diese Kinder eine erhöhte Wahrscheinlichkeit übergewichtig zu sein.

Schlussfolgerung:
Die Erfassung der Lebensmittelumwelt von Kindern in der Schulumgebung ergibt mögliche Ansatzpunkte für Interventionsstudien im Bereich Adipositasprävention.

Poster 9

Hedgehog Signaling – a mediator of the crosstalk between liver and adipose tissue?

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Background:
The morphogenic Hedgehog (Hh) signaling pathway is indispensable for embryonic development and patterning. In adult tissues it has been implicated in the regulation of metabolism. This function was shown for liver, where it regulates lipid metabolism, and adipose tissue, where the pathway is involved in adipocyte differentiation. Previous experiments show a connection between the Hh pathway in the liver and the homeostasis of adipose tissue, as hepatocyte-specific pathway inactivation leads to an increase in white adipose tissue (WAT) of male and female mice.

Methods:
The different types of adipose tissue (brown, BAT; subcutaneous, SAT; visceral, VAT) as well as hepatocytes were isolated from a mouse model with hepatocyte-specific inactivation of the Hh pathway and used for further experiments.

Result:
Our analyses show changes in pathway activity in adipose tissue as a consequence of hepatocyte-specific inactivation of Hh signaling. The regulation of pathway components differs between sexes. In response to the inactivation of Hh signaling in hepatocytes, a browning effect in the VAT leads to the formation of adipocyte subpopulations. As possible mediators of the crosstalk different cytokines were identified.

Conclusion:
The results show the crosstalk between liver and adipose tissue under consideration of the Hh signaling pathway. Hh signaling in hepatocytes seems to be of importance for the homeostasis of adipose tissue, as a loss of activity leads to changes in pathway regulation and a browning effect in VAT, the exact mechanism of which is not yet understood.

Poster 10

Einfluss von BMI und körperlicher Aktivität auf den Knochenstoffwechsel bei Kindern und Jugendlichen

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Einleitung:
Körperliche Aktivität in der Kindheit erhöht die Knochenmasse und reduziert das lebenslange Frakturrisiko. Adipöse Kinder zeigen eine erniedrigte Knochendichte, was durch vermehrte Inaktivität oder metabolisch bedingt sein könnte. Ziel dieser Studie war es, den Knochenstoffwechsel in Bezug auf Ernährungsstatus und körperliche Aktivität im Kindesalter zu untersuchen.

Material und Methoden:
Demographische und biometrische Daten , Stoffwechselparameter für Knochenumsatz (Alk. Phosphatase, OH-25-Vitamin D, Osteocalcin, Procollagen Typ I Propeptid, Beta-Crosslaps) und -resorption (Parathormon) sowie die körperliche Aktivität von 397 Probanden der Kohorte des Forschungszentrums für Zivilisationserkrankungen (LIFE Child) wurden analysiert.

Ergebnisse:
192 Mädchen und 205 Jungen im Alter von 5 bis 18 Jahren (12.0 ± 2.7 J) wurden in die Studie eingeschlossen, 55.2% Normal- bzw. Übergewichtige (BMI SDS 1.282 – 1.881) und 44.8% Adipöse (BMI SDS > 1.881). Mit steigendem BMI SDS zeigte sich bei beiden Geschlechtern eine signifikante Verringerung des Serumspiegels von 25-OH-Vitamin D, Osteocalcin und b-CL bei steigendem PTH Level. Die Steigerung der körperlichen Aktivität war nur bei Mädchen unabhängig vom Ernährungsstatus, signifikant mit vermehrtem Knochenumsatz und vermindertem -abbau assoziiert.

Schlussfolgerung.
Der kindliche Knochenstoffwechsel wird vom Ernährungsstatus beeinflusst. Körperliche Aktivität war nur bei Mädchen, nicht jedoch bei Jungen mit signifikanten Veränderungen der Serumparameter assoziiert. Diese Beobachtungen sollten bei der Behandlung der kindlichen Adipositas Beachtung finden.

Poster 11

Mechanism of calcium-induced activation of macrophages in obesity

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In many patients, obesity is characterized by the development of a chronic low-grade inflammation. On a cellular basis, this is mediated by immune cell immigration into adipose tissue, most prominently of macrophages, which upon activation secrete proinflammatory cytokines such as IL-1β,t-riggering further systemic reactions. Insulin resistance and type 2 diabetes mellitus are strongly connected to adipose tissue inflammation. Extracellular calcium ions ($exCa^{2+}$) were shown to amplify these processes by activating the NLRP3-inflammasome.

To determine the basic principles of obesity-induced inflammation, the calcium-induced reactivity of monocyte-derived macrophages (MDM) of obese and non-obese individuals was examined in a clinical-experimental study. By differentiating MDM with autologous serum, a patient-specific in-vitro model was achieved in order to analyze individual macrophage reactivity under obesity conditions. The obese cohort showed a higher proportion of leukocytes – most prominently monocytes - in the peripheral blood. Furthermore, monocytic cytokine release upon stimulation with $exCa^{2+}$ was significantly higher in the obese cohort, when compared to non-obese controls, regardless of a pre-existing low-grade inflammation. Moreover, MDM from obese patients with higher ionized calcium levels in the blood seemed to react more sensitive to $exCa^{2+}$.

These experiments can lead to a deeper understanding of obesity-induced inflammation, giving us the opportunity to detect new therapeutic approaches and to reduce morbidity in patients suffering from obesity and its comorbidities.

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Poster 12

Low-grade inflammation in insulin resistance associates with bacterial load in adipose tissue

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Compositional and functional alterations of intestinal microbiota are known to contribute to host pathologies including obesity and type 2 diabetes (T2D). Studies in animal models support the “leaky gut” hypothesis suggesting that increased intestinal permeability leads to transmural bacterial translocation to blood and adipose tissue (AT) contributing to chronic low-grade inflammation and insulin resistance. Obesity-associated tissue inflammation is a key factor in altering insulin sensitivity. The aim of the present study was to examine the correlation between bacterial load in subcutaneous, omental and epiploic AT with various inflammatory markers, including macrophages infiltration. We collected AT biopsies and blood samples from 27 subjects with morbid obesity (BMI: 48.09 ± 5.81 kg/m²) who underwent bariatric surgery. Adipose tissue samples were stained for adipocytes and macrophages. The largest adipocytes were found in subcutaneous AT and most ATMs in omental AT. Both parameters correlated positively with HOMA-IR (Homeostasis model assessment – insulin resistance) and HbA1c (Glycated hemoglobin levels).These correlations were also observed for further inflammatory markers such as circulating TNF-α (Tumor necrosis factor-α) and AT specific TNFA gene expression. Most importantly, a positive correlation between ATMs and the bacterial load in omental AT was observed, supporting the “leaky gut” hypothesis.

In conclusion, our data support presence of bacteria in human AT and their role in obesity-associated tissue inflammation.

Poster 13

CXCL 12 and its receptors are differentially expressed during adipocyte differentiation and modulated by high-calorie diets.

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Immune cell infiltration in dysfunctional adipose tissue (AT) during obesity contributes to chronic low-grade systemic inflammation and is controlled by chemokines and their respective receptors. In addition, chemokines have been recognized to link obesity to insulin resistance, via affecting synthesis of pro-inflammatory cytokines.

A chemokine crucially controlling inflammatory processes is CXCL12 and its receptors, CXCR4 and CXCR7. To assess the putative role of the CXCL12 system in obesity, we have now analyzed expression of CXCL12 and its receptors, CXCR4 and CXCR7, in differentiating white and brown adipocytes. In addition, we have asked whether diet and specific origin of adipocytes would influence the CXCL12 system. Quantitative RT-PCR and Western blot analysis demonstrated increased expression of CXCL12 in differentiating "white-like" 3T3-L1 cells as well as a "brown" adipocyte cell line. Notably, whereas in differentiating 3T3-L1 cells, CXCR7 expression clearly exceeded that of brown adipocytes, only expression of CXCR4, but not CXCR7 was detectable in 3T3-L1 cells. High-sugar diet (HSD) or high-fat diet (HFD) for 12 weeks increased expression of mRNA levels encoding CXCL12, CXCR4, and CXCR7 in mouse white and brown fat depots. This increase was more pronounced under HFD than compared to HSD and might reflect the rapid gain of body weight in HFD-mice and the resulting onset of AT inflammation.

Collectively, our findings point to the CXCL12 system as a crucial regulator of inflammatory processes in AT. In addition our findings unravel different functions of CXCL12 and its receptors in white and brown AT.

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Poster 14

Hematopoietic progenitors selectively maintain the pSTAT5 self-renewal response to Interleukin-3 (IL-3) in low energy environments

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Hematopoietic bone marrow contains a range of stromal environments that differ in terms of both signaling and metabolism. It is likely that the self-renewal and lineage specific differentiation of hematopoietic cells is organized and contained within that area. Consistent with previous observations in primary cells, we demonstrate that by using metabolic inhibitors that self-renewing FDCP mix derive their oxidative phosphorylation, but switch to glycolysis during commitment and differentiation. Decreasing the glucose concentration over the range 5-0.1mM progressively decreases the pErk1/2 response to IL-3. In contrast, pSTAT5 levels actually increase under low glucose.Remarkably, a subpopulation of cells maintains pSTAT5 response to IL-3 in the absence of glucose, and even in the presence of inhibitors of both glycolysis and oxidative phosphorylation. We hypothesized that this maintenance of JAK-STAT activity under low-energy conditions may involve local ATP regeneration via an NDP-kinase capable of transferring the ɣ-phosphate from other NTPs to ADP. We have previously found NDP kinase (Nme2) expressed in progenitor cells and expressed in chronic myeloid leukemia.Our preliminary results show that shRNA-mediated knock-down of Nme2 prevents JAK-STAT5 signaling specifically under low energy conditions.Our findings demonstrate that the JAK-STAT pathway has a surprisingly low requirement for free ATP and that the pSTAT5 self-renewal response dominates in a very low energy environment, most likely via Nme2 recruiting. This suggests a mechanism by which self-renewal can be supported and contained by a metabolic niche in vivo.

Poster 15

Investigation of ^{18}F-labelled pyrazolo[2,3-d]pyrimidines for molecular imaging of the adenosine A2A receptor with positron emission tomography (PET)

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Objectives:

The adenosine A_{2A} receptor ($A_{2A}R$) is a promising target for the development of PET radiotracers for molecular imaging of neurodegenerative diseases and cancer. Based on binding-affinities the 4- and 2-fluorobenzyl derivatives 1 ($K_i(hA_{2A})$ = 5.3 nM) and 2 ($K_i(hA_{2A})$ = 2.1 nM) were chosen for radiofluorination.

Methods:

Three different strategies for the synthesis of [^{18}F]1 have been investigated. The first two are using [^{18}F]fluorobenzaldehyde, which was applied either in a reductive amination or in a reduction followed by an Appel and benzylation reaction. The third strategy is based on a one-step radiolabelling starting from a boronic acid pinacol ester precursor employing [^{18}F] TBAF and $Cu(OTf)_2(py)_4$ in n-BuOH/DMA. The specific binding of [^{18}F]1 and [^{18}F]2 on mice brain slices was evaluated by in vitro autoradiography.

Results:

The two- and four-step labelling strategies resulted in a radiochemical yield (RCY) of only 1.4% or 10% [^{18}F]2 (non-isolated). Thus, [^{18}F]1 and [^{18}F]2 were prepared by a one-step procedure with a RCY of 52+7 or 9+1% (EOB), a molar activity of 135+64 or 132 GBq/µmol (EOS) and a radiochemical purity of >98%. In vitro autoradiography performed with [^{18}F]2 demonstrated high binding to the striatum, a brain region with high density of $A_{2A}R$, which could be blocked by selective A_{2A} ligands.

Conclusions:

An efficient copper-mediated one-step radiolabelling procedure was established for two new highly affine A_{2A} radiotracers. The first in vitro study with [^{18}F]2 demonstrated excellent potential for the imaging of adenosine $A_{2A}R$. Current work focuses on further in vitro and in vivo investigations.

Poster 16

Induktion einer Steatosis in primären humanen Hepatozyten

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Mit dem metabolischen Syndrom eng assoziiert, gewinnt die nicht alkoholische Fettlebererkrankung (NAFLD) mit steigender Prävalenz in der Bevölkerung zunehmend an Bedeutung. Welche Mechanismen zur Entstehung, Erhaltung und Weiterentwicklung einer NAFLD beitragen, ist bisher nicht endgültig geklärt. Unser Ziel ist es, in zwei verschiedenen in vitro Modellen die Leberzellverfettung nachzustellen und zu quantifizieren. Für die in vitro Kultur werden primäre humane Hepatozyten (PHH) aus nicht tumorösen Lebergewebe isoliert. Kultiviert werden sie in 2D-Kulturen und 3D-Sandwich-Kulturen, in denen Collagen als extrazelluläre Matrix genutzt wird, um eine Zelladhäsion zu ermöglichen und in vivo Bedingungen zu simulieren. Die Steatose wird durch die freien Fettsäuren (FFA) Palmitat und Oleat induziert. Mit verschiedenen Fluoreszenzfarbstoffen werden die Zellmembran der PHHs und die enthaltenen Lipidtropfen (LD) angefärbt, um diese bioinformatisch quantifizieren zu können. Korrespondierend wird mit Hilfe biochemischer Assays die Menge der enthaltenen Triacylglyceride (TAG) und der sekretierten very low density lipoproteins (VLDL)bestimmt.

Wir rechnen mit einer deutlichen Zunahme des intrazellulär gespeicherten Lipidgehalts und des sekretierten VLDL mit zunehmender Inkubationszeit. Außerdem wird anhand der erhobenen Parameter die Heterogenität der Größe und Anzahl der LD in unterschiedlichen PHH Populationen untersucht.

In den verwendeten 2D- und 3D-Kultur-Modellen kann die kurzzeitige Lipidaufnahme gut untersucht werden. In Langzeitkulturen soll das Verhalten der PHH nach Sättigung mit FFA simuliert werden.

Poster 17

Ischemic but not dilative cardiomyopathy impairs the thioredoxin system in the myocardium

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Background:
Oxidative damage as well as impaired proteasomal activity is believed to facilitate the process of ischemic (ICM) and dilated cardiomyopathy (DCM). The thioredoxin (Trx) system is balancing the production of reactive oxygen species (ROS) and inhibiting pathways of intrinsic apoptosis. We investigated the changes of the Trx system in ICM- and DCM-damaged human myocardium.

Methods:
Myocardial tissue was obtained from ICM (n=13), DCM (n=13) or from septal tissue (control, n=12). Expression of ITCH, TXNIP and Trx was quantified by western blot. NADPH-oxidase activity assay was performed. Pro- and antiapoptotic markers (cCasp3, Casp8, Casp9, PARP1, Akt, Bad, Bcl2, JNK p53), the concentration and activity of Trx reductase 1 (TXNRD1) were determined by multiplexing and ELISA.

Results:
Compared to control, expression levels of ITCH (ICM: 0.32±0.12, DCM: 0.66±0.47, control: 0.70±0.23, p=0.006) and Trx (ICM: 0.84±0.34, DCM: 1.05±0.41, control: 1.36±0.36, p=0.027) were reduced in ICM and DCM. TXNIP (p=0.009) was increased in ICM, but not in DCM. Compared to control, ICM patients showed lower concentrations of TXNRD1 (p=0.035) and activity of TXNRD1 (p=0.005). DCM patients showed an increased caspase 9 expression (p<0.001) and NADPH-oxidase activity (p=0.030).

Conclusions:
ICM, but not DCM impairs the thioredoxin system in myocardial tissue. Increasing ROS production was detected in the DCM-damaged myocardium and caused apoptosis via caspase activation in DCM. Our results implicate that different cellular processes are impaired in DCM and ICM.

Poster 18

Genome-wide analysis of eight steroid hormones reveals 14 novel loci influencing steroid hormone biosynthesis

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Steroid hormones are important regulators of physiological processes in the body. Here, we aim to identify genetic factors influencing steroid hormone metabolism, detecting genetic sexual dimorphisms and investigate possible causal effects of steroid hormones on coronary artery disease (CAD).

We performed genome-wide (meta-) association studies for eight steroid hormones: cortisol, DHEAS, estradiol and testosterone in two independent cohorts (LIFE-Adult, LIFE-Heart, max. n=7667), and progesterone, 17-OHP, androstenedione and aldosterone in LIFE-Heart only. Additionally, we analyzed all hormones regarding sex interactions, tested if previously reported CAD SNPs were associated with our steroid hormone panel and investigated causal links between steroid hormone levels and CAD status using Mendelian Randomization (MR) approaches.

We discovered 14 novel hits with genome-wide significance in our association studies for five hormones and seven of those hits showed significant differences in effect sizes between sexes. We found four candidate genes that are directly involved in steroid metabolism (CYP21A1, CYP17A1, STS, and HSD17B12). We detected a significant enrichment of CAD SNPs associated with cortisol and testosterone. We also found significant causal effects of progesterone and DHEAS on CAD.

With our results, genome-wide significant variants were found for all but two enzymes involved in steroid metabolism. The observed non-random overlap of CAD and steroid hormone associations and the significant MR estimates support the hypothesis of steroid hormones influencing CAD development partly explaining the higher risk of males.

Poster 19

Reducing phototoxicity using new live cell imaging devices

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Phototoxicity is one main reason why fluorescence-based imaging regimes differ fundamentally from real life conditions, due to intense focused illumination of living samples. Hence, the interpretation of experimental data has to be considered under the design of the chosen experimental imaging protocol. Therefore, an approach to assess the harms occurring during imaging, compare various imaging modes, and minimize phototoxicity is required. A known approach measures phototoxicity quantitatively by monitoring the cell division rate in Caenorhabditis elegans embryos, indicating damage distinct from photobleaching and cell death (Tinevez et al. 2012, Academic Press 505). C. elegans embryos are a suitable model because they have a tightly controlled cell fate, which is sensitive to their ambient conditions, such as temperature and incident illumination. Having established C. elegans as a model organism at the Fraunhofer IZI, we are investigating epifluorescence - and laser-scanning microscopy for their phototoxic effect, and will soon test other novel research imaging devices. The method will be adapted to the murine fibroblast cell model 3T3 applied in the 3T3 Neutral Red Phototoxicity Assay.
Finally, we are convinced that our experiments shall include a phototoxic consideration to assure sample integrity. Our approach paves the way for optimization of experimental imaging protocols. The translation of this technique to other host organisms should be pursued further.

Poster 20

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

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In this project we aim to study the mechanisms leading to ulcer formation and evaluate the relation between macrophages and iron in that context. Initially, to mimic erythrocytes-accumulation in skin typical in CVU patients, macrophages (Ma) isolated from human blood, have been co-cultured with erythrocytes or Fe2+ up to 21 days. Cytokine analysis revealed, that M1 released significant less amounts of pro-inflammatory TNF and IL12, after LPS, suggesting a down-regulation of the inflammatory response in M1-like Ma by erythrocytes/ Fe2+. M2 showed a clear pro-inflammatory response with significant increase of TNF, and increase of IL-6 in after stimulation. Further, in vitro phago-assay in Ma cultured with Fe2+ show that M2 are more effective in iron uptake and storage in comparison to M1, suggesting a better capability of M2 to effectively recycle iron.
Subsequently, ROS assay used to evaluate mitochondrial ROS production in Ma stimulated with Fe2+, show an immediate ROS production in M1 and M2 after stimulation and that effect increased exponentially along all time of observation. Lastly, we evaluated whether Fe2+ may activate the NLRP3 inflammasome in monocytes stimulated with LPS and Fe2+ in medium rich of phosphate, as a result, IL-1b was consistently released with after Fe addition (up to 6mM) and its release increased when cells were stimulated with Fe-phosphate particles (IL-1b 9ng/ml), results that effectively showed iron can activate the inflammasome in monocytes.
Gene expression analysis help to deciphering the underlying molecular mechanism of the different response of M1 and M2 after iron uptake.

Poster 21

3D Co-Culture Model to Study Interactions Between Macrophages and Fibroblasts

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The treatment of wound healing disorders requires precise knowledge of the biochemical and biophysical processes. Fibroblasts (FB) and their differentiated phenotype, myofibroblasts (MyoFB), are essential for the repair and regeneration of the damaged tissue by the synthesis of new ECM. Biomimetic in vitro models are considered to allow an in-depth analysis of specific cell-cell and cell-matrix interactions. This work deals with the characterization of a co-culture model of primary human FB and macrophages (MΦ) in defined 3D collagen I matrices. We demonstrate that FB and inflammatory or regulatory MΦ (GM-MΦ or M-MΦ) can be cultivated in direct co-culture in 3D collagen I matrices over at least 6 days. TGF-β1 stimulation of FB resulted in MyoFB differentiation with increased expression of the genes αSMA, EDA-FN, Col-I, Col-III. MyoFB differentiation was reversed by either presence of IL-10 or IL-10 secreting M-MΦ in a dose-dependent manner. In contrast, MyoFB co-culture with GM-MΦ resulted in an enhanced TGF-β1-mediated induction of MyoFB. IL-10 secretion was measured by ELISA and confirmed by IL-10 RT-qPCR. While M-MΦ showed an antifibrogenic effect on FB in co-culture, the co-culture of FB with GM-MΦ showed an increased TGF-β1-mediated induction, which illustrates the profibrotic effect of GM-MΦ. In summary, the developed co-culture of FB and MΦ in 3D collagen I matrices proofs to be an in vitro model for the investigation of fibrotic and antifibrotic processes. Future experiments will expand the 3D co-culture model to regulate paracrine cytokine signalling between both cell types via GAG-modified 3D matrices.

Poster 22

Uptake, distribution and toxicological effects of long term exposure of CeO_2 and $BaSO_4$ nanoparticles in Wistar rats

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To determine potential toxic effects of exposure to low dosages of nanoparticles, female Wistar Rats were exposed over the course of 90 Days to different concentrations of nanoparticles (0,1/0,3/1/3 mg/cm^3 CeO_2 and 50mg/cm^3 $BaSO_4$) with a subsequent recovery phase of 90 Days. Isolated alveolar cells type II (AT II) as well as lung sections of the treated animals were analysed using Raman Microspectroscopy (CRM) and Ion Beam Microscopy (IBM). We were able to show the uptake and the distribution of the nanoparticles in cells and tissues and revealed that exposure to low concentrations of CeO_2 and $BaSO^4$ can lead to accumulation of these particles in AT II cells and the septum of the lung. Analysis by IBM revealed effects on the cellular concentration and homeostasis of important trace elements Iron, Copper and Zinc which act as co-factors in a multitude of cellular processes. With the use of CRM and principal component analysis (PCA) the colocalisation of the particles with certain cell organelles were investigated and subsequent molecular changes in Lipid Droplets, Nucleus and Mitochondria could be determined. These results show that the investigated particles do have an effect even in subtoxic concentrations and the identified elemental and molecular changes can be used as toxicological biomarkers for the determination of cancerogenic and inflammatory long term effects of enduring nanoparticle exposure.

Poster 23

Hyaluronan/collagen hydrogels containing sulfated hyaluronan increase efficiency of HB-EGF during wound healing

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Functional biomaterials that are able to bind, stabilize and release bioactive proteins in a defined manner are required for the controlled delivery of such to the desired place of action, stimulating wound healing in health-compromised patients. Glycosaminoglycans (GAG) represent a promising group since they may be functionally engineered and are well tolerated by the recipient tissues due to their relative immunological inertness. Ligands of the Epidermal Growth Factor (EGF) receptor (EGFR) activate keratinocytes (KC) and dermal fibroblasts (DF) and, thus, contribute to skin wound healing. Heparin-binding EGF-like growth factor (HB-EGF) bound to GAG in biomaterials (e.g. hydrogels) might serve as a reservoir that induces prolonged activation of the EGF receptor. Based on previous findings, the capacity of hyaluronan (HA) and its sulfated derivatives (sHA) to bind and release HB-EGF from HA/collagen-based hydrogels was investigated. Molecular modeling and surface plasmon resonance (SPR) analyses demonstrated that sulfation of HA increases binding strength to HB-EGF. Gels containing sHA displayed a retarded HB-EGF release in vitro compared to pure HA/collagen gels and moreover HA and sHA hydrogels were shown to release bioactive HB-EGF over at least 72 h, which induced KC migration, EGFR-signaling and HGF expression in DF. Importantly, hydrogels containing sHA strongly increased the effectivity of HB-EGF in inducing epithelial tip growth in epithelial wounds shown in a porcine skin organ culture model. These findings suggest that hydrogels containing HA and sHA can be engineered for smart and effective wound dressings.

Poster 24

Acquired von Willebrand factor deficiency is reduced in HeartMate 3 patients

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Objectives

The acquired von Willebrand syndrome (AvWS) which is associated with left ventricular assist device (LVAD) support is caused by the loss of von Willebrand factor high molecular weight multimers (HMWM). The objective of this study was to investigate the differences of the multimeric structure of von Willebrand factor (vWF) in patients with HeartMate 3 (HM 3) or HeartWare ventricular assist device (HVAD) implantation.

Methods

In total, 70 patients with implanted HM 3 (n=35) or HVAD (n=35) were retrospectively investigated. HMWMs, intermediate (IMWMs) and low molecular weight multimers (LMWMs) were quantified by a densitometric methodology. vWF antigen, vWF-activity and vWF collagen-binding activity as well as demographic and clinical data were analyzed.

Results

AvWS, which is characterized by a decrease of vWF HMWMs was found in 97.1% in the HM 3 and 100% in the HVAD group. Compared to normal pooled plasma (NPP), HM 3 induced a reduction of HMWMs (26.4±5.3% vs. 40.8±6.1%, p <0.001) and an increase of LMWMs (42.8Â±6.4% vs. 31.0Â±8.1%, p<0.001), whereas HVAD patients exhibited an enhanced percentage of IMWMs (38.6Â±4.5% vs. 28.2Â±3.8 %, p<0.001) in addition to decreased HMWM (22.7Â±7.0%, p<0.001).Â Further, vWF-activity was elevated in patients with implanted HM 3 device (153.7Â±54.4%) compared to HVAD (126.3Â±39.7%, p=0.019).

Conclusions:

Patients with implanted HM 3 had more preserved HMWMs and a higher vWF-activity during device support. This may reduce AvWS in HM 3 patients and thus could lead to a lower bleeding complication rate.

Poster 25

Selective analysis of reactive oxygen species with LC-MS

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Reactive Oxygen Species (ROS) are of increasing interest for very different fields of science. Hydrogen peroxide and the superoxide anion radical (SAR) in particular are important ROS for medical and biochemical approaches, because these compounds are formed during different, important metabolic processes of organisms. As a consequence, many common analytical approaches were used to quantify the overall concentration of ROS, but in order to determine specific ROS, we wanted to establish a selective and sensitive method.

Thus, for the analysis of hydrogen peroxide, we used the specific reaction with the compound titanium(IV)-oxysulfate. The formed titanium(IV)-peroxo-complex was sensitively detected by using flow-through photometry which made an estimation of the LOD/LOQ of hydrogen peroxide possible. Using our modern instrumental setup, we were able to achieve an improved quantification with respect to sensitivity in comparison with the literature.

For detection of the SAR, the specific reaction with hydroethidium was used. Because of its low life-span in a millisecond range, SAR had to be produced in-situ to establish this assay. The response of the specific reaction product 2-hydroxyethidium was linear and an estimation of the LOD/LOQ was performed via LC-MS and compared with the values and procedure from the literature.

Both assays were finally applied to determination of hydrogen peroxide and SAR in water after treatment with a low-temperature plasma source. While the assay to determine SAR with hydroethidium seems to work accordingly, the hydrogen peroxide could not be detected with the titanium(IV)-oxysulfate assay.

Poster 26

Die Abhängigkeit der mechanischen Eigenschaften humanen Tractus Iliotibialis von der Probenaufbereitung

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Die Ermittlung von Eigenschaften und Materialparametern humanen Weichgewebes ist aktueller Gegenstand der Forschung. Oft werden Gewebe zuvor tiefgefroren, um flexibler in der Handhabe und Probenvorbereitung zu sein. Die Untersuchung des Einflusses von Gefrierprozessen auf die mechanischen Eigenschaften, sowie die Hemmung dieser durch Zugabe von Gefrierschutzmedium (DMSO) zu den Gewebeproben im Vorfeld des Einfrierprozesses sind Gegenstand dieser Arbeit.

Frische Proben von humanem Tractus iliotibialis wurden von Körperspendern entnommen. Jede Tractusprobe wurde longitudinal entlang der parallelfasrigen Hauptkollagenfaserrichtung in vier Streifen geschnitten. Jeder Streifen wurde anschließend im Vorfeld der Testung unterschiedlich präpariert: Frisch (1), fresh frozen (2), fresh frozen 1 w% DMSO (3), fresh frozen 10 w% DMSO (4). Alle Proben wurden partiell plastiniert, mittels einer uniaxialen Zugprüfanlage bis zur Zerstörung gedehnt und die relevanten Materialparameter aufgenommen.

Entgegen den Erwartungen waren keine signifikanten Unterschiede zwischen den Festigkeiten der Zustände (1) „frisch“ und (2) „fresh-frozen“ feststellbar. Der hohe Festigkeitsabfall bei Proben, welche mit 10 w% DMSO modifiziert im Zustand „fresh-frozen“ vorlagen, könnte in der spezifischen Wirkung von DMSO liegen, Quervernetzungen in Kollagen aufzuspalten und somit negativ die Zugfestigkeit zu beeinflussen. Bei fast allen Proben konnte Schlupf vermieden werden und die Proben bis zur gewünschten Zerstörung gedehnt werden. Materialversagen trat bei Zugkräften zwischen 80 und 600 N durch kaskadenartigrd Reißen der Kollagenfaserbündel auf.

Poster 27

Dynamische In vitro Analyse enossaler Dentalimplantate in humanen unfixierten Kieferpräparaten

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Entscheidend für eine erfolgreiche Einheilung von sofortbelasteten enossalen Dentalimplantaten ist die Primärstabilität in den ersten Wochen nach der Implantation.

Zur biomechanischen Untersuchung der Primärstabilität wurde ein Messaufbau genutzt, der die zyklische Mahlbewegung unter Okklusion der Zähne nachbildet. Durch eine wechselnde außermittige Belastung der Zahnkrone mit einer mittleren Kaukraft von 25 N werden die Dentalimplantate weitestgehend physiologisch belastet. Die resultierenden Mikrobewegungen zwischen der Zahnkrone und dem knöchernen Umfeld werden über einen Zeitraum von 10.000 Zyklen betrachtet und mithilfe eines optischen Bildkorrelationssystems zu definierten Zeitpunkten ausgewertet.

Gegenstand der Untersuchungen sind die beiden Implantatsysteme CAMLOG und CONELOG, die nach zahnärztlichen OP-Standards in 13 humane unfixierte Kieferpräparate eingebracht wurden. Die Implantation erfolgte jeweils paarweise randomisiert auf die beiden Hälften eines Kieferpräparats an den Positionen der Prämolaren (Regio 34, 44) und Molaren (Regio 36, 46).

Von den getesteten Implantaten (n = 52) mussten 12 aufgrund frühzeitigen Implantatversagens infolge defizitärer Knochen ausgeschlossen werden. Die beobachteten Relativbewegungen zwischen Zahnkrone und knöchernem Umfeld lagen im Bereich von 0,03 mm bis 0,74 mm. Hinsichtlich der absoluten Auslockerung wiesen die beiden untersuchten Implantatsysteme im humanen unfixierten Knochen keine statistisch signifikanten Unterschiede auf. Die untersuchten Implantat-Abutment Verbindungen haben demnach unter physiologischer Belastung keinen bedeutenden Einfluss auf die Primärstabilität.

Poster 28

Sample preparation as key for the fast and reliable calorimetric detection of microbial contaminations

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All living organisms generate heat as a by-product of the complex metabolic engine. If we look at the smallest scale of organisms, we find out that a single bacteria cell (e.g. Staphylococcus aureus) produces heat of about 2.5 pW[1]. Taking high-performance isothermal micro-calorimeter, the produced heat can be applied to quantify and to identify microbial contaminations in tap water[2], food[3] or on medical devices[4].Often is the detection much faster and more reliable as with conventional techniques[2]. However, the sample preparation and the optimization of the cultivation techniques in the calorimetric vessel are key points for the success of the new method. Therefore, we investigated two microorganisms: Lactobacillus plantarum and Pseudomonas putida as representative for anaerobic and aerobic systems, respectively. We used common microbiological cultivation techniques like direct plating on agar or inoculation of broth as well as membrane filtration as a pre-enrichment step for the sample and compared these different techniques in the context of detection time and reliability of the calorimetric signals.

We were able to show that the concentration-dependent measurements showed a correlation between the number of bacteria and the time required to reach the maximum heat flow. The latter might be the key for the application of real-time monitoring of contaminations in different fields.

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Poster 29

Experimentelle Werkstoffkunde in der Zahnärztlichen Prothetik

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Die experimentelle Werkstoffkunde der Zahnärztlichen Prothetik beschäftigt sich mit der Untersuchung von polymeren, keramischen, mineralischen sowie hybriden Materialien (Komposite) und deren Konstruktionseigenschaften. Dabei steht die genaue Erforschung der Wirkungsmechanismen unter Beanspruchung, zunehmender Alterung oder im Verbund anderer Werkstoffe im Fokus. Auf diese Weise kann ein besseres Verständnis der Struktur-Eigenschafts-Beziehungen und des Verformungs-/ Schädigungsverhaltens erhalten und die Performance, Qualität und Zuverlässigkeit der prothetischen Versorgung vorhergesagt werden. Dazu stehen uns in Kooperation mit dem INSTITUT FÜR MINERALOGIE, KRISTALLOGRAPHIE UND MATERIALWISSENSCHAFT (IMKM) in direktem Zugriff verschiedene Analysemöglichkeiten zur Verfügung.

Je nach den im Rahmen der Herstellung der Restauration angewendeten Verfahren, als auch den entsprechenden Umgebungsverhältnissen in der Mundhöhle erfolgt im Labormaßstab eine zeitraffende chemische (Auslaugverhalten, Säurewiderstand), mechanische (Kausimulation) und thermische Belastung (u.a. Wechselbadlagerung) der dentalen Werkstoffe.

Neben der klassischen Lichtmikroskopie werden die gekrümmten und transluzenten Probenoberflächen mit der hierfür entwickelten Makrofotografie, die sich durch eine große Tiefenschärfe sowie hohe Bildauflösung (80 Megapixel) auszeichnet, dargestellt. Die dabei eingesetzte Stacking-Technik ermöglicht die Berechnung der dreidimensionalen Oberflächen. Um eine detaillierte Vorstellung des Oberflächengefüges im Nanometermaßstab zu bekommen, wird die Rasterelektronenmikroskopie (SEM) mit gekoppelter ortsaufgelöster chemischer Analyse mittels energiedispersiver Röntgenspektroskopie (EDX) angewandt. Eine noch höhere Auflösung bis in den Ångström-Bereich ermöglicht die Transmissionselektronenmikroskopie (TEM), die ebenfalls mit EDX kombiniert werden kann. Die qualitative und quantitative chemische Analyse erfolgt zusätzlich durch Röntgenfluoreszenzanalyse (RFA) und die Phasenanalyse mittels Röntgendiffraktion (XRD). Durch Anwendung der Mikro-Computertomographie (µ-XCT) erhält man eine dreidimensionale, ortsaufgelöste Dichteverteilung mit resultierender Material- und Fehlstellenverteilung im Mikrometermaßstab.

Poster 29

Je nach Probenbeschaffenheit stellen die Verfahren darüber hinaus eine zerstörungsfreie Messmethode dar, um gegebene Fragestellungen im zeitlichen Verlauf der Beanspruchung, Alterung und Schädigung zu beurteilen. Des Weiteren geben zerstörende Analysemethoden wie die Simultane Thermoanalyse Aufschluss u.a. über das Schmelzverhalten, die Phasenzusammensetzung und den Polymerisationsgrad. Die Methodenvielfalt wird durch die Bestimmung mechanischer Eigenschaften wie Festigkeiten, Duktilität, E-Modul, Bruchenergie sowie Härte komplettiert.

Poster 30

Registrierung von Bewegungsintentionen mittels patienten-spezifisch konzipierten Brain-Computer-Interfaces

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Allein in Deutschland erleiden pro Jahr ca. 12.000 Menschen Wirbelsäulentraumen, welche nicht selten mit Rückenmarksverletzungen und daraus resultierenden Querschnittslähmungen einhergehen. Ziel dieser Forschungsarbeit, ist jenen querschnittsgelähmten Patienten, langfristig die Wiedererlangung der Willkürmotorik zu ermöglichen.

Umgesetzt wird dies durch die Entwicklung eines Brain-Computer-Interface, mit Hilfe dessen Bewegungsintentionen des Patienten registriert werden sollen. Basierend darauf wird die entsprechende Muskulatur in den gelähmten Körperregionen entsprechend stimuliert, um die Bewegungsausführung zu ermöglichen.

Im hier eingereichten wissenschaftlichen Beitrag soll der Fokus auf der Gedankenregistrierung mittels Elektroenzephalografie inklusive der hiermit verbundenen hochkomplexen Datenverarbeitung liegen. Die EEG-Daten werden mittels einer kommerziell erhältlichen Elektrodenkappe sowie zugehöriger Messtechnik aufgenommen, während dem Probanden spezifische Bewegungsmuster (Bein-, Arm-, Fingerbewegungen sowie reine Bewegungsvorstellungen) vorgegeben werden.

Aus den akquirierten Datensätzen werden für die Bewegungsinitierung relevante Signalfeatures extrahiert. Diese Features werden anschließend genutzt um unter Nutzung einer Support-Vector-Machine für jeden Porbanden/Patienten individuell effektive Klassifikatoren zu berechnen. Diese ermöglichen anschließend die Übersetzung der registrierten Hinrrindenpotentiale in entsprechende Bewegungsintentionen. Auf diese Weise gelingt es uns bereits beispielsweise Bewegungen des linken und rechten Daumen allein anhand der EEG-Datenverarbeitung zu unterscheiden.

Poster 31

Dynamic in vitro microfluidic system for standardised osteoimmunological evaluation of implant materials

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In the last few decades, ceramics have entered the field of dental and bone implants and there is a variety of suitable ceramic compositions available which remain to be tested for implant research.

At the implant site, blood proteins are being adsorbed by the implant and subsequently immune cells adhere to the surface. Macrophages, as major protagonists in inflammatory responses, polarize and either promote pro- or anti-inflammatory actions at the wound site. Amongst other things, they signal mesenchymal stem cells (MSCs), via cytokine release and hence have a strong effect on bone forming processes. However, studies focusing on macrophage polarization and their effects on MSCs directly on the biomaterial are still elusive due to varying experimental approaches.

With emerging materials and surface functionalizations intended for implant purposes, there is a strong need for a standardized procedure in osteoimmunological evaluation.

We are implementing a modular microfluidic approach that will allow investigation of various biomaterials, co-culture, and simple and rapid secretome analysis. Our interest is particularly vested in the influence of various solid biomaterials on the polarization of macrophages, and cellular communication between them and osteogenic differentiating MSCs. In a novel approach, we incorporate biomaterials in a circular microfluidic system allowing cytokine signalling of immune cells and MSCs that are spatially separated. Cytokine release and concentrations are being monitored by sampling of circulating media and instant analysis via a homogeneous immunoassay in a separate microfluidic module.

Poster 32

Signal suppression in low temperature plasma ionization (LTPI) mass spectrometry

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In recent years, various ionization methods for mass spectrometry (MS) have been published that allow fast and easy analysis of samples under ambient conditions. Among those, plasma-based methods are particularly interesting as they offer great potential for implementation in mobile analytical instruments. However, systematic investigations of the signal response using this technique, such as the influence of the matrix on the signal intensity, are still rare.

We addressed this question and analyzed six anilines in nine different solvents each on a paper target by low-temperature plasma ionization (LTPI) MS under optimized conditions. In a second approach, 1 µL of a 1 mM chlorpyrifos solution, a common pesticide, was analyzed from peels of various fruits, vegetables and fungi. The samples were analyzed using a plasma source coupled to a Bruker 3000+ ion trap.

Our results show that the effect of the compound properties significantly exceeds the influence of simple sample matrices such as different organic solvents and water, with the trend that more volatile solvents tend to reduce the signal response of the analytes. However, there were several specific interactions between solvents and analytes that need to be considered in targeted applications of this method.

When selecting a single compound to assess matrix effects in biological samples, the pesticide chlorpyrifos was detected in all tested fruit, vegetable and fungal species. However, we found a strong influence of the matrix on the signal response. For example, citrus fruits showed a particularly strong signal suppression.

Poster 33

Utilization of paramagnetic relaxation enhancements for structural analysis of the Y2 receptor in complex with NPY and Arrestin

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The G-protein coupled neuropeptide Y2 receptor (Y2R) is involved in a number of key physiological processes. On basis of a structural model of the Y2R in complex with its natural ligand, the neuropeptide Y (NPY) (Kaiser et. al, 2015), we want to determine distances within the Y2R binding pocket and their changes upon interaction with intracellular bound Arrestin. So far, we establish a solid-state MAS NMR approach where we use distance dependent paramagnetic relaxation enhancement (PRE) effects between a paramagnetic tag attached to a free cysteine in the Y2R and specific 13C labeled amino acids in the NPY. E.coli expressed and purified mutants of Y2R mutants with introduced cysteines, yielding in >10 mg receptor/ L medium, were functionally reconstituted into phospholipid bicelles. Successful attachment of the paramagnetic spin label MTSL to the receptor was proven in a CPM fluorescence assay. Next, different isotopically labeled NPY variants will be incubated with the Y2 receptors with and without MTSL attached, and time-dependent relaxation decays will be recorded using cross polarization solid-state MAS NMR with ^{13}C double quantum filter. In a first measurement we used the receptor mutant Y2R_A202C were the MTSL is at the entrance of the binding pocket and detected in the presence of MTSL a relaxation rate increase for I28-Cd in the NPY from 1,3 s^{-1} to 1,9 s^{-1}, while for A14 the rate was constant, which is in good agreement with the model. In the next step we will determine rates for further Y2R mutants and NPY variants, and finally will add Arrestin to investigate changes in the rates upon Y2R activation.

Poster 34

Snap sampling for GC-MS analysis of volatile compounds

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The analysis of olfactory signals of animals has always been of great interest in behavioural science. Within this context, volatile compounds are of highest relevance to understand olfactory communication within and between species. Therefore, in state-of-the-art methods, volatiles are trapped on adsorption materials and subsequently analysed by GC-MS in an off-site lab. However, due to their mobility, rapid in situ sampling is required to analyse the odour of animals.

Recently developed mobile GC-MS devices with direct probes under free ranging conditions could enable the analysis of body odours without additional materials. Here, we present the compound coverage obtained with two methods: first, sampling animals by direct probe for on-site analysis with a mobile device and, second, active sampling using thermal desorption tubes followed by analysis in a state-of-the-art GC-MS for laboratory scale. Both methods were applied to body odour analysis of common marmosets (Callithrix jacchus). We show to what extent the detected compounds match each other and compile the information that would be lost using only either one of the methods. In addition, we compare advantages and disadvantages of these two methods of sample collection for field studies. In comparison to the mobile GC-MS device, active sampling using thermal desorption tubes subsequently analysed with a standard lab GCMS is concluded to be the most appropriate approach for VOC analysis in free-ranging animals. Finally, we present results on VOC sampling efficiency with thermal desorption tubes when shortening the sampling time.

Poster 35

Actin stress fiber dynamics in spatially confined cells

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Cell shape is fundamentally linked to cell function and tissue integrity. Cells strongly change shape during invasive cell migration in wound healing and tumor metastasis, and coordinated shape changes of neighboring cells are essential for a successful completion of morphogenesis. In this context, important questions are how external spatio-mechanical stimuli lead to a successful adaption of cell shape and how main components of the cell cytoskeleton are involved in this process.

We use microstructured substrates to investigate the adaption of human primary endothelial cells to lateral confinement. Live cell staining and time-resolved image analysis are used to investigate the dynamics of the actin cytoskeleton, which is central to cell shape regulation and cell mechanics. Traction force microscopy is used to study the correlated contractile characteristics of confined cells.

We found that, as cells become more polarized due to stronger confinement, actin cytoskeleton dynamics are reduced. In addition, a steady inward transport of actin stress fibers could be observed and quantified, showing an apparent increase of transport in less confined cells. Furthermore, in strongly confined cells, overall cell traction forces were diminished, while being more strongly focused in one direction, correlating with a stronger polarization of the actin cytoskeleton.

In sum, our setup allows analyzing both the cells' morphological and mechanical adaption to spatial confinement in a time-resolved and quantitative manner. With this, we aim to contribute to a better model of the dynamic and complex cell response to geometric constraints.

Can breast cancer cells be distinguished from blood cells by mechanical parameters?

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Background:
Even years after successful treatment of the primary tumor about one third of breast cancer patients are suffering from metastatic relapse. One reason might be hematogenous spread during early disease stages when isolated tumor cells change their physical properties from epithelial to mesenchymal features (EMT) and become able to disseminate from the primary tumor site. After entering the lymphatic system and the blood circulation they can travel to distant organs and seed metastases. Therefore circulating tumor cells (CTCs) might be interesting and easy accessible surrogate markers to monitor disease progression and treatment response in the clinical setting. However, their ability to change phenotypical, mechanical as well as functional properties during cancer growth and treatment courses makes it very challenging to characterize CTCs in the blood in order to investigate their prognostic relevance.

Methodology and Results:
One approach might be the detection of CTCs in the blood based on mechanical properties such as deformability using an optical stretcher device. In an optical rheometer, cells are deformed noninvasively by a dual beam trap. Thus, the softness of a single cell can be measured. PBMC were isolated from the peripheral blood of a healthy donor using density gradient centrifugation. Erythrocytes were incubated with magnetic beads coated with CD235a antigen (glycophorin A) and removed using matching separation columns (MACS; Miltenyi Biotech). Breast cancer cells MDA-MB 231 were cultured under standard conditions and harvested prior to analysis using trypsine. Both cell suspensions were applied separately to the optical stretcher (RS Zelltechnik, Leipzig) and rheological parameters such as deformability and stiffness were measured. Distinct cellular profiles could be obtained from hematopoetic cells and breast cancer cells, respectively. Relative deformation was significantly different between both cell types. Furthermore, 10:1 mixtures of PBMC and MDA-MB 231 cells were analyzed with the optical stretcher. Results indicated that the mixed samples could be sorted into subpopulations of significantly different cellular stiffness based on mechanical parameters such as cell size.

Poster 36

Conclusion & Outlook

Further experiments to test the usability of the optical stretcher for possible CTC detection in peripheral blood of breast cancer patients are currently ongoing. Since CTCs are very rare events in patient‘s blood samples, mixed cell suspensions consisting of PBMC with different numbers of spiked tumor cells will be prepared to mimic clinical samples and to detect sensitivity and specificity of this method. Once significant differences between cellular profiles of the mixed samples with low numbers of spiked tumor cells can be measured, the methodology might be transferred to clinical samples in order to develop a liquid biopsy test.

Poster 37

Physics of Tumor-ECM Interaction

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Tumors are usually stiffer than their environment, but single tumor cells are typically softer than their healthy counterparts. This puzzle raises the question how tumors and their environment, most notably the extra-cellular matrix (ECM), actually interact.
We deploy tumor spheroids from cell lines and from primary tumor tissue on collagen matrices and observe the deformation fields in the ECM that are induced by the tumor-ECM interaction. We characterize the time and force scales of how tumors pull on their environment. Both cell lines and real tumors stiffen their surrounding ECM by the collective traction that they exert. This mechanical stiffening in turn promotes and defines cancer invasion into the tissues.

Poster 38

Untersuchung der Primärstabilitätseigenschaften von Schraub- und Pressfit-Pfannen im Rahmen einer mechanischen Versagensprüfung

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Die Implantation einer Hüfttotalendoprothese ist einer der häufigsten operativen Eingriffe der Gegenwart. Nach der Implantation einer HTEP-Pfanne werden hinsichtlich der Stabilität zwei Zustände unterschieden: die Primär- und die Sekundärstabilität. Die Primärstabilität bezeichnet den Zustand, welcher direkt nach der Implantation vorliegt und aus der Pfannengeometrie und der Implantationsvariante resultiert. Eine Sekundärstabilität hingegen wird erst dann erreicht, wenn das Knochengewebe in die Oberflächenstruktur des Implantats eingewachsen ist. Um eine ausreichend gute Sekundärstabilität zu erzielen, ist es von entscheidender Bedeutung, dass das Implantat zuvor primär ausreichend gut im Knochen verankert wurde. Verschiedenste Pfannengeometrien und Pfannengrößen erschweren hierbei die intraoperative Auswahl.

Schraub- und Pressfit-Pfannen (n = 12) mit den Außendurchmessern 52 mm und 60 mm wurden definiert in speziell geformte Trägermaterialien (Sawbones Europe, Limhamn, Schweden) implantiert. Unter Zuhilfenahme einer pneumatischen Prüfmaschine und eines speziell entwickelten Prüfaufbaus wurden diese anschließend nacheinander in der Prüfmaschine fixiert. Abschließend wurde der Pfannenrand einer jeden HTEP-Pfanne mit einer stetig anwachsenden Druckkraft bis zum Versagen belastet.

Die untersuchten Schraub-Pfannen zeigten gegenüber den Pressfit-Pfannen höhere mittlere Versagenslasten. Das Auskippen führte bei den Schraub-Pfannen jedoch zu einem Ausreißen des Trägermaterials. Die untersuchten Pressfit-Pfannen zeigten geringere mittlere Versagenslasten. Das verwendete Trägermaterial blieb jedoch weitestgehend intakt.

Poster 39

Indium-tin-oxide (ITO) – A beneficial material for advanced multielectrode arrays in bioelectronic applications

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Indium-tin-oxide (ITO) is a standard mixed oxide material for fabrication of touchscreens and solar cells, due to its excellent transparency properties. Depending on the fabrication process, ITO is a semi conductive material that is suitable for conducting paths. Thus, ITO can be used for multielectrode arrays (MEAs) in bioelectronic applications. MEAs are electrodes and conducting paths coated substrates for cultivating cells or binding enzymes on the surface and detecting alterations of the biological component with electrochemical methods like impedance spectroscopy. Commonly, gold and platinum are the most used electrode materials for fabrication of microelectrode arrays (MEAs) due to their superior conductivity and biocompatibility. Since these materials are opaque, photonic analysis methods like transmitting light microscopy are excluded. While ITO is a superior material for combined bioelectronic and photonic monitoring, the clearly lower conductivity is a drawback and for some designs and applications critical. In this context, we used finite element method FEM) simulation for demonstrating how optimized mixed material MEA designs can be identified which combines advantages of optical transparency as well as suitable conductivity to sensitively monitor cellular alterations. Moreover, we were able to optimize ITO electrode arrays for an efficient coupling of redox enzymes like P450 BM3 and more strikingly, we achieved a clearly increased electron-transfer for the direct enzyme regeneration without the need of expensive cofactors like NADPH.

Poster 40

Experimentelle Beurteilung von Hüftgelenkspacern aus Knochenzement

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Spacer aus antibiotikabeladenen Knochenzement werden bei zweizeitigen Revisionen von Hüftgelenksprothesen eingesetzt. Sie sind ein bewährtes Mittel, um in der Zeit ohne Endoprothese die Mobilität des Patienten zu erhalten und gleichzeitig die lokale Gelenkinfektion zu behandeln. Es kommt jedoch zu Brüchen der Spacer in Folge von Belastungen. Ziel ist es daher, die Festigkeit dieser Interimsimplantate zu erhöhen. Dazu muss der Implantatausfall jedoch besser verstanden werden. So ist zu klären, bei welchen Lasten sie versagen und wo genau Brüche auftreten.

Für die Beurteilung von Spacern gibt es kein Standardprotokoll. Aus diesem Grund ist der experimentelle Aufbau an die Norm ISO 7206-6 angelehnt, welche die Prüfung von Hüftgelenksprothesen festlegt. Probekörper eines klinisch eingesetzten Spacers (StageOne™, Biomet) werden mittels Silikonform aus Knochenzement (Palacos® R, Heraeus) hergestellt. Diese werden in einen Versuchstand eingebracht und über den Gelenkkopf bis zum Versagen belastet. Der experimentelle Aufbau wird weiterhin in einem Finite-Element-Modell nachgebildet und simuliert.

Der Bruch erfolgt im Nackenbereich des Spacers. Hier werden auch die höchsten Spannungen berechnet. Somit ist diese Region als kritischer Designbereich zu bewerten.

In nachfolgenden Schritten werden Gestaltoptimierungen des kritischen Bereichs vorgenommen. Eine klinische Alternative ist die Augmentationen mit Steinmann-Nägeln (gebogenen Metallstäbe). Beide Varianten werden experimentell und numerisch hinsichtlich ihrer Haltbarkeit evaluiert. Ziel der weiteren Arbeit ist es das Design der Spacer anzupassen, um sie langlebiger zu gestalten.

Poster 41

Biomechanische Analyse zur operativen Versorgung von periprothetischen proximalen Femurfrakturen bei einliegendenden Hüfttotalendoprothesen

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Die Behandlung von periprothetischen Femurfrakturen (PPF) stellt die Operateure stets vor große Herausforderungen. Als Therapie der Wahl hat sich unter anderem die Anlage von Cerclagen bewährt. Es liegt jedoch keine valide Literatur vor wie sich Anzahl und Art der Cerclagen auf die Primärstabilität auswirken.

Entlang der Schaftachse eines implantierten HTEP-Schaftes wurde ein Frakturspalt gesägt und anschließend mit Cerclagen versorgt. Danach ist das distale Ende abgesetzt und der Femur in einen zylindrischen Sockel aus Polyurethan-Schnellgießharz eingebettet worden. Getestet wurde die uniaxiale Kraft, bei der der versorgte Femur versagt. Die Vorstudie ist in 3 Gruppen (1xBand, 1xDraht, 2xDraht) mit je 3 Kunstknochen und die Hauptstudie in 2 Gruppen (2xDraht, 3xDraht) mit je 11 humanen Femora aufgeteilt.

Die Vorstudie, zeigte, dass die Versorgung mit 2 Drahtcerclagen gegenüber der mit einer Draht- bzw. einer Bandcerclage überlegen ist. Daraufhin wurde die Hauptstudie mit 2 und 3 Drahtcerclagen durchgeführt, um zu untersuchen ob eine weitere Steigerung der Primärstabilität erzielt werden kann. Vorläufige Ergebnisse zeigen, dass 3 Cerclagen eine etwas bessere Primärstabilität als 2 Cerclagen bieten.

Die Versorgung mit 2 Drahtcerclagen weist eine deutliche Verbesserung der Primärstabilität gegenüber einer Draht- bzw. einer Bandcerclage auf. Eine weitere Drahtcerclage bringt lediglich einen Mehrwert von 226,1 N. Mit zunehmender Anzahl an Cerclagen ist jedoch eine Verringerung der periostalen Durchblutung anzunehmen.

Poster 42

A New Enzymatic Strategy for the Selective and Sustainable Synthesis of the Antispastic Drug Baclofen

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Enzymes are an essential tool in the pharmaceutical industry, which enables the efficient synthesis of active pharmaceutical ingredients (APIs) with high enantioselectivity. However, the potential of biocatalysis in the pharmaceutical industry is not fully realized. Recently established biocatalytic processes highlight the possible scope of green synthetic strategies on an industrial scale. The development of new enzymatic scalable processes for the synthesis of APIs and intermediates represents a future prospect of the pharmaceutical industry. In this respect, the design of new synthetic routes for the production of antispastic and anti-inflammatory drugs (e.g. Baclofen, Ketoprofen) is of particular interest.

In our project, we developed a synthetic strategy for the enantioselective synthesis of non-natural amino acids using immobilized Lipase B from Candida antarctica (Novozyme 435®). A convenient procedure was established by conducting the enzymatic reaction in a biphasic aqueous-organic system. This method allows a fast screening of reaction conditions and substrate scope in a commercial reactor and permits the quick and facile separation of unreacted substrate from product at the same time. Using this set-up, the synthesis of the biologically active (R)-enantiomer of Baclofen and its derivatives was successfully realized with enantiomeric excess of up to >99%. The desired products were easily separated from the reaction mixture and the immobilized enzyme may be recycled several times without loss of activity, reducing waste and the consumption of resources.

Poster 43

Design and Analysis of Synthetic Riboswitches for the Regulation of tRNA Processing

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The ligand-dependent regulation of gene expression, which represents one fascinating aspect of the numerous biological functions of RNA, is mediated by riboswitches. Natural riboswitches are often located in the 5‘UTR of bacterial mRNAs. They enable an efficient control of gene expression mostly on the transcriptional or translational level. The regulation is accomplished by two interacting RNA domains: the aptamer domain and the expression platform. The aptamer domain binds small molecules with high selectivity and specificity. This interaction triggers a conformational change in the expression platform that subsequently affects gene expression. Artificial combination of these two structural domains allows the generation of synthetic riboswitches. We designed an artificial riboswitch with a novel regulatory principle different from transcription or translation. The resulting constructs control the RNase P-mediated 5’-processing of a tRNA in a ligand-dependent manner. For this purpose, we fused the well-characterized theophylline-aptamer to in silico predicted sequences, whose secondary structure should mask the cleavage position for RNase P in the absence of theophylline. In vivo analysis of the riboswitch candidates using the reporter gene with an integrated amber-STOP codon and a corresponding suppressor-tRNA, indicated theophylline-dependent tRNA processing. This ligand-dependent tRNA maturation was confirmed by Northern blot analyses as well as in vitro processing reactions. Future experiments will investigate the universal application of such RNase P-dependent riboswitches in all kingdoms of life.

Poster 44

A DNA Origami and LbL Hybrid System for Drug Delivery

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Personalized medication is of high interest for the treatment of a rising number of severe diseases. Here, we present a hybrid carrier system composed of DNA origami nanostructures and polymeric Layer-by-Layer (LbL) microcarriers. Both systems bear unique properties in respect to unconventional drug delivery and have independently shown to act as reliable delivery devices. Their combination promises to overcome individual drawbacks and to improve the overall delivery of active compounds into the cytoplasm of living cells. Overall, the design and characterization of the combined system will be shown. The focus is set on the superior properties of the hybrid system over the individual components and a mechanism to transport a defined amount of active agent into the cytoplasm will be presented.

Poster 45

Phosphate salts as biocompatible bases for the generation of 2-component hydrogels

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Both naturally occurring (i.e. collagen) and synthetic hydrogel forming materials are of interest for tissue engineering and cell culture applications. Previously, our group developed an anhydride-based oligomeric cross-linker, which can effectively form non-cytotoxic, stable 2-component hydrogels for amine-containing materials. The cross-linking reaction requires a base to control amine protonation. Previous work involved organic amine bases, such as N-methyl-piperidin-3-ol (NMPO).

This work investigates the effect of substituting the non-physiological organic bases with potassium phosphate (K_3PO_4) and potassium hydrogen phosphate (K_2HPO_4), salts of phosphoric acid which react as bases when dissolved in water (pK_{a2}=7.20, pK_{a3}=12.37). With both bases, it was possible to generate stable hydrogels by mixing a solution of gelatinous peptides and base with cross-linker. When comparing K_2HPO_4-based and NMPO-based hydrogels, the ultimate storage modulus was shown to be higher for the phosphate-based hydrogels (9.07 kPa to 7.65 kPa). Conversion of hydrogel components was found statistically independent of base chemistry, as indicated by the amount of leachables (25.4±4.5% for NMPO-based and 32.5±6.9% for K_2HPO_4-based hydrogels) and comparable cross-linking degree. For K_3PO_4-based hydrogels, similar results regarding leachables and cross-linking degree could be observed.

Ultimately, these results show the suitability of the inorganic salts as bases to support the cross-linking reaction. In the next experiments, we will investigate whether the use of phosphate bases is beneficial for cell viability and construct cytocompatibility.

Poster 46

The Challenge of Human Liver Tissue Engineering

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A reconstruction of the liver tissue architecture is an ambitious goal but is required for displaying organ functions like e.g. xenobiotic metabolism. To mimic the in vivo structure and functionality differentiated cells and corresponding extracellular matrix (ECM) have to be combined in a suitable culture system. While primary human liver cells (PHC) can be isolated in good quality and quantity from human liver tissue, the sinusoidal ECM required by the cells is still unclear. Therefore, aim of this project is a long-term cultivation of PHC in scaffolds without adding ECM to investigate their stability and matrix production capacities.

Starting point for our approach are freshly isolated PHC. Primary human hepatocytes (PHH) will be cultivated for up to 21 days in Alvetex Scaffold inserts and non-parenchymal cells (NPC) in common cell culture plastics both without ECM coating. In addition, PHH will be cultivated in 2D- and 3D-collagen systems established for short- and long-term cultivation. Preliminary data from PHH cultivation for 7 days showed differences in viability, morphology and cellular arrangement depending on the culture system. So far, results in terms of these properties were better in Alvetex Scaffold inserts compared to 2D-collagen cultures, but best results could be achieved in 3D-collagen cultures. Analysis of cultured NPC is work in progress.

In conclusion, it seems possible to cultivate human hepatocytes in a matrix-free system without a dedifferentiation of the cells for at least 7 days. This will allow to evaluate the matrix homeostasis by PHC using a Proteomics approach in the next step of this project.

Poster 47

Injectable oligomer-cross-linked chitosan hydrogels and nanocomposite hydrogels as potential regenerative materials

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Chitosan is the most promising natural biomaterial utilized for bone tissue engineering due to its inherent antibacterial properties, bioactivity, biodegradability and osteoconductivity. Injectable chitosan formulations typically utilize a physical gelation strategy. Covalent cross-linking, however, might yield materials of higher stability and better control over gel properties. In this project, we aim at the development and characterization of injectable oligomer-cross-linked chitosan hydrogel (iCsgel) and nanocomposite hydrogel (iCsNC), by combination of newly developed protein nanoparticles (NP), as reinforcing fillers and delivery devices, and oligomer-cross-linked chitosan as gel matrix.

iCsgel were fabricated in situ by cross-linking chitosan solution with our anhydride containing oligomers after careful pH adjustment. For iCsNC fabrication, lyophilized protein NP were dispersed in chitosan solution prior to gelation. The resulting gels were rheologically characterized. Cytocompatibility and cell proliferation of cell-laden (L929 mouse fibroblasts) iCsgel and iCsNC were assessed with Alamar blue® assay.

Entrapment of NP into gel matrix increased gel modulus in a concentration-dependent manner. Lyophilized gel/NC showed good swelling after 24h immersion in PBS. Cell-laden iCsgel and iCsNC revealed good cell survival and proliferation in the gel/NC matrix.

iCsgel and iCsNC with biologically relevant mechanical properties represent a promising platform of regenerative biomaterials that can further be functionalized and that is already promising for drug and cell delivery.

Poster 48

Isolation of extracellular vesicles by sequential filtration

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An increasing number of studies have recently investigated the therapeutic potential of extracellular vesicles. A known issue in the field is the lack of a widely accepted isolation method that allows for large-scale production of clinical-grade extracellular vesicles. We developed a method for the reproducible isolation of pure exosome preparations while applying very low magnitude manipulative forces and thus not impairing exosome structure and function. Briefly, the isolation protocol consists of three back-to-back filtration steps. ("sequential filtration") First, floating cells and cell debris are depleted by a simple dead-end filtration. Subsequently, tangential flow filtration is employed in order to concentrate the sample and wash out small contaminants such as free proteins or tissue culture media components. Finally, low-pressure filtration through controlled pore size track-etched membranes allows a size-based separation of exosomes from larger particles present in the sample.

Isolated particles were studied thoroughly by means of Nanotracking Analysis, flow cytometry, and mass spectrometry. We could show that sequential filtration yields a vesicle population of highly homogenous size, expressing typical exosomal surface markers such as CD63 or CD81.

We are using sequential filtration in our current project, which aims to elucidate the pathophysiological function of exosomal bioactive lipids in chronic inflammation. In this context, we are employing LC-MS/MS for the detection of bioactive lipids in isolated exosomes.

Poster 49

Bone tissue engineering: Cross-linked microparticles as drug delivery system for siRNA

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The therapeutic application of the bone inducing protein BMP-2 is known to stimulate antagonistic proteins, such as noggin and chordin as well as sclerostin, which reduces the therapeutic efficiency of BMP-2. Hence, these antagonists are interesting targets for gene silencing in order to improve local bone regeneration [1,2]. The aim of this study was to investigate the stability, release properties and silencing efficiency of siRNA delivered from gelatin microparticles (cGMP) that have been cross-linked with maleic anhydride containing oligomers [3]. The siRNA was complexed with different transfection systems, namely newly developed tyrosine-modified polyethylenimine (P10Y) nanoparticles [4] and Lipofectamine® RNAiMAX. We developed a method for analyzing siRNA release, complex stability and cellular uptake time-dependently involving a transwell system and SaOS-2 cells. Release and uptake of biological active siRNA were detected after 24 h, 48 h and following lysis of cGMP. By treatment of SaOS-2 cells with noggin siRNA-loaded cGMP silencing of noggin and improved osteogenic differentiation were found at gene expression levels and ALP activity. Further analysis is in process.

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Poster 50

Cell-free expression for characterisation of site-specific dynamics of the growth hormone secretagogue receptor using solid-state NMR

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In the past years, the elucidation of numerous crystal structures of G protein-coupled receptors (GPCRs) has been possible due to the important progress made in structural biology of membrane proteins. In parallel, the development of spectroscopic techniques such as solid-state NMR gave the opportunity to investigate the dynamics of these receptors in a native-like membrane environment. In this project, we focus on the growth hormone secretagogue receptor (GHSR) also known as ghrelin receptor according to its natural ligand which, among other functions, stimulates food intake. The dynamics of the fully 13C-labelled GHSR was characterised using DIPSHIFT NMR, highlighting the GHSR as a highly flexible membrane protein [1]. However, the results represent an average of the dynamics of all sites of the receptor. Therefore, we set out to get insight into the dynamics of specific domains of the GHSR such as the termini, loops and transmembrane (TM) domains. To be able to label those specific regions of the GHSR with NMR-active isotopes, a cell free expression system was established with which it was possible to express GHSR in the precipitated form with a yield of up to 1.2mg per 1mL reaction volume. Then, the receptor was reconstituted into deuterated lipid bicelles. As a result, the labelling of the TM domains has shown slightly higher order parameters (reflecting higher rigidity) than the fully labelled receptor while labelling of the C-terminus highlights more flexibility.

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Poster 51

Development of novel dual histone deacetylase-proteasome inhibitors

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Polypharmacology describes the concept of one drug addressing multiple targets to exploit synergistic modes of action and has emerged as a promising new approach in drug discovery. The synergism between histone deacetylase (HDAC) inhibitors and proteasome inhibitors relies on the blockage of the two major protein degradation pathways, the proteasome and aggresome, resulting in misfolded protein accumulation. Recently, we reported the design and synthesis of RTS-V5 as the first-in-class dual HDAC6 and proteasome inhibitor. The activity on both targets was confirmed by biochemical as well as cellular assays and X-ray crystal structures of RTS-V5 in complex with both HDAC6 and the 20S proteasome.
[1] It was demonstrated that RTS-V5 possesses high activities against several leukemia and multiple myeloma cell lines and patient-derived leukemia cells. In addition, RTS-V5 induces apoptosis and blocks the cell cycle, proliferation, colony formation and aggresome accumulation. Despite its high potential as an anticancer agent, however, RTS-V5 also revealed scope for optimisation with regard to HDAC inhibition and isoform selectivity. In this work, we improved the HDAC inhibitory activity by introducing different linker moieties and zinc binding groups into a new MG132-derived scaffold.

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Poster 52

Simultaneous precise CRISPR editing of multiple genes in the same human cell

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CRISPR editing is a powerful tool to introduce mutations via targeted DNA double-strand breaks (DSBs). Cellular repair of DSBs by non-homologous end joining (NHEJ) often results in insertions or deletions (indels) at the cut site, while homology-directed repair (HDR) can use a donor DNA molecule carrying a desired mutation allowing precise genome editing (PGE). Because NHEJ is more efficient than HDR, PGE efficiency is generally low. This results in the inability to introduce multiple precise genetic changes in mammalian cells. To overcome this limitation, we developed an approach where we utilize catalytically inactive DNA-protein kinase catalytic subunit, a key protein of non-homologous end-joining. We observed an increase of HDR for 14 genes, sometimes reaching 87% PGE, irrespective of the CRISPR enzyme used (Cas9, Cas9 nickase, Cpf1) and cell type (human induced pluripotent stem cells, human embryonic kidney cells 293, human immortalized myelogenous leukemia cells K562). The increased HDR efficiency allows for multiplexed precise genome editing of up to four simultaneously targeted genes (8 chromosomes). The genomes of the DNA-PKcs mutant cells were stable as judged by karyotyping and whole genome sequencing analysis. Thus, the inactivation of the DNA-PKcs active site greatly facilitates PGE. Finally, we find several small molecules which target different DNA repair pathways to be potent transient enhancers of HDR.

Poster 53

Rational Design and Synthesis of Belinostat and 4-Acyl-Pyrrol-based Dual HDAC/BRD4 Inhibitors

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Epigenetic modifications and their crucial role in regulation of gene expression have been widely studied and deregulations of these mechanisms are associated with the pathogenesis of several human diseases. Histone deacetylases (HDACs) remove acetyl groups on histone and non-histone proteins. [1] N-Acetyl-lysine marks are recognized by bromodomain containing proteins (BRDs) which recruit enzymes of histone modification, including histone acetyl transferases (HATs) and HDACs. [2,3] Combinations of HDAC inhibitors (HDACi) and BRD inhibitors (BRDi) have shown promising synergistic anti-pro-liferative effects against cancer cells. [4,5] Given the advantages of polypharmacology dual HDAC/BRD inhibitors could be promising new multi-target drugs. [2,3]
Consequently, we herein present the design, synthesis and biological evaluation of a small library of new dual HDAC/BRD inhibitors based on the 4-acyl-pyrrol BRD4(1) inhibitor XD14 [6] and established HDACi Belinostat. [1]
The subsequent biological evaluation confirmed that some of the compounds are dual HDAC/BRD inhibitors with anti-proliferative properties. Collectively, the results provide valuable insights for future design of dual HDAC/BRD4 inhibitors.

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Poster 54

Parallel Synthesis of DNA-Alkylating Histone Deacetylase Inhibitor (HDACi) Hybrid Molecules

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Overexpression of histone deacetylases (HDACs) is frequently observed in a wide variety of tumor diseases including glioblastomas. These enzymes play a crucial role in many different biological processes due to their repressive effect on gene transcription. Because of their essential influence on drug resistance mechanisms of tumor cells, HDACs advanced to become interesting targets in epigenetic cancer therapy.[1] The current treatment of glioblastoma multiforme (GBM), one of the most common and aggressive primary brain tumors with high resistances against standard therapies, is the use of DNA-alkylating agents in combination with radiotherapy after surgical resection of the tumor.[2]

In this study, we designed a scaffold containing a DNA-damaging cap group, different linker types and a hydroxamic acid moiety as warhead to aim at dual targeting. We herein present a facile solid phase-supported parallel synthesis of a library of DNA-alkylating HDACi hybrid compounds. Notably, our novel parallel synthesis strategy offers a straightforward and efficient gateway to different hybrid HDAC inhibitors in a short time. The subsequent testing of a mini library of 14 dual target compounds for in vitro activity against selected HDAC isoforms showed promising results, e.g. IC_{50} values.

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Poster 55

Orthogonal manipulation of ketchup and mayo, two novel adhesion GPCR genes in Drosophila

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Only two homologs associated with adhesion G protein-coupled receptor (aGPCR) have been described in Drosophila to date limiting the use of the fly as a model to investigate other aGPCR layouts. We uncovered two previously un-annotated bona fide aGPCR candidates, CG15556 and CG11318, which we renamed ketchup and mayo, respectively. To investigate the function of the gene pair, we aimed to create novel fly models to study the function of these aGPCRs. While both genes are genetically linked in a 25-kb region on chromosome III, we present a method to permit their manipulation and independent genomic engineering through established φC31 integrase resources. We harbor orthogonal attP sites of different recognizability and specificity to the integrase for this two synthetic homologous genes generating ketchup and mayo single as well as double knock-out/knock-in strains including transcriptional reporters. These experiments show non-overlapping expression domains for ketchup in the excretory system and for mayo throughout the gastrointestinal canal. This provides a basis for loss-of-function studies of the respective single and double null mutants, for instance a loss of ion-intake from the anal pad present in mayo knock-out strains.

Poster 56

Calorimetric investigation of glycolysis reaction 9

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The aim of system biology is the investigation and prediction of metabolic pathways using the metabolic flux analysis (MFA). The biggest disadvantage of this method is that huge underdetermined equation systems are obtained.
Thermodynamics might help with reducing the solution space by eliminating solutions that fulfill mass balances but violate the second law of thermodynamics. In this work, an algorithm called thermodynamic feasibility analysis (TFA) is applied to the glycolysis as an example for a metabolic pathway. This pathway was chosen because it is well understood and therefore poses a good model system for testing the method. An analysis of the feasibility of the glycolysis already exists but leads to the conclusion that, using the available literature data of the reactions, the whole glycolysis pathway is not feasible which is obviously wrong. Reasons for this could be that the literature data was not determined under the conditions present in the cell or that the activity coefficients were neglected in the analysis. Therefore, new determinations and predictions of physical and thermochemical base data of pure metabolites, reaction equilibria of single reaction steps, kinetic data and reaction heats under cell mimicking conditions (e.g. macromolecular crowding, ionic strength) are necessary.

In this work, the reaction 9 was investigated using isothermal titration calorimetry doing single injection measurements. The new data can be used to establish a TFA model which includes activity coefficients, protonation and complexation of the metabolites, new $\Delta Rg0'$ values and new calculated ΔRg values.

Poster 57

Towards Integrating Combined Radiation and Focused Ultrasound Therapy into the Clinical Domain

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Radiation therapy (RT) belongs to the routinely applied treatment modalities for cancer while still causing side effects. Focused ultrasound (FUS) is able to generate hyperthermia (HT; 40-45°C) non-invasively in a target region and thus cause radio-sensitizing effects in a combination regime of FUS-HT and RT.

The aim of this work is to present novel ideas for the combined FUS-HT-RT treatment and to propose concepts for an effective realization in two parts:

In silico simulations:

Preoperative decision support can be crucial in cancer therapy to apply the right treatment at the right time and place. By providing information on treatment outcome for specific tumor cell lines, surgeons can be supported immensely. Therefore first steps towards in silico simulations to predict treatment outcome were made, by implementing an HT-RT model in a cellular automaton approach.

Collaborative robotics:

To provide high precision and low complexity treatment with high user acceptance first steps were made to introduce collaborative robotics into the clinic. By implementing a framework for a KUKA LBR iiwa 7 robot a mobile platform was developed and a touch gesture based interaction concept for the use case of US-guided biopsies was evaluated. Furthermore a user validation was conducted on an abdominal phantom (Triple Modality 3D Abdominal Phantom, CIRS Inc., USA).

Poster 58

Improvement of a neuronavigation system for neurosurgical procedures

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Introduction:

The use of intraoperative ultrasound (iUS) imaging supports the neurosurgeon during brain tumor operations. Neuro-navigation systems perform the visualization of the US images overlapped on preoperative data. However, the limitations are the lack of communication between the devices and of image annotation tools.

Material and Methods:

An image based connector was developed to automatically identify the values of the US parameters set during the acquisition. These parameters are only accessible through the monitor of the US device and variously represented. Moreover, semi-automatic tools were developed to segment the brain tumor, the ventricles and vascular structures in the preoperative MR and iUS images.

Results:

The tools were implemented on a research platform connected with the US device through a video connection and with the neuro-navigation system using a local network. A user modified the image depth on the US device. The connector tool detected the change and communicated the new depth to the navigation system which updated successfully the visualization of the images. Also, brain structures segmented using the tool of the research platform were sent to the navigation system and were successfully displayed on its monitor.

Discussion and Conclusion:

A commercial neuro-navigation system was improved by several tools facilitating the communication with the US device and performing the segmentation of target structures. A demonstrator including the neuro-navigation system, an US device and the research platform was built and tested. The next step is the evaluation in the operating room.

Poster 59

Supervised tissue discrimination during thyroid and parathyroid surgery based on hyperspectral imaging

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Introduction:
The parathyroid gland is located behind the thyroid. The number of glands and the position are individual. It requires an experienced surgeon to distinguish between the two glands and to not harm either of them during an open neck operation. Therefore, it would be beneficial to have a tool that can support the surgeons in their decision of removing one or both glands. This project concentrates on the discrimination of the parathyroid and thyroid using hyperspectral imaging (HSI).

Material and Methods:
HSI data of 7 patients were acquired during open neck surgeries. Those resemble 3D data that includes for spectraland spatial information. A section of those images was identified as thyroid, parathyroid or muscle by the operating surgeon. Those marked areas are then used in a selection of supervised machine learning logarithms: Support Vector Machine (SVM), k-nearest neighbours (kNN) and Neural Networks. Each model was then tested on the classification of HSI data of two patients which have both glands present.

Results:
More than 30.000 and nearly 4.000 spectra of the thyroid and parathyroid were used for the training and test of the classification methods. The best performing algorithm was SVM with a linear kernel. The overall accuracy of the method was 95.77 %. The computing time was 0.33 s and 0.36 s.

Discussion and Conclusion:
Machine learning methods are suitable to automatically discriminate thyroid and parathyroid using HSI. The computing time is acceptable for intraoperative use. The visualization of the classification results can be improved by smoothing the labelled classified regions.

Poster 60

Integrated System for Clinical Decision Models

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Computerized decision models based on Bayesian Networks promise to be a valuable addition to personalized medicine. Clinical decision support systems (CDSS) using these models can evaluate complex diseases, like cancer, and propose different suitable treatments. Their calculations must be based on routinely recorded patient data. Working with these systems must be associated with little to no additional efforts by the physicians. To be fully integrated into the physicians' workflow, CDSS must also interlink smoothly with hospital information systems. We built a modular decision support system using web services to connect the different modules with the underlying information system. The four modules are: 1) a central processing unit containing methods from artificial intelligence to process the patient's status, 2) a model repository for storage and revision control of the patient specific decision models, 3) a data access unit connecting to several clinical data bases and 4) a connector to different user interfaces to provide the results in a suitable form. We prototypically implemented our infrastructure with a decision model for laryngeal cancer. Patient data is provided by a relational data base and processed in the central processing unit. Results, e.g. TNM-staging and personalized treatment options, are presented via a web application. This modular infrastructure allows exchanging individual modules. For instance, the same processing unit could be connected to a different clinical data base or calculated results could be presented in another user interface, e.g., on a mobile device.

Poster 61

Untersuchung des Einflusses der ischämischen Konditionierung auf die Oxygenierung des Schlauchmagens mittels intraoperativer Hyperspektralbildgebung

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Einleitung:
Die intrathorakale ösophagogastrale Anastomose nach abdomino-thorakaler Ösophagusresektion ist eine der komplikationsträchtigsten Anastomosen im Gastrointestinaltrakt. Die ischämische Konditionierung des Schlauchmagens mit zeitversetztem Hochzug ist ein bekanntes Konzept, um die Vaskularisation des Magenfundus im Bereich der späteren Anastomose zu optimieren und somit die Insuffizienzrate zu reduzieren.

Methodik:
Bei n = 22 Patienten wurde der Schlauchmagen direkt vor ösophago-gastraler Anastomosierung mit einer Hyperspektralkamera aufgenommen. Dabei hatten n = 8 Patienten keine und n = 14 Patienten eine ischämische Präkonditionierung des Schlauchmagens 3 bis 7 Tage vor dem Magenhochzug. Aus den Aufnahmen mit hoher räumlicher und spektraler Auflösung wurde je ein Falschfarbbild für die Parameter Gewebeoxygenierung (StO_2) und NIR Perfusion Index berechnet. Die Lokalisation der späteren Anastomose wurde durch eine Pinzette markiert. Die Mittelwerte der Indices im Umkreis von 25 mm (ROI) wurden für jeden Patienten ausgewertet.

Ergebnisse:
Die Gewebeoxygenierung im ROI der Patienten ohne Präkonditionierung war signifikant niedriger als bei Patienten mit ischämischer Präkonditionierung ($StO2_{ohne}$ = 66%; $StO2_{mit}$ = 78%; p = 0,03). Auch der NIR Perfusion Index zeigte deutliche Unterschiede zwischen beiden Patientengruppen (NIR_{ohne} = 62%; NIR_{mit} = 68%).

Schlussfolgerung:
Hyperspektralbildgebung ist geeignet um kontaktfrei die Effekte der ischämischen Konditionierung des Schlauchmagens im Rahmen der Ösophagusresektion darzustellen. Dabei ist HSI möglicherweise praktikabler als die herkömmlichen Methoden.

Poster 62

Process Simulation Techniques for Perioperative Process Optimization

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The main goal of an efficient operating room management is the improvement of patient outcome while maximizing the number of surgical procedures and minimizing the surgery duration at the same time. Based on computer simulation techniques the perioperative processes could be optimized by determining in which way the processes need to be changed considering different procedural, behavioral, structural, operational and temporal parameters.

In this work, different simulation techniques of Discrete Event Simulation (DES) were utilized for the description, analysis, prediction and comparison of various perioperative process alternatives. Eventually, a holistic DES approach for perioperative process optimization in orthopedic surgery was developed. For this purpose, the underlying DES process models were implemented with perioperative data from Total Hip Replacement (THR) and Total Knee Replacement (TKR) surgeries. The optimization objective was the increase to three surgeries per day and OR by reducing the intraoperative time through the optimization of the OR layout. Simultaneously, the OR preparation and surgery follow-up processes were streamlined with methods of Business Process Re-engineering.

The simulation results were evaluated in the real intraoperative OR environment. This results in a decrease of surgery time of 9,45 min for THR and 3,25 min for TKR. In addition, a decrease of the surgery turnover times could be achieved based on perioperative process optimization. The simulation results also demonstrate the improvement of OR utilization, reduction of turnover times and a decrease in personnel workload.

Poster 63

Towards Semi-Automatic Generation of Bayesian Decision Networks in Oncology Using a Hybrid Modeling Approach

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The treatment of cancer is an interdisciplinary process that involves the participation of various clinical departments and experts. The integration of data-driven decision support in the form of patient- and treatment models is able to complement various aspects of the diagnostic and therapeutic pathway by providing an unbiased viewpoint to the respective situation. In our work, we focus on the generation of such models since the proper implementation of the modeling process is crucial in regards to their validity and usefulness. We propose a hybrid approach that combines the advantages of expert-based modeling as well as machine learning to provide dynamic, unbiased and guideline-compliant results.

Poster 64

Research and development of a forceps for MR-guided interventions with the use case endomyocardial biopsy

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Minimally invasive endomyocardial biopsy (EMB) is currently conducted under X-ray fluoroscopy guidance. This procedure implies radiation exposure, administration of nephrotoxic contrast agent, and poor soft tissue contrast. Magnetic Resonance Imaging (MRI) guidance offers a promising option to overcome these disadvantages entailing advantages as high soft tissue contrast and discretionary slice positioning. So far, however, biopsy forcipes are mostly metallic and as per ASTM/ISO regulation MR Unsafe because of radio frequency heating. The objective of this project is the development and evaluation of an MR Safe/Conditional biopsy forceps and a corresponding clinical workflow to realize MRI guided EMB. MR Safe jaw prototypes have been fabricated, equipped with passive markers, and evaluated under 1.5 Tesla MRI, assessing the visibility of the bioptomes. The results are promising in terms of appropriate selection of size, position, and concentration of the markers to identify the opening state: a clear difference regarding the artifact sizes can be observed visually. For intense ex-vivo suitability tests, a life-size phantom of the vessel system has been modeled and manufactured. Further studies are currently conducted to ensure the applicability in terms of reliable MRI guidance and reproducible biopsy quality. Contemporarily, a clinical workflow for MRI guided EMB is developed, considering appropriate MRI sequences, MRI operation, intra-interventional communication, patient care and safety.

Poster 65

Implementation and Evaluation of an Electronic Patient Record for Disaster Relief Missions

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The European Modular Field Hospital (EUMFH) project intents to enhance the potential of the Union Civil Protection Mechanism. Different Member States of the European Union combine their expertise to create a common deployable Emergency Medical Team (EMT) level 3 for international disaster relief missions.

During the project, ICCAS was commissioned with the design, implementation and provision of an electronic patient record (EPR) for EMTs. Subsequently to a comprehensive requirements analysis, a concept for an EPR was derived, taking the special demands (e.g. lightweight, flexibility, robustness) of disaster relief missions into account. After implementation, an early EPR version was evaluated during the MODEX exercise in Bucharest under realistic deployment conditions. The participating personnel was interviewed regarding suitability, performance and operational capabilities of the developed EPR.

The EPR was well received by the 21 interviewed team members from 9 different European countries. Of these, 14 were assigned with medical roles (physicians, nurse) and 7 of them with supportive roles (management, logistics, training). Under the 14 medical interview partners have been 3 medical team leaders.

The evaluation of the EPR during the exercise was very successful, considering the positive user feedback. However, there were various learned lessons about the challenges of EMTs and disasters disaster relief missions. On basis of these, the EPR will be optimized and evaluated in its next version during another EMT exercise in the beginning of next year.

Poster 66

Assessment of automatic perforator detection in infrared thermal images

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Knowledge of the location of the blood vessels supplying the skin and subcutaneous tissue is required during the planning of tissue transfer in reconstructive surgery. Computed tomography angiography and indocyanine green angiography are common imaging techniques but expose the patient to radiation or a contrast agent, respectively. Infrared thermal imaging was successfully used as a non-invasive alternative. To support the interpretation of thermograms, a method to automatically detect the perforators was developed and evaluated.

A system consisting of a thermal camera, a PC and custom software was developed. The temperature variations of the skin surface were analyzed to extract the perforator locations. To assess the performance of the algorithm a study comparing the detection results of the algorithm with manually labelled thermal images by two clinicians of the deep inferior epigastric perforator (DIEP) flap of 20 healthy volunteers was conducted. The F-measure, precision and recall were used to evaluate the system performance. The median F-measure is 0.83, the median precision is 0.80, and the median recall is 0.91.

This study showed that it is possible to automatically and reliably detect the skin perforators in thermograms despite their weak temperature signature. Therefore, IR thermal imaging is a suitable noninvasive and contactless approach for intraoperative use. Combined with a computer-assisted tool for the automatic detection of perforator vessels, it is a relevant alternative intraoperative imaging method to the standard indocyanine green angiography.

Poster 67

Expansion of total monocytes, intermediate and non-classical monocytes in patients with Systemic Sclerosis

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Background:
Many observations indicate an involvement of CD14+ monocytes in the immune-mediated rheumatic disease systemic sclerosis (SSc). Blood monocytes are divided into different subsets, the classical, the intermediate and the non-classical monocytes. CD56+ monocytes are a minor subpopulation of the classical monocytes. Aim of the study was to analyze the monocyte subpopulations in SSc patients.

Method:
Frequencies of monocyte subpopulations of 29 SSc patients and 17 age-matched healthy donors were analyzed by flow cytometry (antibody staining of CD14, CD16 and CD56). Absolute monocyte counts were determined with the white blood cell count.

Results:
The absolute number of circulating monocytes was significantly increased in SSc patients compared to healthy controls (713/µl ± 50 vs. 479/µl ± 30, p=0.001). Calculated absolute monocyte subpopulation numbers of intermediate monocytes (73/µl ± 11 vs. 31/µl ± 5, p 0.0001) and non-classical monocytes (92/Âµl Â± 11 vs. 43/Âµl Â± 8, p<0.001) were increased in patients with SSc compared to controls. In contrast, the calculated absolute numbers of classical and CD56+ monocytes were not different between SSc patients and controls. The frequency of intermediate (9.7% Â± 0.7 vs. 5.9% Â± 0.7, p<0.001) and non-classical monocytes (14.3% Â± 1.7 vs. 8.5% Â± 1.3, p=0.023) was in increased while the frequency of classical monocytes and CD56+ monocytes was decreased in SSc patients compared to controls.

Conclusion:
Circulating CD14+ monocytes are expanded in the blood of SSc patients. This expansion is caused by an increase of intermediate and non-classical monocytes.

Poster 68

The immunoproteome of Cryptococcus neoformans in health and disease

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The fungus Cryptococcus neoformans causes the life-threatening disease cryptococcosis especially in immunocompromised hosts. As antifungal drugs cause severe side effects, the quest for an anti-cryptococcal vaccine or immunotherapeutic approaches remains an urgent aim. We decided to use the immunoproteome of C. neoformans recognized by the human host as a starting point to screen for immunoreactive proteins, which could represent promising candidates for development of new therapeutic strategies. We analyzed sera from HIV-positive (HIV+) as well as HIV-negative (HIV-) Colombian cryptococcosis patients and sera from healthy Colombian persons. Titers of C. neoformans-reactive immunoglobulin G did not differ between HIV+ cryptococcosis patients and healthy persons, but titers were significantly increased in HIV- cryptococcosis patients compared to HIV+ patients, illustrating the influence of the immune status during cryptococcosis. Pre-incubation of the sera with proteins from Aspergillus niger and Candida albicans did not cause a reduction of the titers, pointing to a specific immune response towards C. neoformans even in healthy individuals. Immunoproteome analysis via 2D gel electrophoresis revealed, that most cryptococcal proteins are recognized by the human immune system albeit with a low consistency between different individuals. There were no obvious differences in the spot pattern between HIV+ and HIV- cryptococcosis patients or healthy control persons. Nevertheless, some proteins showed pronounced reactivity with several sera, marking them as immunodominant cryptococcal proteins with potential for further research.

Poster 69

Zusammenhang zwischen bakterieller DNA und Zytokinkonzentration in Aszites bei Patienten mit spontaner bakterieller Peritonitis und Leberzirrhose

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Die spontan bakterielle Peritonitis (SBP) ist eine gefährliche Komplikation bei Patienten mit Leberzirrhose. In dieser Studie soll der Zusammenhang zwischen bakterieller DNA und der lokalen sowie systemischen Entzündungsreaktion untersucht werden.

Aszites- und Serumproben von 37 Patienten mit Leberzirrhose und SBP (Median PMN=1185/µl; Range 281-14762) wurden mittels Kultur und 16S rRNA-PCR auf das Vorhandensein und die Quantität von Bakterien und deren DNA untersucht. Die Konzentrationen von IL-6 und IL-10 (Median pg/ml) wurden in Serum und Aszitesüberstand mittels bead-basiertem Immunassay bestimmt.

Aszites von 16 Patienten (43,2%) war mittels Kulturanzucht positiv, wohingegen bei 67,6% (n=25; p<0,001) der Nachweis bakterieller DNA mit 5,3x10E3 Kopien/ml (Median; Range 2,1x10E2-1,9x10E7) gelang. Die Konzentration von IL-6 (median 92294 pg/ml) war bei baktDNA-positiven Proben nicht signifikant höher als bei baktDNA-negativem Aszites (34615; p=0,455). Dennoch korrelierte die DNA-Kopienzahl mit den PMN (r=0,522; p=0,007) sowie mit der Konzentration von IL-6 (r=0,603; p=0,001) und IL-10 (r=0,591; p=0,002) im Aszites. Darüber hinaus konnte ein Zusammenhang zwischen der Konzentration von IL-6 in Serum und Aszites (r=0,555; p=0,004) gefunden werden.

Bakterielle DNA im Aszites korreliert mit der Konzentration inflammatorischer Zytokine in Serum und Aszites, wodurch eine Verbindung zwischen Anwesenheit und Menge bakterieller DNA und der Reaktion des Immunsystems gezeigt wird. Folglich sind die Quantifizierung bakterieller DNA und die Bestimmung der Zytokinkonzentration potenzielle Marker für die Schwere der SBP.

Poster 70

In vitro analysis of the Streptococcus suis-induced cytokines in porcine PBMCs and blood

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S. suis is a severe problem in pig breeding. Although pigs are commonly colonized at mucosal sites, disease occurs when S. suis becomes invasive, often accompanied by bacteremia. To investigate the immune response to S. suis in a relevant compartment, blood or isolated PBMCs were in vitro-stimulated with S. suis. Different S. suis serotypes (cps2, 7, 9) induce similar cytokine responses, but the stimulation with an acapsular S. suis mutant leads to higher levels of IL-10, IL-6 and IL-17A. To determine, whether monocytes are involved in the cytokine response to S. suis, we separated monocytes from PBMCs with anti-human CD14 beads. Production of IL-10, IL-6 and IL-17A is decreased in CD14-depleted PBMCs. The separated monocytes show strongly reduced or absent IL-10, IL-6 and IL-17A production. We suggest that interaction between monocytes and lymphocytes contributes to IL-6 and IL-10 production. The impact of S. suis-induced IL-10 on cytokine production in PBMCs was investigated with a neutralizing IL-10 antibody. IL-10 neutralization leads only to a marginal increase of IL-6 and IL-17A. In addition, we investigated IL-10 production in whole blood and analyzed killing of S. suis. After 6 h in blood strain 10 and the acapsular mutant induced IL-10 at similar levels. Since only the acapsular strain was killed we suggest that IL-10 induction alone is no essential factor for the survival of S. suis in blood. In summary, we could show that IL-10 is neither important for the induction of pro-inflammatory cytokines nor for killing of S. suis in whole blood.

Poster 71

Evaluation of novel potent inhibitors of respiratory syncytial virus entry

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Human respiratory syncytial virus (RSV) is the most prominent cause of serious respiratory tract infections in infants, elderly and immunocompromised patients worldwide.

RSV infection of the host cell is initiated by the attachment of RSV envelope glycoprotein G to host cell receptors, followed by RSV glycoprotein F mediated fusion of viral and host cell membrane. After the fusion of viral and cell membrane, the nucleocapsid with viral genetic material is released into the host cell. Both attachment and fusion are crucial steps for RSV entry, by blocking one or both of them RSV infection can be inhibited.

Our project entails in silico structure based design and synthesis of novel small molecule and peptide inhibitors that target both RSV surface glycoproteins F and G.

The antiviral activity and cytotoxicity of designed compounds were tested in several cell-based in vitro assays. Different tested compounds showed good ability to inhibit potently viral infection. Furthermore, the combination of antiviral agents preventing RSV attachment and fusion will be assessed for possible additive or synergistic effect. The inhibitors will be further tested in animal models of RSV infection. Potent candidates will be evaluated in clinical trials to develop a treatment strategy to combat RSV infection in humans.

Poster 72

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 act as first responder against pathogen upon injury. However, there is a negative side of neutrophil activity that is the release of proteases and the formation of Neutrophil Extracellular Traps (NETs) leading to tissue breakdown and inflammation. Neutrophils have also important pro-resolution function such as inducing anti-inflammatory macrophage activation, thus is phagocytosed as apoptotic corps or formation of cytokine degrading aggregated NETs. While neutrophil apoptosis is important in resolving inflammation during wound healing, the role of aggregated NETs is not explored. Aim of this project is to in-depth characterize the functions of neutrophils in normal and disturbed healing processes. Thus, in full thickness wildtype and diabetic mice wounds we analyzed neutrophils localization and interactions with other cells. In diabetic mice protease and inflammatory mediators are high, delayed and persist longer, in accordance with delayed 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.

Poster 73

An increased IL-1 β production is observed as a response to extracellular calcium by macrophages of rheumatoid arthritis patients

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Background:
The activation of monocytes due to G protein-coupled receptors CaSR / GPRC6A stimulated by increased extracellular calcium results in NLRP3 inflamasome formation. Monocytes and macrophages release high levels of cytokines during inflammatory responses, inflammase-dependent cytokines-IL-1β and IL-18 and inflammasome-independent cytokines TNF and IL-6. In patients with rheumatoid arthritis, bone erosions and cell necrosis may lead to increased levels of extracellular calcium and the subsequent activation of monocytes / macrophages in the synovial tissue. We aimed to analyze the cytokine response of calcium-induced activation of monocytes / macrophages in RA patients.

Methods:
Using magnetic separation, monocytes were isolated from the PBMCs from peripheral blood . Monocytes were differentiated into macrophages using human serum or GM-CSF. Macrophages were then stimulated with LPS in the presence of increased extracellular calcium. Cytokines were determined by ELISA.

Results:
ELISA revealed that the macrophages from RA patients released significantly higher amounts of the inflammasome-dependent cytokine IL-1β. Macrophages, therefore, have lower levels of calcium than monocytes. Increased concentration of extracellular calcium concentration.

Conclusion:
Macrophages respond to much lower calcium than monocytes from the peripheral blood which might be adapting to lower calcium concentrations in the interstitial fluid of tissues (compared to serum). Macrophages predominantly release cytokine IL-1β .

Poster 74

Characterization of canine CD4$^+$CD8α^+ double-positive T cells in lymphatic and non-lymphatic organs

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Canine CD4$^+$CD8α^+ double-positive (dp) T cells of peripheral blood are a heterogeneous effector memory T cell subpopulation with an extraordinary immunological potential characterized by a high level of IFN-γ production and an increased activation status in comparison with conventional CD4$^+$ or CD8α^+ single-positive (sp) T cells.

In this study, we investigated lymphocytes from secondary lymphatic and non-lymphatic organs within one standardized group of healthy dogs by multi-color flow cytometry. The aim was to establish reliable reference data for a comprehensive understanding of the developmental origin and the functional role of this interesting T cell subpopulation in vivo. CD4$^+$CD8α^+ dp thymocytes of the same dogs served as control.

Our analyses revealed a mature CD1a$^-$ dp population with highest frequencies within intestinal environment and constitutive expression of the activation marker CD25 in all analyzed organs. The majority of the dp T cell subpopulation is TCRαβ$^+$CD8αα$^+$. Dp thymocytes, on the other hand, are CD1a$^+$TCRαβ$^+$CD8αβ$^+$, indicating an extrathymic origin of mature dp T cells. According to literature, CD8αα upregulated on antigen-experienced CD4$^+$ or CD8αβ$^+$ sp T cells does not function as a TCR co-receptor, but as a co-repressor increasing the activation threshold. Therefore, we speculate that CD8αα expression on dp T cells might regulate the immune response of this interesting T cell subpopulation.

The presented data provide the basis for further functional analyses to elucidate the in vivo role of CD4$^+$CD8α^+ dp T cells in health and diseases of dogs.

Poster 75

Effekt eines funktionellen PTPN22 Polymorphismus auf die Phagozytose bei Patienten mit rheumatoider Arthritis

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PTPN22 ist eine 110 kDa intrazelluläre Protein-Tyrosin-Phosphatase (Lyp; lymphoide Tyrosin-Phosphatase), die bevorzugt in hämatopoetischen Zellen und Immunzellen wie T- und B-Zellen, Monozyten, Makrophagen, dendritische Zellen und natürliche Killerzellen exprimiert wird. Ein funktioneller Einzelnukleotid-Polymorphismus (SNP C1858T) im ptpn22 Gen führt zu einer 620Arg > Trp-Substitution innerhalb der ersten Prolin-reichen Region vom Protein und prädisponiert für viele Autoimmunerkrankungen, einschließlich rheumatoide Arthritis (RA).

Monozyten von gesunden Kontrollen und von RA Patienten mit verschiedenem PTPN22 Genotyp wurden mit pHrado Green E. coli Partikel, grün-fluoreszierende P. gingivalis Bakterien (Laborstamm Boston 381) und Latexbeads mit und ohne LPS inkubiert. Die Messungen wurden mittels Durchflusszytometrie durchgeführt. Bilder wurden durch Konfokalmikroskopie aufgenommen.

Die Phagozytose-Analyse zeigte, dass die LPS-induzierte Phagozytose von Latexbeads bei RA Patienten mit TT-Genotyp im Vergleich zu RA Patienten mit CC-Genotyp und zu gesunden Kontrollen signifikant vermindert war. Der SNP in PTPN22 zeigte auch einen Effekt auf die Pahgozytose von E. coli: das RA-assoziiertes Allel von PTPN22 verstärkt die Phagozytose von E. coli. Im Gegensatz dazu war die Aufnahme von P. gingivalis in RA Patienten unabhängig vom Genotyp im Vergleich zu gesunden Kontrollen signifikant verhindert. Eine mögliche Erklärung sind die unterschiedlichen Rezeptoren und Signalwege in Monozyten, die von E. coli und P. gingivalis aktiviert werden. Ein Einfluss von PTPN22 auf diese Signalwege muss in weiterführenden Studien geklärt werden.

Poster 76

Development of immunoassays for the detection of lupin allergens in food

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Innovative plant products made of legume crops gain more and more significance in western nutrition, as admixture in meat and bakery products or as replacement products. Legume protein offers a lot of health benefits along with technological advantages however possess a high allergic potential as well. Lupin, for instance, is one of the 14 listed food allergens in the EU [Regulation (EU) 1169/2011] that has to be declared when used in foodstuff. So far, four lupin proteins have been identified as allergens. Since even traces can cause severe allergic reactions there is a strong need for high specific detection methods especially because of the risk of inadvertent food contamination and consumer safety concerns.

To track allergenic lupin proteins in food products which are treated by diverse food processing steps we are developing test systems based on newly generated and highly specific monoclonal antibodies.

Using these antibodies in a sandwich-ELISA setup even traces of single lupin antigens could be detected otherwise no crossreactions to other legume crops such as peanut or soy could be determined.

Poster 77

Studies on hazelnut epitopes of antibodies in sera from allergy patients and immunized rabbits

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Hazelnut is commonly consumed worldwide and integrates in a variety of foods. At the same time, hazelnut allergy is the most common among tree nuts allergies in Europe. Sensitized reactions can range from mild oral symptoms to a severe systemic allergic reaction, depending on the type of allergen. Although the major allergenic proteins from hazelnut have been reported, precise IgE binding epitopes of these allergens are recently established in our group [1].

The epitope mapping we apply, is a novel combination of peptide phage display, next generation sequencing and in silico data analysis. It is a new approach to identify specific epitopes from serum antibodies. Serum sample from food sensitized patients is required. However, the volume of patient's serum available and the low antibody titre make it worthwhile to look for another antibody source. Therefore, serum obtained from hazelnut immunised rabbits was tested for different applications.

The results from epitope mapping showed that the rabbit sera recognize epitopes on Cor a9 (11S globulin) and Cor a11 (7S vicilin). In western blots, one rabbit serum exhibits cross reactivity with lupine and soy while the second serum cross-reacted with lupine only. The recognized protein on lupine could be identified from the epitope mapping as isoflavone reductase protein which is homolog to hazelnut Cor a 6.

[1] Kern K, Havenith H, Delaroque N, et al. (2018): The immunome of soy bean allergy: Comprehensive identification and characterization of epitopes. Clin Exp Allergy. 1-13

Poster 78

Reliabilitätsuntersuchungen am computergestützten Test- und Trainingsgerätesystem (CTT) Centaur (BfMC GmbH)

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Einleitung:
85 % aller chronischen Rückenschmerzpatienten leiden unter unspezifischen Beschwerden, welche nicht direkt auf Verletzungen oder andere klar zu benennende Pathologien zurückzuführen sind. Ursächlich hierfür sind vielmehr arthromuskuläre Defizite bzw. Dysbalancen im Bereich der autochthonen Rückenmuskulatur, die nicht willentlich ansteuerbar ist und rein reflektorisch reagiert. Eine spezielle Therapierung und Kontrolle dieser Muskulatur ermöglicht das computergestützte Test- und Trainingsgerätesystem (CTT) Centaur (BfMC GmbH). Zur Beurteilung der Qualität der generierten Daten und zur Sicherstellung der Vergleichbarkeit der Patientenergebnisse ist der Reliabilitätsnachweis das Ziel dieser Studie.

Methodik:
Die Untersuchung der Reliabilität erfolgte auf Grundlage der Retest-Methode, bei der drei standardisierte Wiederholungsmessungen (Defizitanalyse) an 20 freiwilligen Probanden durchgeführt wurden. Ausgewertet wurden die Messpunkte im Haltungsverlauf (Abweichung von der Frontal- und Sagittalachse) sowie der Flächeninhalt der darauf basierenden 95 %-Vertrauensellipse. Die Ergebnisse wurden mithilfe des Shapiro-Wilk-Tests auf Normalverteilung untersucht und anschließend mittels des nicht-parametrischen Friedman-Tests ausgewertet. Das Signifikanzniveau wurde auf 5 % ($\alpha = 0{,}05$) festgelegt.

Ergebnisse:
Es wurde nachgewiesen, dass 21 der 24 untersuchten Parameter keine signifikanten Unterschiede aufweisen und als reliabel einzustufen sind. Der Reliabilitätsnachweis wurde somit erbracht und die Grundvoraussetzung für den Einsatz in der medizinischen Trainingstherapie erfüllt.

Poster 79

AMPEL: Analyse und Meldesystem zur Verbesserung der Patientensicherheit durch Echtzeitintegration von Laborbefunden

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70% aller diagnostischen und therapeutischen Maßnahmen basieren auf labormedizinischer Diagnostik, die einer umfassenden Qualitätssicherung unterliegt. Weniger als 10 % der diagnostischen Fehler sind der Analytik zuzuschreiben, treten aber vor allem in der sogenannten Prä- und Postanalytik auf. Die postanalytische Qualitätssicherung beschränkt sich aktuell neben der Erstellung des qualifizierten Befundes auf eine telefonische Sofortalarmierung bei lebensbedrohlichen Konstellationen, ohne dass eine systematische labormedizinische Weiterbetreuung des Patienten erfolgt.
Ziel des AMPEL-Projekts ist es, mithilfe des zu entwickelnden AMPEL-Systems, durch Identifikation von prä- und postanalytischen Problemen die Patientensicherheit zu fördern sowie das klinische Personal zu entlasten.
Die Komplexität der Anforderungen bei steigenden Fallzahlen und patientenindividuellen Diagnostik- und Therapieoptionen stellt eine Herausforderung dar, die mit dem Risiko von Informationsverlusten behaftet ist. So sind sich 80% aller Ärzte bewusst, dass durch nicht berücksichtigte Laborbefunde regelmäßig schwerwiegende Fehler passieren.
Basis des AMPEL-Systems ist die Echtzeitanalyse von Laborbefunden im Kontext von Informationen aus dem Klinikinformationssystem. Bei Hinweisen auf Verzögerung notwendiger medizinischer Maßnahmen erfolgt neben einer Bereitstellung von Hintergrundinformationen die Alarmierung über mehrere Eskalationsstufen bis zur direkten Rücksprache zwischen klinischem Kollegen und Labormediziner. Die Effekte des AMPEL-Projekts auf die Patientenversorgung und -sicherheit werden im Projekt streng wissenschaftlich untersucht.

Poster 80

Pulmonary serotonin transporter availability in patients with COPD and pulmonary hypertension

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Purpose:
Pulmonary hypertension (PH) is a hemodynamic condition characterized by progressive remodeling of the pulmonary vasculature resulting in right heart failure and death. Serotonin transporter (SERT) maybe involved in the pathogenesis of PH in patients with chronic-obstructive pulmonary disease (COPD). This study investigated for the first time SERT in vivo availability in the lungs of patients with COPD and PH (COPD+PH).

Methods:
SERT availability was assessed by means of SERT-selective [^{11}C]DASB measured by positron emission tomography/computed tomography (PET/CT) with dynamic acquisition over 30 min in four groups of five participants each: pulmonary arterial hypertension (PAH), COPD, COPD+PH, and healthy control (HC). Time activity curves were generated based on a volume of interest (VOI) within the middle lobe. Pulmonary tissue uptake after 25 to 30 min ($SUV_{25\text{-}30}$) served as non-model based parameter for group comparison. Tissue- to-plasma concentration ratio ($TTPR_{25\text{-}30}$) served as a correction for plasma activity.

Results:
Both COPD and COPD+PH cohorts showed significant lower values of SUV25-30 compared with HC, while $TTPR_{25\text{-}30}$ was significantly higher in COPD+PH and PAH as compared to COPD. $TTPR_{25\text{-}30}$ positively correlated with invasively measured pulmonary vascular resistance measured by right heart catheterization (Pearson's r=0.62, P=0.03).

Conclusion:
SERT is detectable in the lung vasculature using [^{11}C]DASB-PET/CT. $SUV_{25\text{-}30}$ positively correlated with severity of PH, indicating an implication of SERT in COPD+PH.

Poster 81

Anti-CD123 Targeted Therapy with Talacotuzumab in Advanced MDS and AML After Failing Hypomethylating Agents – Final Results of the SAMBA trial

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Introduction:

Recently, progress has been made in the treatment of patients with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Nevertheless, patients failing hypomethylating agents (HMA) have a dismal prognosis due to very limited treatment options. Targeting CD123 on leukemic stem cells (LSC) is one promising approach in MDS and AML. Talacotuzumab (TAL, JNJ-56022473) is an IgG1 monoclonal antibody targeting CD123 preferentially via antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer cells (NKs).

Aim:

The SAMBA trial, a phase II study of the German and French MDS study groups within the EMSCO network assessed the overall hematological response rate after 3 months of single agent TAL treatment in AML or HR-MDS patients failing HMAs.

Methods:

TAL was given IV at a dose of 9 mg/kg once every two weeks for a total of 6 infusions, responders received up to 20 additional infusions. After the first 3 months, overall hematological response rate (either CR, PR, marrow-CR, HI, SD) has been evaluated by bone marrow biopsy. The study was accompanied by an immune monitoring via flow cytometric analysis to investigate the distribution of T- and NK cells in peripheral blood (PB) and bone marrow (BM) at the time of screening and during therapy in comparison with healthy, age matched controls.

Results:
24 patients with a median age of 77 (range 71-90) years, who either failed to achieve complete- (CR), partial response (PR), hematological improvement (HI) or relapsed after HMA therapy were included in the study.
After TAL administration, 14 patients could be assessed for response after 4 infusions and 10 patients after 6 infusions. The overall response rate (ORR) was 20,8% including 1 (4,16%) complete remission (CR), 1 patient (4,16%) with hematologic improvement (HI-E) and additionally 3 patients (12,5%) with disease stabilization. The median duration of response in these patients was 3 months (range 3-13 months). Two patients are still on treatment, one patient despite losing objective response and one patient with disease stabilization. The median overall survival for the entire cohort of patients was 3.2 months (range 0.4-11.2 months). Therapy resulted in grade 3/4 infusion related side effects (pneumonia, n=1; infusion-related reaction, n=8; septic shock, n=1) in 10 patients (41,6%), which led to early study discontinuation.
Before treatment initiation, patients had lower levels of CD56dim NK-cells in peripheral blood (82% vs. 89% of NK-cells; p=0.069) expressing significantly more inhibiting NK-cell receptors like KIR2DL2 (8.8% vs. 3.2% of NK-cells; $p< 0.001$) and less activating NK-cells receptors like NKG2D (controls (95% vs. 99% of NK-cells; $p< 0.01$) compared to healthy controls. Moreover, expression of PD-1 on lymphocytes and monocytes as well as their matching ligands PD-L1 and PD-L2 on blasts and monocytes in peripheral blood was significantly higher in patients compared to healthy controls ($p< 0.01$), another evidence for an exhausted T-cell immune status in our patients prior to treatment initiation.
We could not detect any difference in NK-cell levels in responding patients compared to non-responders. Interestingly, pre-treatment expression (MFI and percentage) of CD123 on immature MDSC was higher in responders than in non-responders ($p<0.01$). Anti-CD123 targeted therapy with TAL resulted in a decreased CD123+ MFI (4239 vs. 2910; $p< 0.01$) on iMDSCs as well as lower levels of iMDSCs in PB and BM ($p< 0.05$). Responding patients displayed a 10-fold reduction of CD123 MFI after 3 months of treatment (2565 vs. 236; p=0.06), indicating that the CD123 molecule on immature MDSCs is targeted effectively by TAL.

Conclusion:
Single agent TAL has limited efficacy in patients with advanced myeloid malignancies failing HMA. Expression of CD123 on immature MDSCs might serve as biomarker of response for future anti-CD123 targeted approaches.

Poster 82

Evidenzbasierte Pharmazie in der Selbstmedikation - Ein bundesweites Konzept für öffentliche Apotheken zur Implementierung einer wissenschaftlich basierten Beratung

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Hintergrund:
Für Informationen zu rezeptfreien Arzneimitteln sind öffentliche Apotheken für Patienten meist die erste Anlaufstelle. Wie patientenindividuell und evidenzbasiert wird bereits in Apotheken beraten? Wie kann man die Apotheken dabei bestmöglich unterstützen?

Methoden:
Auf Basis einer bundesweiten Onlineumfrage von pharmazeutischem Personal zur derzeitigen Beratungssituation (U1) und begleitenden Routinestichproben von Beratungsgesprächen in bundesweit 5 Apotheken (03-08/2017) wurde ein elektronischer Newsletter entwickelt. In diesem werden den Apotheken regelmäßig und herstellerunabhängig Informationen aus klinischen Studien zur Verfügung gestellt. Etwa ein Jahr nach Erscheinen der ersten Ausgabe wurde der Newsletter mit einer zweiten Onlineumfrage (U2) evaluiert (03-07/2018).

Ergebnisse:
Obwohl 84% der 1068 Teilnehmer der ersten Onlineumfrage (U1) klinischen Studien bei der Beratung eine hohe Bedeutung beimaßen, wurden diese von 52% der Befragten nicht routinemäßig berücksichtigt. Der Umgang mit Studien fiel 69% schwer.
Anhand der 108 beobachteten Beratungsgespräche wurde zusätzliches Optimierungspotenzial erkennbar, wenngleich das Apothekenpersonal überwiegend zufrieden mit der eigenen Beratung war.
In der zweiten Onlineumfrage (U2) zur Newsletter-Evaluation gaben 90% der 150 teilnehmenden Abonnenten an, dass sie der Newsletter bei einer wissenschaftlich fundierten Beratung unterstützt.

Fazit:
Die evidenzbasierte Beratung ist den Apotheken ein wichtiges Anliegen. In der täglichen Routine bedarf es dafür geeignete unterstützende Maßnahmen. Mit dem entwickelten Newsletter wurde ein hilfreiches Tool geschaffen.

Poster 83

Gender differences in the predictive value of biomarkers in end-stage liver disease

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Background:
Organ allocation for liver transplantation is based on the MELD score (calculated from bilirubin, INR and creatinine). The MELD score applies equally for women and men although there are known gender differences in these biomarkers.

Methods:
We performed a retrospective observational cohort study of 774 patients with end-stage liver disease and quantified gender differences of several biomarkers and their predictive values in this cohort.

Results:
The most relevant biomarkers with significant gender differences where creatinine (median: ♂ 83 µmol/l, ♀ 71 µmol/l [p<0.001]) and the MELD score (♂ 11.5, ♀ 10.2 [p=0.007]). Considering only the patients who died during follow-up without receiving an organ (n=110), MELD score showed a different tendency and doesn't differ significantly (♂ 19.0, ♀ 20.7; [p=0.212]). Among these patients, men showed a higher creatinine (♂ 115 µmol/l, ♀ 85 µmol/l [p=0.002]) but lower values for bilirubin (♂ 51 µmol/l, ♀ 100 µmol/l [p=0.021]) and INR (♂ 1.5 µmol/l, ♀ 1.7 µmol/l [p=0.014]). The predictive value of creatinine for mortality without transplantation was higher among men compared to women (area under ROC [95%-CI]: ♂ 0.71 [0,63-0,79],♀ 0.62 [0,51-0,72]). However for other biomarkers the predictive power was higher among women (bilirubin: ♂ 0.74 [0,67-0,81],♀ 0.85 [0,80-0,90]; INR: ♂ 0.72 [0,64-0,79],♀ 0.85 [0,79-0,91]; MELD score: ♂ 0.80 [0,73-0,86],♀ 0.87 [0,81-0,92]). Cystatin C predicted mortality better than creatinine and equally for women and men (♂ 0.75 [0,68-0,82],♀ 0.75 [0,68-0,82]).

Poster 84

Selbstmedikation in öffentlichen Apotheken - Ist eine Beratung aus Patientensicht notwendig?

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Hintergrund:
Die Selbstmedikation mit OTC-(Over-the-Counter-)Arzneimitteln stellt einen bedeutenden Anteil der medikamentösen Behandlung dar. Da OTC-Arzneimittel bei falscher Anwendung mit erheblichen Risiken für den Patienten verbunden sein können, sollten diese über die Anwendung hinreichend informiert sein. Dabei stellt sich jedoch die Frage, ob Patienten überhaupt durch einen Apotheker evidenzbasiert zur Selbstmedikation beraten werden wollen?

Methoden:
Mithilfe einer standardisierten Befragung von Juni bis September 2018 im Stadtgebiet Leipzig sollten Passanten beurteilen, wie zufrieden sie mit bisherigen Beratungsgesprächen zur Selbstmedikation sind, unter welchen Umständen sie beraten werden wollen und welche Erwartungen sie an die Entscheidungsfindung des Apothekers haben.

Ergebnisse:
Die Passanten waren mit einer Mehrheit von 92% (883/963) „eher“ oder „sehr zufrieden“ mit der Beratung in der Apotheke. 90% aller 963 Befragten finden es „sehr wichtig“ bis „eher wichtig“ zu rezeptfreien Medikamenten beraten zu werden, selbst wenn sie nicht direkt darum bitten (69%). Ein Apotheker soll nach Auffassung der Befragten überprüfen, ob ein OTC-Arzneimittel für den Patienten geeignet ist (94%) und wenn nötig ein anderes empfehlen (87%) oder an den Arzt verweisen (85%). Für 71% der Befragten ist es wichtig, dass die Wirkung der empfohlenen Medikamente in Studien nachgewiesen wurde.

Fazit:
Passanten einer großen Universitätsstadt fühlen sich in der Apotheke gut beraten. Sie erwarten allerdings auch eine fundierte evidenzbasierte Beratung, interessanterweise selbst dann, wenn sie nicht explizit danach fragen.

Poster 85

Comparison of INR values between self- and telemedicine-managed anti-coagulation in LVAD patients

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Introduction:
Monitoring of therapeutic-range International Normalized Ratio (INR) after left ventricular assist device (LVAD) implantation is an important aim to reduce the risk of thrombosis or bleeding complications. Various service providers offer a telemedical anti-coagulation service (TACS). We investigated if telemedicine supervision increased the INR-specific time in therapeutic range (TTR) during anti-coagulation.

Methods:
LVAD patients applying TACS (n=15) were compared to LVAD patients applying self-managed anti-coagulation (SMAC) (n=15) in a prospective, randomized study. All patients received a self-management training for falithrom medication according to their INR value. INR values were documented for 12 months. TTR by Rosendaal method was calculated. A survey (scale: 1=very unsatisfied, 10=very satisfied) was used to determine patient‘s satisfaction and psychological well-being.

Result:
Both groups were comparable regarding gender, age, comorbidities, thrombembolic events and bleeding complications prior and following LVAD implantation (p>0.05). In total, 1,798 INR measurements were analyzed. TTRRosendaal was higher in patients with SMAC (78.1% ± 14.3%) compared to TACS (52.3% ± 33.2%, p=0.012). Patient‘s satisfaction with the coagulation setting (SMAC: 6.7 ± 3.1, TACS: 7.2 ± 3.0, p=0.736) and the psychological well-being (SMAC: 6.5 ± 1.9, TACS: 6.5 ± 2.7, p=0.967) were comparable between both groups.

Conclusions:
Telemedical (TACS)-based INR management does not improve the efficiency and quality of post-LVAD anti-coagulation therapy. An intensive training by experienced personnel is able to replace TACS.

Poster 86

Mittelfristige Funktion und Mortalität nach geriatrischen Frakturen des Acetabulums

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Einleitung:
Frühe Operation geriatrischer Acetabulumfrakturen kannSchmerzen nach OP reduzieren und zügige Mobilisation ermöglichen.Für diese Studie wurden mittelfristige Mortalität und Funktionalität nachOperation erhoben.

Methoden:
Eingeschlossen wurden PatientInnen mit Niedrig-Energie Trauma des-Acetabulums von 2009-2016, sowie Mindestalter von 60 Jahren.Telefonisch wurde der modifizierte Merle D'Aubigne-Score erhoben. BeiUnerreichbarkeit, wurden Angehörige und Hausärzte für Mortalitätsdatenkontaktiert.

Ergebnisse:
Für diese Voranalyse gab es 74 PatientInnen (23 Frauen)von durchschnittlich 80 Jahren. Am letzten follow-up (60 Monate, 24-115) waren32 (43,2%) verstorben. Die Ein-Jahres-Mortalität lag bei 21,6%, die Zwei-Jahres-Mortalität bei 29,7%. Während des Krankenhausaufenthaltes kames bei 20 (21,6%) zu Komplikationen. 17 Infektionen traten auf, vier hattenein Delir. Sechs verstarben noch im Krankenhaus. RelevanteThromboembolien gab es nicht. Bei fünf lag eine periprothetische Frakturvor. Eine Fraktur wurde primär mit einem endoprothetischenHüftgelenksersatz versorgt. Von den restlichen 68 PatientInnen erfolgtebei 14 (20,6%) nach durchschn. 20,8 Monaten (0 bis 113) eine Konversion aufendoprothetischen Hüftgelenksersatz (HTEP). Der durchschnittliche MerleD'Aubigne Score zum follow-up von den noch lebenden 42 PatientInnenbetrug 9,9/12 (SD 2,4).

Schlussfolgerung:
Mittelfristige Mortalität und Komplikationsrate sind weiterhin hochbei geriatrischen Acetabulumfrakturen, selbst bei früher OP. Die Raten von-Konversion auf HTEP sind ähnlich hoch, wie die bei Jüngeren. Dasfunktionelle Outcome von noch lebenden PatientInnen ist gut.

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Poster 87

Mechanical Characterization of Adhesion G Protein-coupled Receptors

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G protein-coupled receptors (GPCRs) play crucial roles in physiological processes. The family we focus on are Adhesion-GPCRs (aGPCRs), which are characterized by an extended extracellular domain (ECD) containing structural domains. Furthermore they include a seven-transmembrane-spanning domain. The auto proteolytic cleavage site within the GPCR auto proteolysis-inducing (GAIN) domain, is another common feature that can be found in all aGPCRs. The cleavage leads to a noncovalently bound complex of N- and C-terminal fragments (NTF and CTF). Recent studies showed that some of the aGPCRs are mechanosensitive. In order to characterize mechanical properties of receptors, many factors have to be considered regarding their complex structures. We aim at determining the binding strength of the receptor to its extracellular ligand and the intramolecular binding force holding NTF and CTF together. Further, we will analyze the amount of force necessary to activate the signaling pathways of aGPCRs.

For the quantitative analysis, we currently use an atomic force microscopy-based force spectroscopy (AFM-FS) setup combined with fluorescence microscopy. The first challenge was the preparation of suitable sensors. We integrated optical markers into the receptors and tags as targets for the surface-modified AFM probes. In addition, it had to be ensured that the receptors in the selected expression system show a sufficient cell surface expression.

The investigation of the mechanical properties of these receptors will allow a deeper understanding of the broad functionality of aGPCRs and human diseases associated with mutations in aGPCRs.

Poster 88

Fishing for tRNAs – Hairpin based library preparation of mature tRNAs for High Throughput Sequencing

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Transfer RNAs belong to the most abundant ribonucleic acid type in cells. Recent research gave rise to the association of tRNAs and their processing enzymes to several diseases. Additionally, high-throughput tRNA sequencing showed connections between devastating diseases such as breast cancer and alterations in tRNA pools. For the efficient quantitative and qualitative analysis of tRNAs various tools were developed. However, many of them have a low tRNA-specificity leading to a high amount of undesired and unspecific RNA sequences. Methods that are more specific on the other hand, do not include prematurely terminated products of the reverse transcription, which lowers the amount of high-throughput sequencing data. By combining and optimizing several high-throughput sequencing methods such as a T4 DNA ligation with hairpin adapter and Illumina sequencing, we developed a highly specific protocol for analyzing the tRNA pool of cells in a very efficient manner. The ligation of a hairpin adapter with a 3'-TGG-overhang allows a highly specific selection of tRNAs with a 3'-CCA end, which also obviates the need for previous tRNA enrichment. Following steps were designed so that also prematurely terminated products of the reverse transcription could be analyzed. This leads to a powerful tool to analyze the tRNA pool of cells under different conditions and for a variety of tRNA-related diseases. Furthermore, the development of tRNAs as biomarkers for diseases such as cancer could may be more feasibly with our method.

Poster 89

Myeloperoxidase is Elevated in Atrial Fibrillation and Originates from the Atria.

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Background:
Myeloperoxidase (MPO) is secreted by neutrophiles under inflammatory conditions and its serum levels are known to be elevated in patients with atrial fibrillation (AF). Current research suggests its involvement in the fibrotic atrial remodeling which is thought to be both cause and result of AF. Clinically ongoing AF is characterized by progression from paroxysmal to persistent AF. In this study we investigated MPO serum levels in paroxysmal and persistent AF determined from peripheral as well as central blood samples.

Methods:
Serum samples were periinterventionally collected from both the femoral vein as well as the left atrium in patients with AF during catheter ablation (n = 117). In addition, serum samples were drawn from the cubital vein from healthy no AF control probands (n=39). AF patients were grouped as either paroxysmal AF or persistent AF. MPO concentrations were measured using sandwich ELISA and analyzed in AF groups and controls.

Results:
Although MPO serum levels were significantly increased in AF compared to control (median, ng/ml 28.6 [interquartile range 14.5 – 72.4] vs. 13.3 [interquartile range 10.2 – 19.5], $p < 0.001$) there were no differences between AF types. Interestingly, we found a 10-fold increase in MPO concentration in atrial blood compared to its peripherally collected counterpart (median, ng/ml 28.56 vs. 296.28, $p < 0.001$) in patients with AF.

Conclusion:
The pro-fibrotic enzyme MPO was found to be elevated in AF patients irrespective of AF type. Our data suggests that MPO directly originates from the atria and further supports the notion of AF being an inflammatory disease.

Poster 90

ADGRG6 - The United Fragments of Extracellular Signaling?

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Adhesion G-protein coupled receptors (aGPCRs) constitute the second largest family of GPCRs in humans, however, they are least investigated regarding their signal transduction mechanisms, physiological interaction partners and in vivo functions. They distinguish themselves by mostly large extracellular domains (ECD) that are composed of a variety of subdomains. The most characteristic subdomain within the aGPCR ECD is the GPCR autoproteolysis inducing domain (GAIN), which performs a posttranslational self-cleavage reaction in most aGPCRs.

ADGRG6 (former GPR126) is a member of aGPCR subfamily VIII in mammals, that has been partially deorphanized. The receptor has been shown to bind to type IV collagen and the cellular prion protein (PrP^C) in Schwann cells, likely controlling myelin homeostasis.

Based on homology modeling, the extracellular domain (ECD) of ADGRG6 consists of a N-terminal complement C1r/C1s, Uegf, Bmp1 (CUB) domain adjacent to a pentraxin-like (PTX) domain, followed by a putative linker region which disembogues to a hormone receptor binding motif (HRM) and the C-terminal GAIN domain, where autoproteolysis occurs. Besides the GPCR proteolysis site (GPS) buried in the GAIN domain, there lies a furin cleavage site within the linker connecting CUB-PTX and HRM-GAIN part. The physiological reasons for this second cleavage site and consequences of fragmentation remain unknown.

We present preliminary data shedding light on molecular features of the ADGRG6 ECD in vitro, including PAGE, differential scanning fluorimetry (DSF), microscale thermophoresis (MST) and different light scattering methods in solution.

Poster 91

Nachweis gewebespezifischer Methylierungsmuster mittels qPCR

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In der forensischen DNA-Analyse ist neben dem Nachweis von individualspezifischen Personenprofilen die Spurencharakterisierung ein wichtiges Werkzeug zur Rekonstruktion des Tathergangs. Hierzu werden Körperflüssigkeiten (Spermasekret, Blut, etc.) derzeit in der Regel über spezifische Proteine mittels immunchromatographischer Nachweisverfahren (Antigen-Antikörper-Bindung) bestimmt. Dabei wird Probenmaterial verbraucht, welches später nicht mehr für die DNA-Analyse zur Verfügung steht, sodass für den Nachweis der Körperflüssigkeit und die Bestimmung des Personenprofils unterschiedliche Spurenbereiche untersucht werden müssen. Alternativ wurde hier ein Nachweis gewebespezifischer Methylierungsmuster über qPCR nach Restriktionsverdau mit dem methylierungssensitiven Enzym HpaII erprobt. Es wurden drei Marker gewählt, welche nach Literaturangaben für die Körperflüssigkeiten Spermasekret, Vaginalsekret und Speichel unterschiedliche Methylierungsgrade aufweisen. Für die Versuche wurde aus verschiedenen Sekret- und Gewebeproben DNA extrahiert, mit HpaII inkubiert und im Vergleich zu unbehandelten DNA-Proben quantifiziert. Aus der Differenz der C_T-Werte der mit HpaII behandelten und unbehandelten DNA-Proben wurden anschließend Rückschlüsse auf das jeweilige Sekret gezogen. Für zwei der Marker konnten jeweils für Spermasekretproben im Vergleich zu den übrigen untersuchten Körperflüssigkeiten signifikant abweichende C_T-Wert-Differenzen ermittelt werden. Eine Eignung des vorgestellten Assay konnte somit nachgewiesen werden, wobei für Speichel, Vaginalsekret und Blut weitere Versuche mit zusätzlichen Markern notwendig sind.

Poster 92

Morphogens in the adult liver – an insight into distribution, interaction and regulation

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Morphogens like Hedgehog (Hh) and Wnt/β-Catenin (Wnt) are known to govern developmental processes. Recently the impact of those morphogens on adult cell physiology and metabolism has sparked increasing interest. Most metabolic pathways in the liver are strongly zonated. For long, the Wnt pathway was thought to be exclusively responsible for metabolic liver zonation. Recently our group could demonstrate a dramatic impact of the Hh pathway on liver lipid metabolism.

For a better understanding of metabolic liver zonation under morphogenic control we aimed at demonstrating the mutual impact and zonal distribution of Hh and Wnt signaling in the adult liver.

Different mouse models were bred which allow a hepatocyte-specific modulation of both pathways in adult mice. To depict the porto-central distribution of pathway marker periportal (pp) and pericentral (pc) hepatocytes were isolated, followed by qPCR analysis of both hepatocyte populations. Moreover protein distribution on IHC stained liver slices were quantified via the modular software tool TiQuant. In addition a proteomic and metabolomic analysis from isolated pp and pc hepatocytes as well as liver material was performed.

Our results indicate a strong crosstalk between Wnt and Hh in the adult liver for the first time. The immunohistological analysis indicates how central proteins of Hh and Wnt are localized and how they influence each. Furthermore the outcome of the proteomic and metabolomic approach gives a deep insight how morphogens regulate liver metabolism in detail and contribute to a better understanding of the fine tuning mechanism on metabolic liver zonation.

Poster 93

Der Einfluss des Vasodilatators Relaxin auf die kardiopulmonale Funktion hypoxie-exponierter Ratten

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Mehrstündige Hypoxieexposition (10% O_2 in N_2) bewirkt bei Ratten eine Depression der Pumpfunktion des linken Ventrikels (LV) und aufgrund pulmonaler Vasokonstriktion die Entwicklung eines Lungenödems. In der aktuellen Untersuchung sollte geklärt werden, ob Relaxin (RLX) als potenter Vasodilatator die kardiopulmonale Funktion unter Hypoxie verbessern kann, da RLX sowohl bei Herzerkrankungen (z.B. akutem Herzversagen) aber auch bei experimentellen Lungenschädigungen (z.B. Ischämie-Reperfusionsschäden) positive Effekte gezeigt hatte. Zur Dosisfindung wurden 3 RLX-Dosen eingesetzt: D0 3, D1 15, D2 75 µg kg^{-1} d^{-1}. Die Untersuchungen wurden an 6 Gruppen weiblicher Sprague-Dawley-Ratten durchgeführt: normoxische Kontrolle (NaCl,N), hypoxische Kontrolle (NaCl,H), normoxische RLX-Gruppe (RLX-D1,N) und drei hypoxische RLX-Gruppen (RLX-D0,H; RLX-D1,H; RLX-D2,H). Nach 24 h erfolgten hämodynamische Messungen und die Lungen wurden zur histologischen Aufarbeitung entnommen.

Erste Ergebnisse zeigen eine deutlich eingeschränkte LV-Funktion nach 24h Hypoxie. RLX-D1 konnte diese Depression teilweise aufheben, die LV-Kontraktilität blieb jedoch unter allen RLX-Konzentrationen vermindert. Die Lungenödeme waren mit RLX stärker ausgeprägt, als in den Kontrollgruppen, am stärksten jedoch bei RLX-D1, N. In allen RLX-Gruppen ab der Basisdosis betrafen die Ödeme vor allem den Oberlappen. Diese Verteilung wurde in früheren Untersuchungen noch nie beobachtet. Wir vermuten, dass die Wirkung des Vasodilatators die hypoxische pulmonale Vasokonstriktion weitgehend aufhebt und damit die Lungendurchblutung erhöht und entsprechend der Schwerkraft verteilt.

Poster 94

Bacterial tRNA Modifications in Temperature Adaptation

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Transfer RNAs (tRNAs) are structurally highly conserved molecules that act as key players in protein biosynthesis. Among all RNAs, tRNAs show the highest density and variety of post-transcriptional modifications. Such base and ribose alterations play a major role in decoding as well as structural stabilization and depend to a certain extent on environmental factors like temperature.

Here, we analyse tRNA modification patterns of psychrophilic, mesophilic and thermophilic Bacillales to learn about temperature-dependent tRNA modifications. These bacteria were cultivated at temperatures ranging from 10 to 70 °C, depending on the organism. We detected RNA modifications via an RT-based deep-sequencing approach combined with specific chemical treatments. Hereby, we focused our research on dihydrouridine (D) and pseudouridine (Ψ) that locally introduce structural flexibility or stiffness, respectively. We also identified modifications that produce an accumulation of mismatches in RNAseq reads by impairing the Watson-Crick edge of the nucleobase (e.g. inosine, N1-methyladenosine). Starting with the analysis of our RNAseq data, we discovered interesting m^1A modification patterns. Whenever there is a non-canonical R13-A22 base pair in the D-stem of the tRNAs, A22 is modified to N1-methyladenosine (m^1A). This phenomenon was detected in about 30 % of the tRNAs in all organisms. However, the function of m^1A22 in this unusual purine-purine base pair remains elusive.

We expect to identify more interesting and temperature-dependent modification patterns, allowing us to draw further conclusions on temperature adaptation in tRNAs.

Poster 95

Functional screening for novel self-cleaving ribozymes

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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. For this screening, we use adapter-ligation methods to specifically enrich ribozyme fragments. To capture the fragment with a 2',3'-cP, we successfully established a procedure consisting of ligation using the A. thaliana tRNA ligase, dephosphorylation of 2'-phosphate and RT-PCR. Spike-in experiments using E. coli total RNA showed that RNAs, derived from a self-cleaving ribozyme, can be selectively recovered. To capture the fragment with 5'-OH group, we successfully established the adapter ligation using the RtcB ligase. In the future, we want to use the method to screen ribozymes in S. mansoni.

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.

Poster 96

Bacterial tRNA nucleotidyltransferases with dual activities

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Some bacterial tRNA nucleotidyltransferases seem to represent bifunctional enzymes, as they combine the catalytic domains of two large and diverse protein superfamilies. The N-terminal nucleotidyltransferase domain adds the invariant CCA-sequence to the 3'-end of tRNAs and belongs to the polymerase β superfamily. The C-terminal HD domain is a metallo-dependent phosphohydrolase that cleaves 2'-3'-cyclophosphates at the 3'-terminal ribose of tRNAs. Such 2'-3'-cyclophosphates may result from a spontaneous hydrolytic damage or nucleolytic attack by RNases. In principle, after the HD domain has reconstituted the 3'-terminal OH-group of a damaged tRNA by dephosphorylation, the nucleotidyltransferase domain could add missing nucleotides, restoring the full-length tRNA. Therefore, it was assumed that both domains collaborate during the tRNA repair. However, we found that both domains do not seem to work in concert during tRNA repair, as the HD domain is inhibited by NTPs that are required for CCA-addition. Furthermore, both domains have divergent substrate specificities in vitro as well as different requirements regarding buffer composition.

This raises the question as to whether the phosphohydrolytic activity of the HD domain has another function beyond the repair of damaged tRNA. Further studies in vitro as well as in vivo will help to elucidate the functional role of this HD domain in the cellular metabolism.

Poster 97

A temporal order in 5′- and 3′-processing of eukaryotic tRNAHis

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Transfer RNAs (tRNAs) are essential key players in protein synthesis. To accomplish their function, the transcripts undergo a series of maturation steps, including processing events at their 5'- and 3'-ends, where leader and trailer sequences are removed and additional nucleotides incorporated. At the 3'-end of each tRNA, the invariant sequence CCA is maintained by tRNA nucleotidyltransferase (CCA-adding enzyme), generating the site of aminoacylation. At the 5'-end, nucleotide addition occurs only in the case of $tRNA^{His}$, where a single G residue is incorporated at position -1 (G_{-1}). This extra residue is added by $tRNA^{His}$ guanylyltransferase and serves as an important identity element for the histidyl-tRNA synthetase. While in many bacteria and some archaea, the guanine residue is encoded in $tRNA^{His}$ genes, in almost all eukaryotes the G_{-1}-position has to be added post-transcriptionally. As these 5'- and 3'-positions are in close vicinity in the tRNA molecule, it is conceivable that the maturation status of one terminus has an impact on the processing of the other. Here, we report that the in vitro studies support a preferred pathway in which CCA addition precedes 5'-end maturation by Thg1. Furthermore, the conserved A residue at position 73, immediately upstream of the CCA triplet, prevents multiple 5'-G-incorporation templated by the 3'-CCA end. Obviously, the 3'-CCA triplet is a prerequisite for G_{-1} incorporation and serves as a quality criterion for Thg1. These data indicate that a sequential order and therefore a temporal dependency of nucleotide incorporation is essential to provide a mature $tRNA^{His}$.

Poster 98

Characterization of the Interaction between the Wnt Signaling Inhibitor Sclerostin and Glycosaminoglycans

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The Wnt signaling pathway is a regulator of bone development and remodeling in the human organism. A known negative regulator of this pathway is the protein sclerostin. Its inhibitory effect is based on suppressing the binding of the Wnt ligand and its co receptors LRP5 and 6 (LRP5/6). Furthermore, glycosaminoglycans (GAGs) binding to sclerostin has been observed to disturb the binding of sclerostin towards the LRP5/6 receptors. Interestingly, GAGs do not bind to the receptor interface of sclerostin but interact with different segments of the molecule. Therefore, we are interested in a detailed picture of the sclerostin/GAG interaction to understand how it suppresses the binding towards LRP5/6, as this may be a promising target to improve bone healing in bone related defects and diseases.

To study the interaction of sclerostin and GAGs via solution NMR, we established a purification and refolding protocol with a yield of 30 mg per liter fermented culture. In initial titration experiments with ^{15}N-labeled sclerostin and different GAGs, varying in the number and positions of sulfate residues, we observed shifting peaks in the ^{1}H-^{15}N-HSQC spectrum. To describe the binding modes and sites we now aim to assign these shifts to their respective amino acid to identify those residues that alter their chemical environment in the presence of GAGs. From the observable chemical shift perturbation upon GAG binding or induced secondary structure movements we will be able to characterize the binding site of the sclerostin/GAG interaction as a first step towards a more detailed picture of the interaction of sclerostin, GAGs and LRP5/6.

Poster 99

Mechanisms of Vaspin Internalization into Adipocytes

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Vaspin belongs to the serpin family and the only known protease targets so far are kallikreins KLK7 and KLK14. Vaspin protects mice from diet-induced obesity and adipose tissue inflammation and inhibition of KLK7 by vaspin was linked to parameters seriously affected by obesity. In addition, vaspin is believed to activate various intracellular signaling pathways such as AKT and NFkB by binding to GRP78. Here, we analyzed the cell surface interaction of vaspin in adipocytes. Using TAMRA labeled vaspin, we observed that vaspin is internalized into mouse 3T3-L1 preadipocytes. We synthesized various peptides derived from the vaspin N-terminus and all were essentially cell penetrating peptides in 3T3-L1 cells. Yet, an N-terminally truncated vaspin variant demonstrated that the internalization process is independent of this CPP activity. Instead, vaspin internalization was inhibited in competition experiments with unlabeled vaspin protein and also by using the endocytosis inhibitor chlorpromazine. These data provide strong evidence for a receptor mediated internalization process. Using BIX, an inducer of GRP78 expression, we observed increased vaspin internalization in 3T3-L1 cells.

Together, our results provide first evidence for a receptor dependent endocytosis process of vaspin internalization and this may be initiated by binding of vaspin to membrane or extracellular matrix components. The identification of receptors involved in vaspin internalization will give further insights into intracellular signal transduction induced by vaspin and will help elucidating the beneficial effects of vaspin associated with obesity.

Poster 100

Keratin-dependent regulation of the mitochondrial fission protein Drp1.

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Epidermolysis Bullosa Simplex (EBS) is a skin blistering disease arising from mutations in keratin genes K5 or K14, the products of which form the major cytoskeleton of the basal epidermis. Affected patients suffer from fragile skin, inflammation and itch. Furthermore, an altered distribution of mitochondria in the epidermis of EBS patients has been noted. Given the role of mitochondria in epidermal differentiation, wound healing and metabolism, we questioned if the keratin cytoskeleton is involved in mitochondrial dynamics and activity. To address that, mice and keratinocytes lacking all keratins were generated which revealed an altered composition and activity of mitochondria. Here, we show that keratin free keratinocytes contain highly fused mitochondrial networks compared to normal keratinocytes where mitochondria are mostly small and punctuated. Mitochondria are active organelles constantly undergoing fusion and fission events to adapt to cellular energy demands, to assure removal of damaged organelles and equal mitochondrial DNA distribution. Mitochondrial fission is regulated by the GTPase Drp1, which is activated and recruited to mitochondria by posttranslational modifications and mitochondrial membrane proteins like Mff and Mid49/51. We found that mRNA of Drp1 remained unaltered in keratin-deficient keratinocytes, whereas total protein levels and its recruitment to mitochondria was significantly diminished indicating keratin dependent Drp1 regulation and function. Next we want to understand the molecular mechanisms by which keratins interfere with the fission protein Drp1 leading to hyperfusion of mitochondria.

Poster 101

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.

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. Especially in which combination the exons are sliced out of the mRNA and which isoforms emerge. We are studying different tau isoforms started by nervi ischiadici, skeletal muscle, pancreas up to tissue of the parotic gland. These very different samples expose a totally different amount of tau isoforms We are detecting the special forms and combinations by use of RT-PCR, cloning and sequencing methods.

Poster 102

Functional interaction between CIRL and TRP channels in chordotonal neurons

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Drosophila melanogaster utilizes specialized organs for the perception of mechanical cues which are essential for survival. These so-called chordotonal organs (CHOs) consist of multicellular units (scolopidia) with each unit containing one bipolar, monociliated neuron. They are required for sensing tactile, proprioceptive and auditory stimuli. One particular CHO is the lateral pentascolopidial chordotonal organ (lch5), which is located laterally in the body wall of each larval hemisegment and consists of five scolopidia.

Previous studies showed that CIRL, an adhesion-type G protein-coupled receptor (aGPCR), shapes the perception of sensory input in lch5 neurons on the level of the receptor potential. Within the GPCR superfamily, aGPCRs constitute a group compromising 33 members in humans with crucial functions in a variety of physiological processes. Latrophilins form a well conserved subfamily of aGPCRs and CIRL is one of few homologs in Drosophila.

In this project, electrophysiological recordings of lch5 axon bundles were conducted to further elucidate the interaction between CIRL and the receptor potential generating TRP (transient receptor potential) channels.

Furthermore, we are currently establishing a novel approach to discriminate between individual lch5 neurons in order to unravel possible differences in activation modalities. To this end, MARCM (mosaic analysis with a repressible cell marker) combined with optogenetic inhibition will be used to stochastically silence individual neurons, thereby subtracting their contribution to compound recordings in a reversible manner.

Poster 103

The adhesion-GPCR CIRL promotes mechanosensory signal discrimination

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Research on the sense of touch has long been a center stage for receptors that directly convert mechanical force into electrical signals. The function of such mechanosensing ion channels remains a research focus. In contrast, evidence for mechano-metabotropic signal transduction and compelling models of force conversion into an intracellular second messenger response are limited, despite the vital role of metabotropic modulation in all corners of physiology.

Adhesion-type G protein-coupled receptors(aGPCRs), a molecule family with over 30 members in humans, operate in a vast range of physiological processes. Correspondingly, these receptors are associated with diverse human diseases, such as developmental disorders, defects of the nervous system and cancer. Several aGPCRs have recently been linked to mechanosensitive functions suggesting that processing of mechanical stimuli may be a common feature of this receptor family.

Drosophila Latrophilin/CIRL modulates mechanosensory signal transduction. In addition to shaping sensory responses to gentle touch and sound we show here that CIRL also influences mechanonociception in vivo. Cirlis expressed in peripheral larval nociceptors where it adjusts nocifensive behaviour under physiological conditions and in a chemical neuropathy model. By combining behavioural analyses with optogenetic manipulation of cyclic AMP levels in vivo, we find that CIRL exerts opposing modulatory effects in low-threshold mechanosensory neurons and high-threshold nociceptors. This bipolar action likely facilitates the differentiation of mechanosensory signals carrying different physiological information.

Poster 104

Investigating Isoform-Specific Functions of the Adhesion GPCR Latrophilin/dCirl

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Latrophilins, also known as CIRL (calcium independent receptor of a-latrotoxin), belong to the class of adhesion G-protein coupled receptors (aGPCRs). They share a common architecture with an extracellular N-terminal domain (ECD), seven transmembrane-spanning helices (7TM) and an intracellular C-terminal domain (ICD). aGPCRs contain adhesive domains as part of their ECDs enabling them to interact with cell-surface and/or extracellular matrix components, as well as an autoproteolysis inducing domain catalyzing self-cleavage into a C- and N-terminal fragment.

Latrophilin is evolutionarily conserved and has homologues in vertebrates and invertebrates. Previously, the Drosophila homologue dCIRL was shown to bear mechanosensitive features.

dCirl undergoes alternative splicing leading to the generation of eight transcripts. These encode receptors with varying ECD layout and TM number, and most notably, two isoforms featuring only a single TM domain. However, the functions of these isoforms remain completely unresolved.

We intend to uncover the biological purpose of producing this set of dCIRL receptors, especially the atypical 1TM receptor variants. We performed ELISA assays and immunofluorescent stainings of HEK293T cells transiently transfected with different dCIRL isoforms indicating that dCIRL1TM receptors are more abundant at the cell surface than 7TM receptors. In vivo both 1TM and 7TM receptor variants are expressed throughout the larval central nervous system as well as in a specific set of mechanosensory neurons. Interestingly, their expression pattern appears indistinguishable in brain, but not mechanosensory neurons.

Poster 105

Endogenous mouse Huntingtin is highly abundant in cranial nerve nuclei, co-aggregates to Abeta plaques and is induced in reactive astrocytes in a transgenic mouse model of Alzheimer's disease

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Pathogenic variants of the huntingtin (Htt) protein have been investigated in great detail in brains of Huntington's disease (HD) patients and htt-transgenic animals. However, little is known about the physiological brain region- and cell type-specific Htt expression pattern in wild type mice and a potential recruitment of endogenous Htt to other pathogenic protein aggregates such as amyloid plaques in cross seeding events. In brains of wild type mice, we observed ubiquitous neuronal Htt expression in a large number of brain regions, particularly in cranial nerve nuclei by immunohistochemistry. In Tg2576 mice with amyloid pathology, similar neuronal Htt expression patterns and a distinct association of Htt with Abeta plaques were revealed by immunohistochemical double labelling. Additionally, the localization of Htt in reactive astrocytes was demonstrated for the first time in this transgenic Alzheimer's disease mouse model. Both, Htt recruitment to plaques and localization in astrocytes appeared to be age-dependent. The astrocytic Htt expression was also detected in primary cultures by immunocytochemistry and by RT-qPCR. We provide the first detailed analysis of endogenous Htt expression in mouse brain and demonstrate Htt aggregation in proximity to Abeta plaques and Abeta-induced astrocytic expression of endogenous Htt in Tg2576 mice.

Poster 106

Characterization of pathological changes in peripheral nerves of patients with Alzheimer's disease

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Due to an overall aging population the prevalence of the Alzheimer's disease is constantly increasing. Pathologic changes in brains comprise extracellular plaques consisting of the amyloid-beta-protein and intracellular protein aggregates containing the microtubule associated protein tau.
The tau protein acts by regulating stability and dynamics of the microtubule lattice. It is subject to many posttranslational modifications. In Alzheimer's disease tau becomes excessively phosphorylated. The hyperphosphorylation decreases its affinity towards microtubules and promotes its amyloidogenic aggregation. Ultrastructurally, tau aggregates are present as paired helical filaments and can be found in vulnerable neurons such as pyramidal cells in certain brain regions. However, central and peripheral nervous system are not separate entities but rather functionally connected. So far, little information is known about the occurrence of these pathological structures in the peripheral nervous system. The investigation of tau aggregates within peripheral nervous tissue could provide a deeper insight into the disease and provide a tentative approach towards a diagnosis via peripheral nerve biopsy.
Analysis of human sciatic nerves as an example of peripheral nervous tissue is conducted by immunohistochemical labelling of paraffin slices with DAB nickel enhancement. Epitopes of interest contain phosphorylation sites of tau associated with its aggregation, as well as structural protein of the cytoskeleton. Furthermore, part of the tissue was homogenized to quantify certain proteins with western blot analysis and ELISA.

Poster 107

Evaluation of flow cytometry as a platform for the analysis of single extracellular vesicles in human serum.

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Extracellular vesicles (EVs) are a heterogeneous group of membrane coated structures, that are secreted by almost every tissue. Therefore, EVs have gained interest as potential biomarkers of various pathological conditions.

Extracellular vesicles include exosomes (40-200nm) and microvesicles (200-1000nm). Conventional flow cytometry (FCM) cannot discriminate particles smaller than 500nm from background noise based on their forward scattering properties. Therefore, EVs are usually first bound onto various kinds of beads before being detected by FCM. Yet, this prevents the analysis of one or more parameters of a single particle – which is a mayor advantage of FCM. However, the application of specific modifications during sample preparation and data acquisition helps to overcome the limitations and enables the analysis of non-bound EVs by FCM.

We evaluated this bead-free method to characterize EVs in human serum using FCM. In order to test the limitations and consistency of this method, we analysed serum EVs from different subjects and screened for both, common and tissue-specific EV-epitopes.

Here we show the advantages and shortcomings of this method over the indirect bead-based approach. Also, we will compare the promises of FCM to biochemical methods, such as Western Blot and Enzyme-linked Immunosorbent Assay, as a means to screen for biomarkers in human serum.

Poster 108

Characterization of Smad3 interactions with oligonucleotides

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Smad3 belongs to Smad protein family and regulates the gene expression as a transcription factor. Smads play an essential role in cell growth and development and are the main signal transducer for transforming growth factor beta (TGF-β) receptor pathway. Defects in Smad signaling are found in many cancers and in Alzheimer's disease (AD). The latter is characterized by a significant reduction of nuclear Smad proteins and their translocation into cytoplasmic compartment. It is assumed, that the diminished transcriptional activity of Smads leads to a disturbance of gene expression which is observed in AD. Though reduction of promoter/DNA binding activity, which is due to interaction of Smads with specific nucleic acid motifs (Smad binding elements, SBE), may explain several AD relevant alterations. However, information about interaction of Smad3 with alternative nucleic acid molecules is limited. Therefore the aim of our study is to examine the interaction of Smad3 to single stranded oligonucleotides and ribonucleic acid sequences. For this purpose we used electrophoretic mobility shift assays (EMSA) and surface plasmon resonance spectroscopy (SPR). Initial data demonstrate that Smad3 is able to bind to alternative nucleic acid molecules. Using SPR we started to determine kinetic parameters of this binding activity. Recombinant Smad3 protein expressed in E.coli, was immobilized on a SPR sensor chip and the association and dissociation constant for Smad3 interaction to selected binding partners was examined.

Poster 109

Essential contribution of NBCe1 to modulation of astrocytic metabolism by neuronal signals

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A major prerequisite for proper brain function is the appropriate supply of energy. Based on their strategical location, astrocytes crucially contribute to brain energy metabolism. The numerous processes closely enwrap neuronal synapses but also contact blood vessels. In a process called neurometabolic coupling, astrocytes take up energy metabolites from capillaries and provide them to neighboring neurons. However, the underlying mechanisms of this metabolic cooperation between astrocytes and neurons remain unclear. To address this issue we investigated the regulation of astrocytic metabolism by neuronal signals. The metabolic situation of astrocytes is portrayed by the NADH/NAD$^+$ redox state due to its central integrating position between metabolism and signaling. To measure cytosolic NADH/NAD$^+$ redox ratio we took advantage of the fluorescent biosensor Peredox-mCherry. Expressing Peredox in cultured cortical astrocytes we observed an increase in NADH/NAD$^+$ upon enhanced extracellular potassium concentrations and also upon application of ATP and glutamate, all together reflecting universal signs of neuronal activity. These results indicate the propagation of astrocytic catabolism by neuronal signals. The sodium-dependent bicarbonate cotransporter NBCe1 is known to stimulate glycolysis in astrocytes via activation of sAC and cAMP production. Inhibition of NBCe1 abolished the neuronal effects on astrocytic NADH/NAD$^+$ redox ratio. Taken together, our findings establish the NADH/NAD$^+$ redox state in astrocytes as metabolic key point and unlock one mechanism of adapting astrocytic metabolism to the energetic needs of the brain.

Poster 110

Detection of alpha-synuclein immunoreactivity in Lewy body-like aggregates, amyloid plaque-associated dystrophic neurites and reactive astrocytes in a mouse model of Alzheimer's disease

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Parkinson's disease is a progressive neurodegenerative disorder which is neuropathologically characterized by the degeneration of dopaminergic neurons of the substantia nigra and by formation of Lewy bodies and Lewy neurites composed of aggregated α-synuclein (α-syn). It is assumed that specific disease-related protein variants are responsible for the initiation and manifestation of pathogenic protein aggregation processes. There is also evidence for co-aggregation of proteins characteristic for different clinical entities.

Here, we aimed at revealing a potential cross seeding of α-syn in a transgenic mouse model of Alzheimer's disease (AD) characterized by aggregation of β-amyloid peptides. A panel of 13 different antibodies directed against defined α-syn epitopes was tested on sections of wild type (wt) and transgenic mouse brain. Labeling patterns permitted classification into different categories. Subcellular neuronal staining in wt brain differed between prominent somatic versus predominant synaptic labeling. Lewy body-like aggregates in hypothalamus and β-amyloid plaque-associated reactive astrocytes in transgenic animals were only detected by antibodies that also stained neuronal cell bodies in wt tissue. In contrast, α-syn antibodies which strongly labeled synapses in wt, particularly highlighted dystrophic neurites in brains of AD mice.

We conclude that differential binding of α-syn antibodies in healthy tissue and at sites of β-amyloid pathology reflects distinct physiological and pathological conformational states of α-syn including co-aggregation with β-amyloid.

Poster 111

Human Microstructural Connectomics: Computational modelling and validation with histology and CLARITY

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The human brain is a big network of connecting elements comprising the so called connectome. It can be differentiated into three levels: the macrostructural level formed by the corresponding brain areas, the mesostructural level formed by cortical layering and possible columns and the microstructural level formed by individual neurons linked to each other. All levels need to be combined to understand the functional organization of the human brain. Information is distributed between neurons and across the brain by so called long-range fibers (~10% of cortical connections). By tracking the diffusion of water molecules within the brain axonal pathways can be spatially visualized in/ex vivo. This diffusion tensor imaging (DTI) alone is very limited and eventually creates lots of false positive results. Hence, the goal is to verify this in/ex vivo imaging by afterwards reconstructing the same long-range fiber tracts en bloc on a microscopic and ultrastructural level. The combination of clearing techniques (Clarity, iDISCO$^+$) immunohistochemistry and 3D microscopy (LSM 880, Ultramicroscope ll and diSPIM) allows for the microscopic visualization (330nm – 1µm) of neuronal connections over large brain volumes (≤ 5mm). Focusing on clearing techniques two main approaches were isolated: the CLARITY method using an acrylamide hydrogel matrix linking all proteins before removing lipids via active electrophoreses; and the iDISCO method using immersion in Methanol and Dibenzylether. Both lead to stained, cleared brain tissue blocks sized 25 x 25 x 5mm allowing the investigation of cyto- and myeloarchitecture with a subcellular resolution.

Poster 112

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 toxic species of Tau protein and Aβ peptides, leading to progressive cell death in neuronal tissue. Interestingly, there is a selective vulnerability of neurons in AD. Especially neurons surrounded by perineuronal nets (PNs) seem to be protected against AD pathologies. PNs are composed of chondroitin sulfate proteoglycans (CSPGs) which are believed to mediate the neuroprotective function of PNs. However, the underlying mechanisms are not clear. Here, we aim at identifying the basic principles behind the neuroprotective action of CSPGs.

Initial experiments in primary neuron cultures indicate that CSPGs suppress internalization of extracellular Tau. Further, the application of ocadaic acid which inhibits PP2A phosphatase failed to elicit hyperphosphorylation and aggregation of Tau in PN-bearing neurons. Immunohistochemical analysis of brains from CSPG mutant mice (aggrecan$^{+/-}$) crossbred with P301L mice (model for Tau pathology) show that the loss of aggrecan in PNs increases the vulnerability of the PN-bearing neurons for hyperphosphorylation of Tau.

In conclusion, the present data suggest that CSPGs of PNs act both on the extra- and intracellular level to serve their neuroprotective function. CSPGs may protect neurons from the extracellular side by inhibiting internalization of extracellular Tau and may further mediate intracellular processes which protect neurons from the generation of pathological forms of Tau. Future experiments need to clarify whether the neuroprotective action of CSPGs can be transferred to neurons that are not naturally shielded by PNs.

Poster 113

Evaluation and validation of tau protein in neuronal derived extracellular vesicles from human serum

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Neuronal derived extracellular vesicles (ECV) may be a potential culprit in the cell-to-cell transmission of pathologically modified tau protein in Alzheimer's disease. The ability of these vesicles to cross the blood brain barrier does not only make them easily assessible in peripheral biological samples, but also may provide useful and early diagnostic information on susceptible Alzheimer's disease patients. Here, we attempt to explore several techniques and methodologies that can provide an analytical platform for evaluating tau protein in neuronal derived ECVs from human serum samples.

As a proof of principle, we first evaluated tau protein from the exosomes of SH-SY5Y cultured cells that has been transfected with the cDNA of human tau. ECVs were pelleted from the harvested cultured cell supernatant using ultracentrifugation technique. The presence of ECVs was verified using flow cytometry and western blot. Neuronal derived exosomes were discriminated from other forms of exosomes by using magnetic beads that has been coupled with anti-CD171 biotin antibodies. To evaluate tau protein, the isolated and verified neuronal derived exosomes were lysed with Triton X-100, and the content analysed using ELISA-technique. Further, neuronal derived ECVs and tau were evaluated from the serum of mild to moderate cognitive impaired patients on one hand and the also in healthy control individuals on the other hand.

Poster 114

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

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There are various forms of dementia. One common form is the frontotemporal dementia (FTD), which belongs to the subgroup of tauopathies. Subject of this work is 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. Transgenic hTauP301$^{L+/+}$ / mTau$^{-/-}$ mice, mTau$^{+/+}$ wild type mice and mTau$^{-/-}$ knockout mice were examined by immunohistochemistry, Western blot 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 physiologically phosphorylated TP and the amount of pathologically phosphorylated TP. In addition, three other proteins/ enzymes have been investigated that may influence the spread of the TP pathology in the brain. 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. There was a strong heterogeneity regarding the TP in between the studied neuroanatomical areas as well as between the different mouse groups.

Poster 115

Enhanced and depressed aggressiveness - social experience establishes behavioural differences in crickets

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Social experience, particularly dominant-subordinate relationships are thought to have a major impact on the development of consistent inter-individual behavioural differences in mammals (animal personality). Surprisingly, different personalities have even been reported for various invertebrate species, but their proximate cause is unknown. We are investigating how the early social experiences of winning and losing an aggressive encounter influences other aspects of behaviour such as exploratory behaviour, general motility and learning (Poster Borstel & Stevenson) in adult male crickets (Gryllus bimaculatus). Using an automated video-tracking software (Noldus EthoVision), we tested the extent to which social experiences during larval life influences the future adult behaviour profile. To a limited extent, larval crickets interact aggressively with each other, but these interactions had no effect on subsequent behaviour. We next compared cohorts of adult crickets that we raised as larvae either with or without adult males in the colony. Interestingly, larvae raised without adult males were more aggressive and more proactive in their general behaviour as adults compared to those raised as larvae with adult males present. We conclude that early, pre-adult social experience forges long term, possibly life-long inter-individual changes in behaviour in crickets. Aggressive experience is thus a major determinant of behavioural syndromes or personality. We are currently studying how multiple aggressive experiences influence general behaviour and the part played by neuromodulators.

Supported by the DFG (STE 714/5-1)

Poster 116

Influences of dominance and social subjugation on learning and memory in crickets

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Inter-individual differences in behaviour and aggression can be induced by social experiences such as winning (dominance) or losing (social subjugation) an aggressive interaction with a conspecific. In insects, our work on adult male crickets (Gryllus bimaculatus) has shown that winners tend to be more proactive than losers (Rose et al. Animal Behav. 123:441-450, 2017; Poster Balsam & Stevenson) and we are now investigating how fighting experience influences learning and memory. In our first set of experiments, we applied a simple appetitive olfactory learning paradigm. Aggressive interaction between weight-matched pairs of adult male crickets (isolated & deprived of water for 48 h) generated clear winners and losers; a third cohort had no fighting experience (naive). Two hours after the fight, individual crickets were trained (3 times; 5 min intervals). They were presented with an odour, followed by a drop of water as reward. After 60 min, the response to the odour alone was tested again. Animals which responded with clear searching behaviour, typified primarily by head bobbing and antennal waving in the direction of the odour, were considered as having learnt. Non-learners, showed no change in ongoing behaviour. Significantly more winners showed learning (78%) compared to losers (22%; p = 0,0001), whereas naive crickets had an intermediate learning frequency (45%). We are currently applying additional learning paradigms, also with the aim to reveal how neurotransmitters that influence winning and losing in crickets determine experience dependent differences in learning ability.

Supported by the DFG (STE 714/5-1)

Poster 117

Increase of neuronal activity by 4-Aminopyridine in vivo, improves sensory-motor dysfunction in a mouse model of SMA

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Dysfunction of neuronal circuits are important determinants in neurodegenerative diseases. Spinal muscular atrophy (SMA) — caused by deficiency in the ubiquitously expressed SMN protein — is characterized by loss of central synapses, neuromuscular junction (NMJ) denervation, motor neuron death and skeletal muscle atrophy. SMA vulnerable motor neurons exhibit a reduced firing frequency as a response to impaired premotor synapses early in the disease process in mice, suggesting a pharmacological increase of neuronal activity could be a therapeutic strategy. The FDA approved 4-aminopyridine (4-AP) increases neuronal activity by block of voltage activated K+ channels.

To address whether an increase of neuronal activity could be beneficial to the SMA phenotype in vertebrates, we injected daily SMA-Δ7 mice with 4-AP (1mg/kg, BID). The treated SMA mice displayed slightly increased lifespan and bodyweight compared to vehicle-treated SMA mice. Furthermore, 4-AP treated SMA mice show an improvement in motor behavior at the end stage of disease, resulting in better righting times and ability to walk. Strikingly, proprioceptive synapses and innervated NMJs in SMA animals were significantly improved in number and function compared to untreated mutant littermates, with no rescue of vulnerable motor neurons, suggesting that 4-AP either prevents synaptic degeneration or induces sprouting. Our in vivo study reveals that sufficient increase of neuronal activity by 4-AP may have a beneficial long-term effect on motor function for SMA patients by improving central and peripheral synaptic connectivity.

Poster 118

Enriched environment accelerates action potentials

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Environmental enrichment for rodents enhances motor performance skills. Structural and molecular changes have been reported to be coupled with enriched environment, but functional alterations of single neurons remainelusive. Here, we compare mice grown up under control conditions and enriched environment. We tested the motor performance on a Rota-rod and subsequently preformed whole cell patch clamp recordings from granule cells of lobule IX of the cerebellum, an area of the brain known to be involved in motor coordination. We show that neurons undergo a certain functional adaptation to enriched environment, manifested in faster action potentials and higher maximal frequency of action potential firing. These data show that enriched environment causes specific alterations in the biophysical properties of neurons. Furthermore, we speculate that the ability of granule cells in lobule IX of the cerebellum to generate higher firing frequencies improves motor performance.

Poster 119

Significance of the brain extracellular matrix in schizophrenia

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Objective:
Perineuronal nets (PN) in brain extracellular matrix (ECM) consist of chondroitin sulfate proteoglycans (CSPG), covering specialized neurons in a grid-like fashion. PNs control various neuronal processes that are modified in patients suffering from schizophrenia (SZ). Recent studies showed a contribution of CSPG-modification on SZ. However, the impact of each PN-component to SZ-pathophysiology is scarcely investigated until now. Therefore I investigated key CSPG proteins, e.g. aggrecan (ACAN) and brevican (BCAN) to understand how CSPGs influence formation and progression of SZ.

Methods:
We investigated human post mortem samples (frontal cortex; 6 SZ-patients, 7 controls). Brain material was analysed by standard immunohistochemistry techniques. Specific antibodies against BCAN, ACAN, parvalbumine (PARV) and ionized calcium binding adaptor molecule (IBA) were used to detect major ECM-components and potential inflammatory processes. CSPG-components were evaluated qualitative by lightmicroscopy and quantificated by unbiased stereology.

Results:
The determination of net-covered neurons shows significant differences between SZ-samples and controls, varying according to the CSPG-component. BCAN, involved in brain maturation, is decreased on SZ-samples. IBA, marking neuronal inflammation, is considerably increased.

Conclusion:
Expanded knowledge of biochemical modifications is essential to further investigate pathomechanisms of SZ. This research project focusses on CSPGs as new target in SZ-pathology.

Poster 120

Differential presynaptic short-term and homeostatic plasticity of excitatory and inhibitory transmission

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Activity in neuronal circuits arises from the interplay of excitatory and inhibitory synaptic signaling, which is delicately balanced to maintain stable network activity. There is evidence that excitatory and inhibitory synaptic transmission show diverging short-term plasticity. However, which of the multiple factors governing synaptic transmission cause differential short-term plasticity is not fully understood. Additionally, long-term perturbation of network activity is known to homeostatically affect excitatory transmission, while the impact on inhibitory transmission remains largely elusive. Here, we explore short-term plasticity by extracellular stimulation of excitatory and inhibitory inputs onto whole-cell patch-clamped neurons in cortical cell culture. We isolate presynaptic short-term plasticity by pharmacologically alleviating postsynaptic contributions. We find fundamentally different short-term plasticity of inhibitory and excitatory synapses, with stronger synaptic depression due to higher vesicular release probability in inhibitory compared with excitatory synapses. Furthermore, 48 hours of activity deprivation by Tetrodotoxin inversely affects synaptic transmission, leading to strengthening of excitatory and weakening of inhibitory transmission mediated by several mechanisms including differential changes in release probability. Thus, our data reveal biophysical mechanisms stabilizing neuronal network activity levels.

Poster 121

Gradients in the cerebellar cortex enable Fourier transformation and improve storing capacity

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Accurate information processing in our brain relies on precise timing of action potentials in feed-forward neuronal networks. Here, we investigate the mechanisms that support efficient feed-forward information processing in the cerebellar cortex and identify a gradient in the biophysical properties of granule cells (GC), which allows a partial Fourier transformation of the mossy fiber (MF) input. GCs closer to the white matter are tuned for higher frequencies, have faster axonal conduction velocity, and preferentially project to the base of the Purkinje cell (PC) dendritic tree to elicit faster postsynaptic potentials. Computational modeling of the cerebellar network revealed that these gradients in the biophysical properties improves spike-timing precision of PCs and dramatically reduces the number of GCs required to obtain a specific temporal precision. Our data reveal how Fourier transformation and specialized downstream signaling pathways improve temporal precision whilst reducing the number of required neurons in neuronal networks.

Poster 122

Chemical cues of female fertility states in a non-human primate

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An increasing number of studies verify that olfaction is an important way of communication throughout the order of primates. Evidence from behavioural studies indicates that primates of different taxa are able to distinguish species, group membership, kinship and/or individual traits such as age or the fertile state. Callitrichids in particular have well-developed olfactory systems and use specialized anogenital scent glands to produce scent marks. Behavioural studies showed that these scent marks convey information about the sex, dominance status or female ovulatory states. However, large gaps remain in understanding the chemical underpinnings of olfactory cues. Bioassay studies showed that male common marmosets are able to distinguish between odours from the peri-ovulatory and luteal phase of females, suggesting that they use chemical cues to optimise mating effort and ascertain paternity. To investigate those differences of the chemical profiles in accordance with fertile states, we analysed the anogenital odours of female common marmosets with gas chromatography-mass spectrometry. We collected odour samples of twelve female common marmosets using thermal desorption tubes and compared the odour profiles between cycle phases (i.e. follicular, follicular late, ovulation and luteal), age and parity. We found that all three factors of female reproductive quality have an impact on the similarity of whole chemical profiles and further identified affected chemical substances. Our results thus complement existing behavioural evidence for cues of fertility.

Poster 123

Insight into synaptic transmission and plasticity on the fly – Characterizing presynaptic release by electrophysiological means in Drosophila larvae

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Neurotransmitter (NT) release at synapses is subject to mechanisms that control neuronal plasticity. Presynaptic plasticity shapes the amount of transmitter that is released at active zones (AZs) upon an arriving action potential by defining variables such as the amount of readily releasable synaptic vesicles (SVs) and the probability of SV fusion. These variables can be characterized by electrophysiological means: Monitoring a cell's membrane potential or ion flux through the cell membrane in response to evoked or spontaneous NT release.

This work presents an electrophysiological approach to characterize an interaction between two presynaptic proteins, Bruchpilot (Brp) and Complexin (Cpx), and to discern their roles in NT release. Different stimulation protocols were applied to observe short-term plasticity at the larval neuromuscular junction (NMJ) of the experimentally accessible fly Drosophila melanogaster that allows investigations on the mechanisms of synaptic plasticity in a physiological context.

Hypomorphic mutants of both proteins (brp^{nude} & cpx^{1257}) exhibit short-term depression (STD). This is further enhanced in the double mutant, yet the prominently enhanced spontaneous SV release observed in cpx^{1257} larvae is partially rescued and the number of AZs is reduced to brp^{nude} levels. Compared to wildtype, the amount of readily releasable SVs is not decreased and overexpression of cpx neither reverts nor rescues STD in brp^{nude} mutants. These results support a model where Brp and Cpx act in a common pathway to accumulate SVs near release-sites and act in parallel downstream pathways during release.

Poster 124

Validation of MRI-based biophysical models with high-resolution histology

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Recent advances in magnetic resonance imaging (MRI)-based biophysical models facilitate the estimation of white matter properties such as g-ratio, axonal diameter, and axonal density in vivo. G-ratio is the ratio between inner and outer axonal diameter and quantifies the relative myelination of a fibre. The main limitation of biophysical models is the simplification of the underlying tissue composition, e.g., axons are modelled as long cylinders with invariable diameters. These assumptions lead to systematic over- or underestimation of the derived parameters. Furthermore, the signal of an MRI voxel is only a summary measurement reflecting the underlying tissue composition. In contrast to MRI, high-resolution microscopy images of 2D histological data provide a better understanding of white matter properties. We aim to correlate the estimations of g-ratio, axonal diameter, and axonal density in biophysical models with histology.

As a first step towards this goal, we obtained a human medulla oblongata sample at autopsy with prior informed consent (female, 89 years, heart failure, procedure approved by the responsible authorities) and fixed it in formalin. We dissected the corticospinal tract from a 500µm slice of the sample. This section was contrasted in osmium tetroxide, dehydrated in graded acetones, and embedded in Durcupan resin. Semithin sections (0.5 µm) were preparedwith an ultramicrotome (Reichert Ultracut S, Leica). Sections were stained for myelin sheaths with toluidine blue, coverslipped, and digitized with an AxioScan Z1 slide scanner (Zeiss). AxonDeepSeg will be used for segmentation of axons and myelin sheaths.

Poster 125

Presynaptic $GABA_A$ Receptors Modulate Glutamatergic Transmission at the Endbulb of Held

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Spherical bushy cells (SBCs) in the ventral cochlear nucleus integrate acoustically driven excitatory input from the auditory nerve with non-primary glycinergic and GABAergic inhibitory inputs to precisely encode the temporal structure of sounds. GABA increases the overall inhibitory strength particularly during ongoing synaptic activity when GlyR currents undergo depression, and provides slow, tonic-like inhibition. However, it is not known whether the functional role of GABA may extend beyond the SBC inhibition by modulating the endbulb of Held terminal through presynaptic $GABA_AR$. To examine whether the endbulb of Held expresses functional $GABA_AR$, whole cell recordings from the terminals were performed in acute brainstem slices from P13-15 gerbils. Brief application of GABA evoked a prominent chloride conductance at the endbulb. Gramicidin perforated patch recordings revealed a depolarizing chloride gradient within the terminal (E_{Cl}=-28mV; estimated intraterminal $[Cl^-]$=40 mM). Such $GABA_AR$ mediated depolarization decreased the amplitude of presynaptic APs evoked by electrical stimulation of auditory nerve fibers and subsequently attenuated AP triggered calcium influx. The functional role of $GABA_AR$ at the endbulb was assessed with whole cell recordings from SBCs upon stimulation of AN fibers. Brief application of GABA to the presynaptic terminal transiently reduced EPSC amplitudes and this effect was blocked by the $GABA_AR$ antagonist SR95531. The present results suggest that $GABA_AR$ can modulate the strength of glutamatergic transmission at the endbulb of Held-SBC synapse.

Poster 126

Developmental easing of short-term depression in 'winner' climbing fibers

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Cerebellar climbing fibers (CFs) undergo a substantial pruning during the first three postnatal weeks. As a result, the innervation of Purkinje cells, their main targets in the cerebellum, switches from multiple- to single-CF innervation. The associated strengthening of the remaining ‚winner' CF is thought to be guided by long-term potentiation (LTP). In contrast, ‚loser' CFs were proposed to be weakened by presynaptic long-term depression (LTD), ultimately leading to their elimination. It remained unclear whether LTP of winner CFs is pre- or postsynaptically expressed and whether corresponding changes in paired-pulse depression (PPD) occur in the pruning period: an increase of PPD would accompany presynaptic LTP, while postsynaptic LTP would not affect PPD. We, therefore, analyzed the developmental profile of CF-PPD in the first three weeks after birth.
Our data unexpectedly reveal that maturation of winner CFs is associated with an easing of PPD, denoting a decrease in the release probability and that PPD in loser CFs remains unchanged. This easing of PPD seems neither to be due to substantial changes in positional priming of synaptic vesicles nor due to unequal effectiveness of kynurenic acid on saturation of postsynaptic receptors. These findings indicate that winner CFs undergoing activity-dependent LTP, undergo a further step of maturation that eases their PPD. The data would be in agreement with a scenario in which synapses on dendrites (harboring the growing winner CF) and somata (harboring loser CFs and to-be-disintegrated synaptic contacts of the winner CF) are characterized by different release probabilities.

Poster 127

High-resolution current clamp recordings from small cortical nerve terminals

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The shape of the presynaptic action potentials critically controls the strength of synaptic transmission. However, knowledge about the properties of action potentials in small nerve terminals is limited. Studies indicate that potassium channels dynamically regulate the amplitude of presynaptic action potentials in some small nerve terminals, conflicting direct patch clamp recordings from larger presynaptic terminals. Therefore, we have investigated presynaptic action potentials in cultured cortical neurons by direct whole-cell patch clamp recordings with quartz glass pipettes. Using electrical circuits we systematically investigated errors related to pipette capacitance and amplifier performance. We found large action potentials with ~120 mV amplitude. Pharmacologically blocking potassium channels prolonged action potentials but did not affect their amplitude. Thus, potassium channel activation regulates the duration but not amplitude of action potentials at small nerve terminals in the cortex, providing support for the text-book knowledge of the all-or-none action potential amplitude.

Poster 128

Algorithm for Automatic Real-Time EEG Artifact Correction

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Background:
EEG is a non-invasive brain activity recording technique that allows the use of real-time applications, such as neurofeedback. Its susceptibility to electrooculographic (EOG) and electromyography (EMG) artifacts (i.e., jaw clenching, teeth squeezing and forehead movements) greatly obscure the information and power spectrum of EEG signals. A software-only real-time method for correcting multiple types of EEG artifacts of high-density EEG remains a significant challenge.

Methods:
The algorithm was tested on three healthy subjects using 64 EEG channels (Brain Products GmbH) and a sampling rate of 1,000 Hz. Captured EEG signals were imported in MATLAB with the labstreaminglayer interface allowing buffering of EEG data. EMG artifacts were detected by channel variance and adaptive thresholding and corrected by using channel interpolation. Real-time independent component analysis (ICA) was applied for correcting EOG artifacts.

Results:
Our results demonstrate that the algorithm effectively reduces EMG artifacts, such as jaw clenching, teeth squeezing and forehead movements, and EOG artifacts (horizontal and vertical eye movements) of high-density EEG while preserving brain neuronal activity information. The average computation time of EOG and EMG artifact correction for 80 s (80,000 data points) 64-channel data is 300 – 700 ms depending on the convergence of ICA and the type and intensity of the artifact.

Conclusion:
An automatic EEG artifact correction algorithm based on channel variance, adaptive thresholding, and ICA improves high-density EEG recordings contaminated with EOG and EMG artifacts in real-time.

Poster 129

Assoziation von motorischen, sensiblen und Sprachdefiziten nach Schlaganfall mit segregierten thalamokortikalen Netzwerken

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Hintergrund:
Läsionen des Thalamus können neben sensomotorischen Defiziten auch Sprachstörungen verursachen, die kortikalen Aphasien ähneln. Unklar ist ob die Symptome Folge der gestörten Verarbeitung in den thalamischen Nuclei (TN) selbst (Relay-Hypothese) oder den verbundenen thalamo-kortikalen Netzwerken (TCN) sind. Dabei könnten Symptome nach der sog. Integrations-Hypothese, die annimmt, dass der Thalamus die effektive Informationsverarbeitung zwischen nachgeschalteten Regionen reguliert, erklärt werden.

Methode:
Untersuchung von 72 Patienten (30 weiblich, 66±12.7 Jahre) mit thalamischen Ischämien mittels voxelbasiertem Läsions-Symptom-Mapping (VLSM) und Läsionsnetzwerk-Symptom-Mapping basierend auf Resting-State MRT Daten 100 gesunder Probanden (LNSM).

Ergebnis:
Es zeigte sich eine Assoziation (VLSM) von Sprachstörungen (SP), rechtsseitigen motorischen (MO) und sensiblen Symptomen (SE) mit partiell überlappenden Lokalisationen in Projektion auf mediodorsale, ventrolaterale und ventrale postero-laterale TN links. Der Vergleich der Läsionsnetzwerke (LNSM) von Patienten mit und ohne SP, rechtsseitigen MO und SE ergab ein jeweils eine höhere normative Läsionsnetzwerk-Konnektivität zu abgrenzbaren linksseitigen Regionen des Sprachnetzwerkes (SP), dem motorischen und prämotorischen Kortex (MO) sowie dem parietalen Kortex und G. frontalis superior (SE).

Schlussfolgerung:
Die Assoziation von Defiziten mit anatomisch plausiblen, segregierbaren TCN zu primären und Assoziationskortizes favorisiert die Hypothese einer Störung nachgeschalteter komplexer Verarbeitungsprozesse (Integration) gegenüber einer lokalen Funktionsstörung.

Poster 130

Correlation of Human Hypothalamus Volume and Anxiety Symptoms in Affective Disorders

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Essential features of the hypothalamus play a constitutive role in the depressive symptomatology and the anxiety generating stress response system. The few studies which dealt with the association of anxiety symptoms in psychiatric disorders and the hypothalamus volume remained contradictory results. This substantiated our interest to verify the correlation of the hypothalamus volume and the anxiety score of affective disorder patients.

Method:
61 patients, aged 20 to 62 years and suffering from major depressive or bipolar disorders participated in the study. The hypothalamus volumetry was performed using 7T MRIs and the anxiety score was calculated with items from the Inventory of Depressive Symptomatology.

Results:
Kendall's correlation shows a significant moderate correlation between the left (τ_b = 0,391, p = 0,019) and bilateral (τ_b = 0,34, p = 0,047) hypothalamus volume and the anxiety score of patients with a medicated major unipolar depression. For patients with unmedicated major depressive or bipolar disorder the effect was not significant. The left, right and bilateral hypothalamus volume of the investigated men was significantly larger compared to the women.

Conclusions:
To our knowledge, this is the first study exploring a positive correlation of an anxiety score and the hypothalamus-volume, investigated with high-resolution 7T images, in affective disorders.
The medicated depression is mostly recurrent and characterized by an increased number of episodes. The volume change can be interpreted as a neurobiological correlate of a different pathophysiology of the diagnostic groups with increasing anxiety intensity.

Poster 131

Metabolic heterogeneity of astrocytes: insights from nanosensor imaging in the brain

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Protoplasmic astrocytes in the grey matter are complex cells with numerous fine processes mainly contacting synapses, blood vessels and other brain cells. Fibrous astrocytes in the white matter have fewer branching processes which are in close structural interaction with axons, oligodendrocytes and their myelin. Functionally, the major task for neurons within grey matter is transmission and computation of information at synapses, while white matter tracts are specialized to allow reliable axon potential propagation along axons for long distances. Astrocytes display molecular and structural properties that are perfectly matched to the function of neighbouring neurons. We hypothesize that astrocytes in grey and white matter differ in their basal energy metabolism as well as in main regulatory mechanisms affecting astrocytic metabolism, but also providing feedback from metabolism to signaling events. Taking advantage of genetically encoded, fluorescent biosensors for ATP and NAD^+/NADH-redox state specifically expressed in astrocytes combined with 2-photon-microscopy in acutely isolated brain slices we investigate heterogeneity of astrocytic energy metabolism by addressing the dynamics of these key metabolites. We identify distinct differences in astrocytic energy metabolism and in main regulatory mechanisms between astrocytes located in the grey (cortex) and white matter (corpus callosum). These results support the hypothesis that astrocytic metabolism is subject to cellular heterogeneity between different brain regions and contribute to a deeper understanding of how brain energy metabolism is embedded in brain physiology.

Poster 132

The role of chemical cues for indicating female fertility in humans and chimpanzees

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The role of olfaction in primate social and sexual communication is increasingly ascribed more importance based on compelling evidence from various behavioural studies. Yet, still large gaps exist in understanding olfactory communication during human evolution. In my PhD project, I study the chemical composition of female body odour as a potential fertility cue in humans and chimpanzees, two species which differ in their patterns of visual fertility advertisement. While the reproductive state is suggested to be concealed in humans, it is visually indicated by their sexual swellings in female chimpanzees. In a pilot study, I collected volatile organic compounds of the genital region of three adult, regularly cycling chimpanzees across three menstrual cycles per individual using a highly sensitive sampling method (thermal desorption tubes) that is novel to studying mammalian body odour. Whole body odour profiles varied in association with sexual swelling sizes, but concurrently a considerable inter-individual variability in odour composition became apparent. By applying the same method, I am complementing these preliminary data with an ongoing study on women. This will allow valuable implications on how to improve sample quality by adjusting methodological aspects as well as providing first candidate substances that might function as fertility cues. Eventually, this study will help to reconstruct the evolutionary history of human sexual signalling.

Poster 133

Pavlovian threat expression generalizes along relational memory for orderly representations

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Predicting potential environmental threats is crucial for survival. Individuals learn via Pavlovian conditioning what constitutes impending danger and generalize their acquired defensive behavior to cues that resemble a learned threat along a unimodal sensory dimension. Yet, real world situations involve cues that are not isolated but embedded in an existing network of memory representations reflecting a stable structure of one's environment. Here, we show that Pavlovian threat conditioning integrates with a structure of relational memory where its representations are organized as closer or further away from one another leading to orderly expressed conditioned threat responses beyond the initial learning. We trained participants to associate novel and perceptually dissimilar images with one another to form a linear graph of relational memories. The next day, they were threat conditioned to two images located at the opposite ends of the graph where only one of them was paired with electrical shocks. Subsequently, they were exposed to all images from the graph while their shock expectancy ratings, skin conductance, and pupil diameter were collected to measure generalization of conditioned threat responses. In all three measures, the conditioned threat responses decrease exponentially with a link distance to the cue previously paired with the shocks suggesting a spread of an aversive value across relational representations. Individuals employ their knowledge about the relations between entities in their environment to infer which constitute potential danger beyond the perceptual similarity to previous aversive experience.

Poster 134

Salivary cortisone, as a biomarker for psychosocial stress, is associated with state anxiety and heart rate

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Background:
Stress activates the central nervous, the autonomic nervous, and the endocrine system. This study aimed to (1) test the usability of salivary cortisone as a stress marker, (2) create a comprehensive profile of hormonal responses, and (3) analyze their association with psychometric and autonomic stress measures.

Methods:
Healthy men (18-35 yrs) completed either the Trier Social Stress Test (TSST) (n=33) or a Placebo-TSST (n=34). Blood and saliva were collected at 14 time points along with state-anxiety (STAI) and heart rate. Serum steroids (cortisol*, cortisone*, dehydroepiandrosterone-sulfate, androstenedione*, progesterone*, 17-hydroxyprogesterone*, testosterone, estradiol*, aldosterone*), salivary cortisol* and cortisone*, copeptin*, adrenocorticoptropic hormone*, corticosteroid-binding globulin, and salivary alpha-amylase* were analyzed. We used mixed-design ANOVAs, receiver operator characteristic (ROC) curve analyses, and Spearman correlation analyses.

Results:
The largest area under the ROC curve was observed in salivary cortisone at 20 minutes after the end of the TSST (AUC=0.909±0.044, p <0.0001). Significant time-by-group interactions were found in the parameters marked with * above, indicating stress-induced increases. The peak response of salivary cortisone was significantly associated with those of STAI (rho=0.477, p=0.016) and heart rate (rho=0.699, p<0.0001) in the TSST group.

Conclusion:
Our study with a laboratory stressor identified salivary cortisone as a promising stress marker. Furthermore, our finding emphasizes the importance of optimal sampling time for specific laboratory parameters.

Poster 135

Efficacy and cost-effectiveness of two online interventions for children and adolescents at risk for depression (E.motion trial): a randomized controlled trial within the ProHEAD Consortium

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Depression is a serious mental health problem in children and adolescents. Online interventions are promising in overcoming the widespread undertreatment of depression and in improving the help-seeking behavior. The multi-centre, randomized-controlled E.motion trial is part of the German ProHEAD consortium (Promoting Help-seeking using E-technology for ADolescents). The trial aims to investigate the efficacy and cost-effectiveness of two online interventions to reduce depressive symptomatology in children and adolescents with subsyndromal symptoms of depression in comparison to an active control group. Participants will be randomized to a clinician-guided self-management program (iFightDepression®); a clinician-guided group chat intervention; or a psycho-educational website on depressive symptoms. In total, N = 363 children and adolescents aged ≥ 12 years with subsyndromal symptoms of depression will be recruited at five German study sites. Online questionnaires measuring depression symptomatology, help-seeking behavior, adherence to and satisfaction with the interventions, depression stigma, and utilization and cost of interventions will be administered before and after the intervention and at 6 months follow-up. This first RCT investigating efficacy and cost-effectiveness of online interventions in children and adolescents at risk for depression aims to provide a better understanding of the help-seeking behavior of children and adolescents and potential benefits of E-mental-health interventions for this age group. The study design of the trial and current recruitment status will be presented.

Poster 136

Implementierung psychosozialer Diagnostik in die Lehre

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Die psychosoziale Ersteinschätzung ist ein relevanter Aspekt bei der Diagnosebildung von Patienten mit Verdacht auf Craniomandibuläre Dysfunktion (CMD). Besonders Studierenden fällt es oft schwer, ihre Patienten hinsichtlich psychosozialer Aspekte zu beurteilen.
Im Rahmen des ersten klinischen Kurses der Zahnärztlichen Prothetik und Werkstoffkunde wurden 30 Patienten mit Verdacht auf CMD von 30 Studierenden untersucht. Dabei nutzten sie Fragebögen um Neigungenen zu Depressionen, Angst, Somatisierung und Chronifizierung von Schmerzen mithilfe eines Auswertungsbogens zu charakterisieren.
60% der Studierenden fiel es leicht die Fragebögen mit Hilfe des Auswertungsbogens zu nutzen, 23% gaben Schwierigkeiten damit an und 17% fiel die Anwendung schwer. 90% würden die psychosoziale Ersteinschätzung von CMD Patienten auch weiterhin mithilfe dieses Konzepts durchführen.
Die Anwendung der Fragebögen und des Auswertungsbogens erleichterten die Diagnostik und das Verständnis der CMD-Patienten in der klinischen Ausbildung erheblich. Das Konzept wird daher seit dem Wintersemester 2018/19 in beiden klinischen Kursen der Zahnärztlichen Prothetik und Werkstoffkunde angewendet.

Poster 137

Sensation seeking bei 3 bis 6jährigen Kindern: Zusammenhang zwischen soziodemographischen Parametern und Verhaltensauffälligkeiten

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Hintergrund:
In der Studie wurde den Fragen nachgegangen, ob das persönlichkeitspsychologische Konstrukt „Sensation seeking“ bei Kindern vom Alter, deren Geschlecht sowie dem sozioökonomischen Hintergrund abhängig ist, und ob Kinder, die eine hohe Punktzahl im „Sensation seeking“ erreichen, Verhaltensauffälligkeiten zeigen.

Methode:
Mittels Fragebogen wurden dazu 423 Eltern von Kindern im Alter von 3 bis 6 Jahren befragt. Zur Erfassung kamen die deutsche Übersetzung des Fragebogens „Sensation Seeking Scale for Young Children“ (SSSYC), ein Fragebogen zur Soziodemographie sowie ein Fragebogen zu den Stärken und Schwächen der Kinder (SDQ: Strengths and Difficulties Questionnaire) zum Einsatz. Multiple lineare Regressionsmodelle mittels SPSS 24 wurden verwendet, um Zusammenhänge zwischen Sensation seeking und Alter, Geschlecht, der familiären Herkunft sowie Verhaltensauffälligkeiten wie Hyperaktivität, Probleme mit Gleichaltrigen sowie emotionalen Auffälligkeiten herzustellen. Der SSSYC umfasst drei Unterkategorien: der Suche nach Neuem (Suche nach Erfahrungen die neu und abwechslungsreich sind), der Suche nach dem Nervenkitzel (Suche nach emotionaler Aufregung) und nach intensiven Verhaltensweisen (Suche nach physischem Abenteuer).

Resultate:
Sensation seeking war signifikant höher bei Jungen im Vergleich zu Mädchen. Es gab keine Zusammenhänge zum soziökonomischen Hintergrund der Kinder. Weiterhin war Sensation seeking positiv assoziiert mit Verhaltensauffälligkeiten bei Kindern, und negativ assoziiert mit emotionalen Schwierigkeiten und Problemen mit Gleichaltrigen.

Poster 138

Prediction errors by action intention occur independently from global tone regularity: ERP evidence

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We act efficiently in the environment because our brains constantly predict the forthcoming input by extracting regularity patterns from the incoming stimulation. We also learn that certain actions have specific sensory consequences – based on action intention, our brains predict the sensory events associated with specific actions.

Our aim was to see whether in the context of action-related predictions, the two represent independent sources and whether they interact leading to stronger predictions, when present together. The electroencephalogram (EEG) was recorded while participants generated high or low pitch tones which were presented with high or low probabilities, by performing "random" sequences of left and right button presses. Manipulating the action-tone association, as well as each action's probability, the tones were predictable based on either regularity (REG), intention (INT), or both (BOTH).

We found regularity effects on the N1b and Tb event-related potentials (ERP), while action intention evoked mismatch negativity (MMN) responses. Importantly, we show that action intention represents a reliable source regardless of global tone probability. It seems like the two represent distinct prediction sources, which do not necessarily interact when presented together in the context of self-generated tones (i.e. we did not observe stronger prediction errors in the BOTH condition). Moreover, the following deviance-processing step (involuntary attention switch) is evenly effective regardless of whether the sensory predictions were based on either REG, INT, or BOTH, as indicated by similar P3a effects across conditions.

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Erfahrungen und Einstellungen deutscher Studienanfänger bezüglich psychischer Krisen

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Einleitung:
Im Alter zwischen 18 und 24 Jahren manifestieren sich die meisten psychischen Erkrankungen erstmals. Studienanfänger stellen hierbei eine Subgruppe dar, der ein besonders hohes Maß an Anpassungsleistung abverlangt wird. Zudem liegen Zusammenhänge zwischen negativen Einstellungen zu psychischen Störungen und einem reduzierten Hilfesuchverhalten vor, was sich krankheits- und chronifizierungsbegünstigend auswirken kann.

Methode:
Im Rahmen einer Präventionsveranstaltung während der Einführungswochen zu Studienbeginn wurden 327 Studierende im ersten Semester ohne bisherige Studienerfahrung deutschlandweit u.a. hinsichtlich ihrer Erfahrungen mit psychischen Krisen sowie zu Stigmatisierung, stereotypen Vorstellungen und ihrem Wunsch nach sozialer Distanz befragt.

Ergebnisse/Diskussion:
Das Durchschnittsalter beträgt knapp 23 Jahre (M=21,51; SD=4,35), darunter 82,8% Frauen. Der Großteil der Befragten (75,5%) ist in einem sozialen Fächertyp eingeschrieben wie Soziale Arbeit.
Nahezu alle Befragten kennen jemanden, der psychisch krank ist/war oder haben bereits etwas über psychische Krisen gelesen. 65,2% geben an, eigene Erfahrungen mit psychischen Krisen gemacht zu haben; davon knapp ein Drittel häufig wiederkehrend. Der Wunsch nach sozialer Distanz zu psychisch Kranken ist sehr gering ausgeprägt. Etwa die Hälfte der Befragten nimmt die Gesellschaft stigmatisierend wahr. Stereotype Vorstellungen sind in der befragten Gruppe eher schwach ausgeprägt.
Deutsche Studienanfänger sind als Risikogruppe anzusehen. Hier bieten Antistigmaprogramme eine gute Möglichkeit präventiv anzusetzen.

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Verarbeitungsmuster psychosozialer Krisen von Jugendlichen: Ein biographieanalytischer Blick auf Verlaufsformen diskontinuierlicher schulischer Bildungswege

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In Deutschland verlassen jedes Jahr eine Vielzahl von Schülerinnen und Schüler die Sekundarstufe I des allgemeinbildenden Schulsystems ohne einen Abschluss, im Jahr 2017 waren dies 14% der 15- bis 25-jährigen. Soziale Teilhabechancen und berufliche Aufstiegsmöglichkeiten sind jedoch eng an den Erwerb von formaler Bildung gekoppelt und langfristig von besonderem Einfluss auf soziale Lebenslagen sowie die Lebensqualität und die psychische und körperliche Gesundheit der jungen Erwachsenen.

Die vorliegende Untersuchung befasst sich auf der Basis einer qualitativen, biografischen Methodik mit den Entstehungszusammenhängen und Verlaufsformen schulischer Abbrüche und Wiedereinstiege aus der Perspektive der Betroffenen. Im Fokus steht die Frage, welche subjektiven Verarbeitungsmuster Jugendliche in diesen Situationen aktivieren und wie adaptiv diese einzuschätzen sind. Ein wichtiges Ziel ist weiterhin die Ableitung von praktischen Implikationen, um gefährdete Jugendliche psychosozial adäquat zu unterstützen und schulisches Scheitern möglichst abzuwenden.

Poster 141

Traumatische Erfahrungen, Posttraumatischen Belastungsstörungen und das Auftreten kognitiver Beeinträchtigungen im Alter

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Traumatische Erfahrungen und Posttraumatische Belastungsstörungen (PTBS) sind mit verschiedenen langfristigen und komplexen psychischen und körperlichen Erkrankungen assoziiert. In den letzten Jahren weisen immer mehr Studien darauf hin, dass traumatischer Erfahrungen und daraus resultierende PTBS mit Inzidenz und Prävalenz dementieller Veränderungen assoziiert sind. Dies wurde bislang an Stichproben von Kriegveteranen und anderen Gruppen, in denen eine höhere Traumaprävalenz als in der Gesamtbevölkerung zu erwarten ist, nachgewiesen. Eine Prüfung in einer unselektierten Bevölkerungsstichprobe steht noch aus.

In der LIFE-Adult-Kohorte wurde ein unselektiertes Sample von insgesamt 10000 Leipziger_innen ausführlich befragt und untersucht, dabei wurden auch traumatische Erfahrungen und das Vorliegen einer PTBS erfasst, sowie Untersuchungen zu kognitiven Leistungseinbußen und dementiellen Erkrankungen durchgeführt. Auf dieser Basis wird nun an 4600 Personen ab 60 Jahren über die Lebensspanne hinweg der Zusammenhang von traumatischen Erfahrungen, PTBS und kognitiven Leistungseinbußen zum ersten mal an einer Bevölkerungsstichprobe untersucht werden. Dazu werden in Regressionsanalysen die Zusammenhänge unter Kontrolle anderer gemeinsamer Risikofaktoren, sowie von Alter und Geschlecht, untersucht.

Die Häufigkeit von traumatischen Erfahrungen, PTBS und kognitiven Veränderungen werden dargestellt und die Bedeutung traumatischer Erfahrungen und PTBS für kognitive Veränderungen analysiert. Die Ergebnisse sollen vor dem Hintergrund der komplexen und langfristigen gesundheitlichen Folgen traumatischer Erfahrungen diskutiert werden.

Poster 143

Das neue Unterrichtskonzept für die klinischen Seminare am Institut für Anatomie der Universität Leipzig

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Ziel dieser Lehrforschungsarbeit war es, den Mehrwert des neuen Konzepts für die Seminare mit klinischem Bezug im vierten Semester im Fach Anatomie im Vergleich zu dem der Vorjahre zu ermitteln. Zentrale Frage war, ob es noch besser als zuvor gelungen ist, eine Brücke zwischen dem vorklinischen und dem klinischen Teil der humanmedizinischen Ausbildung zu schlagen. Die neuen Erkenntnisse sollen dazu beitragen, klinische Bezüge in die anatomische Lehre curricular zu verankern.

Methode:
1. erfolgte die Erarbeitung des Konzepts und geeigneter Fragebögen. In den Seminarheften sind themenbezogene klinische Fälle integraler Bestandteil. Lernziele zu Beginn jedes Themas wurden formuliert. Die Veranstaltungen fanden neuerdings auf dem Präpariersaal statt, ergänzt durch Monitore für bildgebende Verfahren und histologische Bilder. Vorbereitend fand eine fakultative klinische Einführungsvorlesung zum jeweiligen Thema statt.
2. führten wir in Sommersemestern 2016 und 2017 eine papierbasierte Datenerhebung durch.
3. Zielgruppe (2016/2017) und Kontrollgruppe (2011/2013/2015) wurden mit geeigneter statistischer Verfahren miteinander verglichen.

Ergebnisse:
Qualitätskriterien wie Nutzen der klinischen Beispiele, Klarheit/ Gliederung des Lehrstoffes, praktische Arbeit und Lernziele wurden in der Zielgruppe besser bewertet. Insgesamt fiel die Benotung noch besser bei Studierenden aus, die bereits eine medizinische Ausbildung durchlaufen hatten.

Poster 144

Welchen Einfluss haben Missbrauchserfahrungen in der Kindheit auf die Capability for Suicide?

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Auch wenn verschiedene Studien einen Zusammenhang zwischen Kindesmissbrauch und Suizidalität im Lebensverlauf belegen konnten, sind zugrunde liegende Mechanismen noch weitgehend unklar. In einer früheren Untersuchung konnten wir zeigen, dass Kindesmissbrauch indirekt mit suizidalem Verhalten zusammenhängt und dass dieser Zusammenhang durch die Capability for Suicide (CS) mediiert wird. Dies wirft die Frage auf, wie und warum emotionaler Missbrauch, der nicht körperlich schmerzhaft ist, CS beeinflusst. Möglicherweise stellt Kindesmissbrauch einen Risikofaktor für die Entwicklung einer Störung der Emotionsregulation dar, welche wiederum mit selbstverletzendem Verhalten (SVV) einhergehen könnte. Ziel der Untersuchung ist es, die Zusammenhänge zwischen verschiedenen Arten des Kindesmissbrauchs mit CS zu untersuchen und inwiefern diese durch SVV mediiert werden. Die Stichprobe besteht aus 308 psychiatrischen Patienten (nach Suizidversuch oder mit akuter Suizidalität). Zur Überprüfung der Hypothesen wurden mit den Ergebnissen aus Fragebogendaten Mediationsmodelle gerechnet. Während emotionaler und sexueller Missbrauch SVV vorhersagen, konnte kein Zusammenhang zwischen körperlichem Missbrauch und SVV gefunden werden. Sowohl sexueller als auch emotionaler Missbrauch hängen indirekt über SVV mit der wahrgenommenen CS zusammen. Die Zusammenhänge zwischen emotionalem und sexuellem Missbrauch mit CS konnten auch in dieser Untersuchung repliziert werden. Weiterhin scheinen diese beiden Arten ein Risikofaktor für die Entstehung von SVV zu sein, wohingegen körperlicher Missbrauch weder mit SVV noch mit CS assoziiert war.

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Reziproke Zusammenhänge zwischen Mediengebrauch und Verhaltensauffälligkeiten im Vorschulalter

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Hintergrund:
Die Studie hat Assoziationen zwischen dem Gebrauch elektronischer Medien und Verhaltensauffälligkeiten im Vorschulalter untersucht. Zusätzlich wurden Zusammenhänge zwischen Mediengebrauch und Alter, Geschlecht und Sozialstatus betrachtet.

Methoden:
Die Studie wurde im Rahmen der LIFE Child-Studie realisiert. An der Studie haben 527 2- bis 6-jährige Vorschüler teilgenommen. Mediengebrauch und Verhaltensauffälligkeiten wurden anhand von Elternangaben zu zwei Zeitpunkten – Erstbesuch und Zweitbesuch (1 Jahr nach Erstbesuch) – erfasst. Multiple Regressionsmodelle wurden angewandt um längsschnittliche reziproke Zusammenhänge zwischen Mediengebrauch und Verhaltensauffälligkeiten zu untersuchen.

Ergebnisse:
Ältere Kinder und Kinder aus niedrigeren Sozialschichten zeigten einen höheren Gebrauch elektronischer Medien als jüngere Kinder bzw. Kinder aus höheren Sozialschichten. Der Gebrauch von Handys ist zwischen 2011 und 2017 zudem signifikant angestiegen. Der Gebrauch von Computern/Internet und Handys zum Erstbesuch ging mit einem Anstieg von externalisierendem Problemverhalten zum Zweitbesuch einher, unabhängig vom Sozialstatus und dem Problemverhalten zum Erstbesuch. Gleichzeitig wurde ein Zusammenhang zwischen sozialen Problemen zum Erstbesuch und einem ansteigenden Gebrauch von Computern und Handys zum Zweitbesuch beobachtet.

Schlussfolgerung:
Die Ergebnisse deuten darauf hin, dass sich Mediennutzung und Verhaltensauffälligkeiten bereits im Vorschulalter gegenseitig bedingen und aufschaukeln können.

Poster 146

Entwicklung eines Selbsthilfe-Manuals für Patienten mit Anpassungsstörungen

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Es besteht ein dringender Bedarf an ambulanten therapeutischen Angeboten für Personen, die an Anpassungsstörungen leiden. Ziel dieses Projektes war, einen Beitrag zur problematischen Versorgungssituation psychisch kranker Personen zu leisten. Es wurde ein tagebuchartiges Therapiemanual entwickelt, um Patienten, die unter Anpassungsstörungen leiden, zu strukturieren und zu unterstützen. Ihnen soll die Möglichkeit der Hilfe und der Selbsthilfe zuteilwerden.

In einer zehnwöchigen Intervention, die durch das TAPS (Therapieprogramm für Patienten mit Anpassungsstörungen) unterstützt wurde, lernten die Patienten, ihren Alltag zu strukturieren und zu erschließen. Es folgte die Analyse der Daten aus den Tagebüchern und diversen psychodiagnostischen Tests von Erhebungsbeginn und -ende sowie ein Fokus-Interview mit den Teilnehmern.

Im Allgemeinen zeigen die Ergebnisse eine subjektive Verbesserung der Symptome über einen Zeitraum von zehn Wochen, was durch geringe Verbesserungen in den quantitativen Tests unterstrichen wird. Leider konnte deren Signifikanz noch nicht durch statistische Nachweise belegt werden. Das Handbuch besitzt gute Qualitätskriterien und wurde von den Teilnehmern als verständlich beschrieben. Es wurde eine Überarbeitung und Änderung vorgenommen, um eine effektivere und individuell besser passende Variante des Handbuchs zu entwickeln.

Poster 147

Zwang zur Konfrontation – wie weit reicht die ärztliche Verpflichtung zu Gesprächen am Lebensende?

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Hintergrund:
Wenn Entscheidungen am Lebensende (EOLD) rechtzeitig thematisiert und Patientenwünsche vorausverfügt werden, profitieren die Patienten, ihre Angehörige und auch die behandelnden Ärzte. In der klinischen Realität finden solche Gespräche dennoch häufig nicht oder zu spät statt.

Ziele:
Empirische Untersuchung, ob Patienten Selbstbestimmung am Lebensende wünschen und wahrnehmen wollen. Normative Analyse, ob Ärzte verpflichtet sein können, mit ihren Patienten über EOLD zu sprechen und wie mit Patienten umgegangen werden soll, die nicht über das Thema sprechen wollen.

Methoden:
Statistische Auswertung der Antworten von 194 Krebspatienten zu Wünschen bezüglich Gesprächen über EOLD und medizinethische Analyse der Ergebnisse.

Ergebnis:
Selbstbestimmung wurde von 95,4% der Befragten als abstrakter Wert geschätzt. Patienten mit inkurabler Erkrankung waren signifkant häufiger bereit, Entscheidungen an Dritte abzugeben. Weniger als ein Drittel der Patienten hatten bisher mit einem Arzt über EOLD gesprochen. 22,1% wollten überhaupt nicht auf die Thematik angesprochen werden.

Diskussion:
Krebspatienten legen Wert auf Selbstbestimmung am Lebensende, nehmen diese häufig aber nicht wahr. Bei Patienten mit begrenzter Lebenserwartung sollten Ärzte das Thema nicht vermeiden, sondern Gespräche über EOLD anbieten. Ein scheinbarer Verzicht auf selbstbestimmte Entscheidungen sollte nicht voreilig vermutet werden. Eine paternalistische Intervention zur Ermöglichung von Autonomie kann legitim sein. Vertrauensangebote des Patienten sollten als solche erkannt und aufgegriffen und das Angebot zum Gespräch regelmäßig wiederholt werden.

Poster 148

Versorgung am Lebensende bewerten: Übersetzung und Inhaltsvalidierung der deutschen Version des ICECAP-SCM

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Im deutschsprachigen Raum mangelt es an Instrumenten zur Erfassung der gesundheitsbezogenen Lebensqualität am Lebensende oder für gesundheitsökonomische Analysen im pflegerischen und palliativen Bereich. Basierend auf dem Projekt „Versorgung am Lebensende bewerten: Übersetzung, Inhaltsvalidität und Berechnung eines präferenzbasierten Wertesets für den ICECAP-SCM-Fragebogen“ war das Ziel dieser Arbeit die Bestimmung der Inhaltsvalidität der übersetzten deutschen Version des ICECAP-SCM.

Anhand einer Expertenbefragung bestehend aus Senioren innerhalb der Allgemeinbevölkerung, im Pflege- oder Altenheim lebend, in palliativer Versorgung und Fachkräften der Palliativversorgung wurden strukturierte Befragungen durchgeführt. Zur Bestimmung der Inhaltsvalidität wurden spezifische Indizes berechnet.

Die Ergebnisse zeigten exzellente Werte für die Relevanz der ICECAP-SCM-Bereiche (I-CVI = 0,95-1; S-CVI/Ave = 0,96). Ebenso wurde die Klarheit der Formulierung als exzellent bewertet (I-CVI = 1; S-CVI/Ave = 1). Umfang und Struktur des Fragebogens wurden von den befragten Experten als angemessen für den Einsatz bei älteren Menschen am Lebensende beurteilt. Die Inhaltsvalidität der deutschen Version des ICECAP-SCM kann als gegeben angesehen werden kann.

Im Rahmen des Projekts wurde eine zuverlässige und valide deutsche Version des ICECAP-SCM vorgelegt, welche im Rahmen der klinischen und wirtschaftlichen Evaluierung der Versorgung am Lebensende bzw. Palliativversorgung eingesetzt werden kann. In zukünftigen Studien sollte das ICECAP-SCM auf der Basis größerer Stichproben einer weiteren Prüfung der psychometrischen Güte unterzogen werden.

Poster 149

Schnittrandkontrolle von Basalzellkarzinomen mittels ex-vivo konfokaler Laserscanmikroskopie

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Die konfokale ex-vivo Laserscanmikroskopie stellt eine innovative Methode dar, mit der Hautresektate innerhalb von Minuten feingeweblich untersucht werden können. Die Software neuerer Geräte erzeugt durch digitale Einfärbung der Fluoreszenz- und Reflexionssignale ein an die Hämatoxylin-Eosin-Färbung angelehntes Bild. Ziel der Studie war es, diese Technik hinsichtlich ihrer Eignung für die Diagnostik und Schnittrandkontrolle von Basalzellkarzinomen zu evaluieren.

Es wurden 122 Hauttumor-Resektate von Patienten untersucht und 101 Präparate mit Basalzellkarzinom identifiziert und eingeschlossen.

Für die Untersuchung wurden die zugeschnittenen Tumorresektate und die Schnittränder der mikrografisch kontrollierten Exzisionen 30 Sekunden in Acridinorangelösung gelegt (Kernfärbung) und 15 Sekunden in PBS-Puffer gewaschen. Im Anschluss wurden sie auf einen Objektträger aufgelegt und mit dem Mikroskop gescannt. Die Ergebnisse der am nächsten Tag erfolgten histopathologischen Untersuchung des Paraffinschnitts wurden erfasst und die Bilder verblindet durch einen Dermatohistopathologen befundet.

Die Tumorzellen des Basalzellkarzinoms sind im digital gefärbten Bild hervorragend zu erkennen. Probleme ergaben sich aus den großen generierten Datenmengen mit Überschreitung der Speicherkapazität des zum System gehörenden PCs.

Die konfokale ex-vivo Laserscanmikroskopie erlaubt eine schnelle und qualitativ hochwertige histopathologische Befundung von Basalzellkarzinomen. Die Qualität der Bilder ist hoch ohne dass ein Gewebeverlust entsteht. Perspektivisch kann dadurch die Schnellschnittdiagnostik an Kryostatschnitten ersetzt werden.

Poster 150

Alternative treatment of prostate cancer: new strategies using focused ultrasound

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Introduction:
Prostate cancer (PCa) is common in men and some subtypes exhibit high metastatic rate. Clinical treatment includes surgery, hormone therapy, radiotherapy and chemotherapy. Hormone therapy with testosterone (T) could reduce invasiveness of androgen dependent PCa. Besides the use of focused ultrasound (FUS) for PCa ablation, it's reported to enhance effects of other treatment modalities. The aim of this study is to characterize thermal and mechanical effects of FUS on PCa and hormone metabolism.

Methods:
Androgen independent (PC-3) and androgen dependent (LNCap) PCa cell lines were cultured in FUS penetrable 96 well plates (Greiner-Bio-One) for treatment with a 1.14 MHz single focused transducer. To investigate mechanical effects, cavitation dose was evaluated with terephthalic acid method (Sigma) and via hydrophone (Precision Acoustic). For analysis of T metabolism, cells were treated with T (Sigma) at different concentrations for 12 days. Cell viability (WST-1 assay, Roche) was evaluated afterwards.

Results:
Generation of free radicals (•OH) serves as marker of cavitation dose and depends on the FUS power and duration (3 W, 1 min: 150 AU; 10 W, 1 min: 1500 AU). Preliminary experiments of T metabolism lead in LNCap to a concentration dependent loss in cell viability to 34%, 25% and 23% for 1, 8 and 32 ng/ml, respectively. No effects on cell viability could be observed in PC-3.

Conclusion:
The first data suggest that increased acoustic power can enhance amount of cavitation, thus mechanical effects will be studied. In the future, cell sensitivity to T and metabolism combined with FUS treatment will be investigated.

Poster 151

Prognostic biomarkers for Prostate Cancer

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Background:

Prostate cancer is the most prevalent cancer disease among men. Patients often face unnecessary surgeries, because clinical and histopathological risk factors as well as biomarkers and their according classification models lack discrimination accuracy. Clinical behaviour of localized prostate cancer is highly variable. Some men will have aggressive cancer leading to death of disease but many others will have indolent cancers that are cured with initial therapy or may be safely observed. Hence, there is a high clinical need of biomarkers for early prognosis of prostate cancer. We hence strive for a better understanding of the molecular dysregulation in prostate cancer.

Methods:

Within the Fraunhofer RIBOLUTION consortium, we assessed tissue specimens of more than 200 prostate cancer patients with long term follow up data by custom expression microarrays and transcriptome-wide next-generation sequencing. We applied the Cox proportional hazards model and combined evidences from different types of samples by a meta-analysis. We used the fixed effect model to determine the overall prognostic effect for individual genes.

Results:

We developed a prognostic multi-gene expression score, which we confirmed in an independent cohort of representative sample size.

Poster 152

Ursprungskorrelationen des Cholangiozellulären Karzinoms

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Das Cholangiozelluläre Karzinom (CCC) ist ein seltener maligner Tumor der Gallenwege mit schlechter Prognose, da er häufig erst in fortgeschrittenem Stadium entdeckt wird. Ca. 60% der Fälle können nicht mit Risikofaktoren korreliert werden. Eine erhebliche Prognoseverbesserung könnte durch die genaue Bestimmung des CCC-Ursprungs erzielt werden.
Mithilfe der 3 D Slicer 4.8.1 Software können aus Leber-CTs und -MRTs dreidimensionale Organmodelle erstellt werden. Aus Datensätzen gesunder Patienten ermitteln wir anatomische Varianten der Leber und nutzen diese als Referenzdaten. Aus CT- und MRT-Datensätzen von CCC Patienten wird die Tumormasse digital rekonstruiert, entfernt und auf gesunde Lebern der jeweiligen anatomischen Variante registriert. Der so ermittelte Tumorursprung soll anschließend mit Anamnese-, Labor- und Pathologiedaten der erkrankten Patienten korreliert werden.
Bei den CCC erwarten wir anatomische Zusammenhänge in ihrem Ursprung, die uns über anschließende histologische Untersuchungen mechanistische Einblicke ermöglichen und als Marker in der CCC-Früherkennung genutzt werden können.
Ziel unserer Untersuchung ist es, verlässliche Marker für die schnellere Diagnose des CCC zu finden und darüber Risikofaktoren zu identifizieren, mit denen die Früherkennung und Prognose verbessert werden kann.

Poster 153

Central neurocytoma: case report with SNP array analyses and subtel FISH

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Introduction:

Central neurocytoma (CN) is a benign, WHO grade II tumor carrying a good prognosis. However, some CN occur as histological "atypical" variant, accompanied increasing proliferation and poor clinical outcome. As shown for other intracranial tumors molecular markers provide prognostic and predictive information. Therefore, detailed genetic knowledge could be helpful to elucidate causal genetic events for tumorigenesis in CN.

Methods:

Cytogenetic analyses from blood, tumor tissue and primary tumor cells of an intraventricular neurocytoma WHO grade II were performed by genome-wide high-density single nucleotide polymorphism array and subtelomere FISH.

Results:

We confirmed known chromosomal aberrations. Interestingly, we identified six previously undescribed chromosomal aberrations with mosaic gains of 1p36.33-p36.31, 2q37.1-q37.3, 6q27, 12p13.33-p13.31, 20q13.31-q13.33, and mosaic loss of 19p13.3-p12. Similar chromosomal imbalances are found in several intracranial tumor entities, including oligodendroglioma, neuroblastoma, and glioblastoma.

Conclusions:

Our data indicate a distinct molecular pathogenesis of CN compared to neuroblastoma and/ or oligodendroglioma and may provide additional evidence in the genetic characterization of CN resulting in atypical behavior. Genetic analysis of an extended cohort of CN is necessary to elucidate new candidate genes and chromosomal regions to define pathogenetic and prognostic factors for this rare tumor entity.

Poster 154

Metabolic Tumor Staging of Hepatocellular Carcinoma

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Hepatocellular carcinoma is the most frequent type of primary liver cancer, but therapeutic options are rare. The only existing systemic therapy is the tyrosine-kinase inhibitor Sorafenib, enabling in approximately 30% of the applications the decrease of proliferation and tumor cell growth by interference with Akt- and Erk-signalling. These pathways also control the energy metabolism in hepatocytes. In tumor cells the energy metabolism is changed using anaerobic glycolysis instead of oxidative phosphorylation (Warburg effect).

The aim of the study was to determine a metabolic fingerprint of hepatic tumor cells and primary human hepatocytes (PHH) to understand the mechanisms of energy metabolism and related signalling as a basis for the optimization of therapeutic strategies.

PHH and hepatoma cell lines (HepG2, Huh7) were used. All cells were cultivated cell-type specifically and samples were collected for analysis on transcriptome (qRT-PCR), proteome (Western Blot) and functional level (biochemic assays) for 15 targets of the hepatic energy metabolism.

The quantitative functional analysis showed a glucose production in PHH, while hepatoma cells consume glucose over cell culture period. The amount of ketone bodies, pyruvate and lipids were increased in PHH compared to HepG2 and Huh7. Most of the analyzed genes were overexpressed in cell lines in comparison to PHH, while differences between hepatoma cells were less pronounced. Western Blot experiments are work in progress.

In conclusion, the differentiation state of the cell types was determined and should allow a classification of the metabolic dedifferentiation state.

Poster 155

Keratinocyte-melanocyte interaction as a platform for drug screening und identification of prognostic parameters

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Malignant melanoma is the most aggressive form of human skin cancer and shows an increasing incidence. The transformation from a normal melanocyte to a melanoma cell is a stepwise process and the heterogeneous mechanisms of melanoma development and progression, especially in an early stage of tumor development, are poorly understood. We hypothesize that keratinocytes (KC) affect early melanoma development through direct interactions or via indirect mechanisms that are initiated downstream of mutations in keratin genes. The aim of this project is to characterize underlying mechanisms by which keratin gene mutations in KC affect cell-cell-contacts, adhesion, migration and invasiveness of melanocytes/melanoma cells.

Therefore, epidermis and tumor regions of human malignant melanoma samples were collected by laser capture microdissection. Keratinocyte DNA was used for exome sequencing in order to identify putative genetic variations in cytoskeletal proteins associated with melanoma development. Keratinocytes with candidate mutations were co-cultured with melanoma cells to analyse their influence on melanoma cell migration in high-throughput scratch assays. First experiments show a reduced migration of Bro and RPM-MC melanoma cells co-cultured with keratin-mutated KC compared to wild type KC.

Taken together, keratin and possibly other intermediate filament proteins exert an influence on cell-cell interactions between KC and melanoma cells and the migratory behaviour of melanoma cells. In further experiments, a drug library screen will be performed to identify putative drugs that may influence this process.

Poster 156

Tumor- und Gewebeklassifikation mittels hyperspektralem Imaging

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Das hyperspektrale Imaging (HSI) ist ein innovatives Bildgebungsverfahren. Durch die Anwendung einer speziellen HSI-Kamera, werden die Spektroskopie und die Bildgebung technisch kombiniert. Mit dieser Technik sollen Zellen in histologischen Präparaten erkannt und klassifiziert werden.

Mittels einer HSI-Kamera werden Spektren in den Bereichen des visuellen Lichts und nahen-infrarot Bereich an histologischen Präparaten aufgezeichnet (500-995nm). Für die hier gezeigte Machbarkeitsstudie wurden ein Kollektiv von gesundem ösophagealen Plattenepithel (n=22) und ösophagealen Adenokarzinomen (n=45) aufgenommen, die mittels Eosin und Hematoxilin angefärbt wurden.

In allen n=45 untersuchten Gewebeschnitten konnten Zellen eines ösophagealen Adenokarzinoms detektiert und mittels HSI-Kamera aufgezeichnet werden. Beim Vergleich des spektralen Verhaltens des Plattenepithels und der Adenokarzinomzellen konnten Unterschiede in der Absorption im Wellenlängenbereich von 500-700nm aufgezeigt werden. Die Intravarianz der untersuchten Präparate hinsichtlich der Eigenschaften von Plattenepithel und Adenokarzinomzellen war gering und wies eine geringe Streuung auf.

Areale mir unverhorntem Plattenepithel und Zellen eines ösophagealen Adenokarzinoms weisen spezifische spektrale Charakteristika auf. Diese Merkmale können dazu dienen mittels computerassistierte Algorithmen eine automatische Diskriminierung auf das Vorhandensein eines Adenokarzinoms in histologischen Präparaten zu genieren, um eine Entscheidungshilfe bei der histopathologischen Diagnose zu liefern.

Poster 157

SNP array analyses of colorectal cancer, liver and brain metastases

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Brain metastasis (BM) occurs as a late stage phenomenon of colorectal cancer (CRC) and is associated with an extremely poor prognosis. BM occurs primarily in late phase of CRC as a result of improved oncological therapy and therefore longer survival of the patients. Although the incidence of BM is low (0.6 to 3.2%) the implications for affected patients are severe and further research is necessary for a better understanding of biological mechanisms of metastasis and risk factors.

Therefore, in this study, analyses of four patients with colorectal cancer and metachronus liver and brain metastasis were performed using SNP array analyses.

Applying these SNP array analyses, we identified 189 chromosomal aberrations (66/189 chromosomal aberrations not previously described). Interestingly, we could reveal 5 copy neutral Loss of Heterozygosity (cn-LOH) regions at primary tumor, 4 cn-LOH regions at liver metastases and 23 cn-LOH regions at brain metastases, (25/32 cn-LOH not previously described). We were able to detect chromosomal aberrations in BM consisting of gains in chromosome 7, 20q and losses of 1p, 10 and 22 with highly concordance to chromosomal alterations in glioblastoma. Our results showed different genetic aberrations during tumor progression and metastasis of CRC. Interestingly, cn-LOH regions were identified predominantly in the samples of BM comparing to LM and CRC. Further analyses on an extend cohort are necessary to find more genetic information in comparison between primary tumor and metastasis.

Poster 158

A melanoma mutation panel for individualized treatment of melanoma short-term cultures

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Melanoma is the most aggressive and lethal form of skin cancer. Classical therapeutic options comprise surgery, chemotherapy and radiation. More recently, immunotherapy has been established targeting CTLA-4 and PD-1 molecules. However, response rates are low for single agent treatment and only slightly increase for combination treatment. In case of a specific mutational pattern targeted therapy directed against the RAS-RAF-MEK-ERK pathway may be used which reaches response rates of up to 80%. The prevalence of mutations in this pathway is ~50 % for BRAF mutations and ~ 30% for NRAS mutations. Relevant treatment responses are currently only observed for BRAF mutant patients. Moreover, the vast majority of patients show drug resistance after few months of treatment. But most patients have activating mutations in other drugable pathways. Therefore, an individualized combinatorial treatment approach might help to overcome many of the current treatment failures. The aim of this project is to find individual treatment combinations based on the individual mutational patterns. Therefore, a pre-clinical model is set up using melanoma short-term cultures and tumor microfragments. To select individual treatment combinations, a panel of 83 genes is sequenced by high-throughput sequencing. Afterwards, the biological effects of different drug combinations are tested to examine the optimal treatment strategy. The results of this project may in future lead to a more individualized treatment for metastatic melanoma patients.

Poster 159

Circular RNAs as potential biomarkers for Prostate Cancer Diagnosis

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Background:
Prostate cancer is the most prevalent cancer disease among men. However, patients often face unnecessary biopsies with frequent postoperative complications, because available biomarkers and diagnostic tools still lack high discrimination accuracy. More promising biomarker candidates are non-protein coding RNAs, since they are involved in the regulation of multiple cellular processes and their expression patterns are often specific to tissues or developmental stages. One special class of non-protein coding RNAs are circular RNAs, which are closed RNA loops formed by an inherent covalent 3' to 5' bond. This circularization makes them resistant to degradation by RNAse R and leads to half-lives twice as long as those of linear RNAs. We, hence, assess the potential of circular RNAs as diagnostic biomarkers for prostate cancer and assess their detection level in urinary sediments.

Methods:
In this work, we studied circular RNA splice sites in benign prostate hyperplasia (BPH) versus prostate cancer (PCa) by sequencing of total RNA from 8 BPH and 46 PCa fresh frozen prostate tissue samples. Circular splice sites were confirmed in 6 BPH vs. 5 PCa urinary sediment samples. We used segemehl for the detection of circular splice sites, DESeq2 for differential expression analysis and the R package pathfindR for pathway analysis.

Results:
We detected twice as many circular RNA splice sites upregulated in BPH than in PCa tissue specimens. For a subset of circular RNA splice sites regulated in tissue specimens, we could confirm expression in urinary sediments.

Poster 160

An in vitro study of focused ultrasound induced hyperthermia and radiation therapy combination treatment on glioblastoma and prostate cancer cells

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Introduction:

Focused ultrasound (FUS) is able to generate localized hyperthermia (HT, 40-46°C) to a target region non-invasively. HT has previously been reported to support radiation therapy (RT), but no HT technique is used in clinical routine. We hypothesize that FUS induced HT will sensitize cancer cells to RT.

Method:

Glioblastoma (T98G) and prostate cancer (PC-3) cells were cultured in ultrasound-penetrable 96-well plates (Greiner bio-one). A FUS in vitro system (IMSaT, Dundee) with a 1.14 MHz focused transducer at intensity of 214 W/cm^2 was applied to generate FUS-HT (45°C, 30 min). A motor system moved the plates and heated 3 wells in parallel, with real-time temperature monitoring by a thermal camera (Optris). Control HT (45°C, 30 min) was performed in a thermal cycler. RT was delivered as single dose of 10 Gy with X-Ray tube (DARPAC 150-MC) after FUS-HT or HT. Effects on cell viability (WST-1 assay, Roche) and apoptosis (Annexin V assay, Cayman chemical) were evaluated at different time points after therapy.

Results:

Cell viability was significantly decreased 72 h after both combination regimes (i) HT+RT (T98G: 27%; PC-3: 59%) (ii) FUS-HT+RT (T98G: 52%; PC-3: 45%) compared to RT alone (T98G: 64%; PC-3: 75%).Significant effect of increased time interval between HT and RT was not observed. Apoptotic and necrotic cells were observed in combination group 24h post treatment.

Conclusion

In vitro data suggest that combination of HT and RT had additional benefits compared to RT alone, independent of the used heating technique. Thus, FUS induced hyperthermia could be a potential method to induce radiosensitization in tumors.

Poster 161

In vitro studies on extracellular vesicles as delivery system for small therapeutic RNAs

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Extracellular vesicles (ECVs) represent a heterogeneous group of cell-derived membranous structures comprising exosomes and larger vesicles. After secretion, the exosomes can be taken up by neighboring or other specific target cells via endocytosis. Physiologically, exosomes are known to transport different macromolecules, like siRNAs, miRNAs, peptides or proteins between cells, and, since they present different receptors on their surface, to play an important role in intercellular signaling. In our project, we employ exosomes isolated from tumor cell culture for the delivery of small RNA molecules into tumor cells. RNAs include siRNAs for the induction of RNA interference (RNAi), miRNAs for miRNA replacement therapy, or antimiRs as efficient miRNA inhibitors. A purification protocol of exosomes from supernatants of different tumor cell lines was established. Using Nanoparticle Tracking Analysis and Dynamic Light Scattering as high resolution particle-by-particle technologies, particle sizes and particle surface charges were measured, as well as particle concentrations and aggregation events of exosomes. For siRNA loading into monodisperse ECV populations, chemical methods and electroporation were explored. In vitro delivery of siRNAs for gene knockdown or antimiRs for miRNA inhibition, each loaded into ECVs, reveals the efficient knockdown of siRNA or of antimiR target genes, as determined in luciferase reporter cell line assays or by RT-qPCR tumor-relevant gene expression level analysis. All in all, our data indicate the usability of ECVs as delivery system for otherwise hard-to-deliver drugs like small RNA molecules.

Poster 162

The long noncoding RNA STAiR18 - a keyplayer in glioblastoma cell invasion?

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With an average survival of about a year, glioblastoma is the most common and aggressive human cancer that arises within the brain. It is characterized by an uncontrolled proliferation and infiltration of glioblastoma cells into the adjacent healthy tissue, forming a tumor without clear margins. Given that the indefinable borders impede a complete surgical removal and the microenvironmental heterogenity causes resistance to radio- and chemotherapy, glioblastoma remains essentially untreatable. Thus, analyzing the molecular mechanism of glioblastoma cell invasion is crucial in order to optimize therapeutic approaches.

In a genome-wide transcriptome analysis performed in different human cell lines, we previously identified several yet unknown long non coding RNAs differentially regulated in oncologically and cell cycle relevant processes. Amongst these transcripts, STAiR18 - an ubiquitously expressed lincRNA- maps to two actively transcribed genomic loci originating from a recent duplication event specific for the human lineage. STAiR18 was found to be overexpressed in every tested tumor entity compared to the corresponding healthy tissue and therefore may serves as a general tumor marker. RNAi-mediated knockdown of STAiR18 in the glioblastoma cell line A172 led to an altered cell migration and invasion. Further, STAiR18 knockdown and subsequent genome-wide transcriptional analysis uncovered a pattern of differentially expressed genes involved in cytoskeleton regulation. Moreover STAiR18 seems to interact with the transcription factor FoxM1, which is overexpressed in malignant glioma and inversely correlated with prognosis.

Poster 164

Increased circulating cell-free DNA in insulin resistance

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Aims:
Obesity-induced cell-free DNA (cfDNA) release from adipocytes stimulates chronic adipose tissue inflammation via Toll-like receptor 9 (TLR9). Here, we tested the clinical relevance of circulating cfDNA in metabolic disease. Material and Methods: CfDNA from serum of 851 subjects from an observational cross-sectional study with detailed metabolic phenotyping was measured and tested for association with anthropometric parameters and traits related to obesity and type 2 diabetes. Results:CfDNA was increased in patients with impaired glucose metabolism as supported by correlations with fasting insulin, HOMA-B, HOMA-IR, Stumvoll index (all $p < 0.005$).

Conclusion:
Clinical correlations along with genetic analyses suggest that circulating cfDNA is related to insulin resistance and type 2 diabetes.

Poster 165

A unified covariate model for the LIFE Adult, LIFE Heart & Sorb cohort blood metabolites

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Circulating human blood metabolites are a prominent target for understanding a variety of traits and disease phenotypes and offer promising candidates in the search for biomarkers. Integration of metabolite data with other functional layers such as the genome or the transcriptome can further strengthen the knowledge on disease and regulatory pathways. However, sources of variation in the studied metabolite data can cause biased results when not accounted for in the model employed in the analysis. Adjusting for covariates in regression models is a widely applied practice. However, identification of covariates and assessment of their relevance is often done in a non-systematic way and/or is insufficiently documented.
We analysed data for 63 metabolites quantified via targeted high-throughput tandem mass spectrometry and 27 covariate candidates for 16,412 samples from the LIFE Adult, LIFE Heart and the Sorb study cohorts. Our primary goal was to identify relevant candidates for a joint covariate model for these metabolite by utilizing the maximum explained variance per covariate in a multivariable association model. By stepwise removal of covariates not explaining a minimum of variance in an iterative backwards elimination procedure, a set of variables relevant for at least one metabolite was selected and a respective confounder model defined. For instance, requiring at least 2.5% of metabolite variance, we found age, sex, BMI, hours fasted, diabetes status, hematocrit, platelet and leucocyte count as relevant modulators of metabolite levels. The model will be the basis for sound subsequent (multi-omics) analyses.

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Zivilisationserkrankungen
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Klinisches Imaging

Poster 166

Species richness and diversity of xylobiont beetles in the Leipzig floodplain forest

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Studying the processes determining species rarity, abundance and community assemblies is crucial to understand the evolutionary and ecological mechanisms shaping biodiversity. Forest canopies provide an ideal system to study these mechanisms, as they provide diverse habitats for many organisms, including arthropods in high abundance. Especially xylobiont beetles are excellent modelling organisms to study species richness and communities, as they are speciose, functionally highly diverse and well known.

One of the most frequently used measures of biodiversity is species richness. However, the actual number of species is difficult to obtain and may differ substantially from the number of observed species. For these cases, different types of estimators can make reliable and comparable estimates of species richness. We sampled the canopy fauna at the Leipzig Canopy Crane site by means of window traps in high spatial and temporal solution and estimated species richness of xylobiont beetles as a prerequisite to investigate the processes shaping their community assemblies.

Our results give an overview over the diversity of xylobiont beetles in the floodplain forest, and further provide the first opportunity to compare species richness between tree species and stratum for a central European floodplain forest. The estimated species richness is higher in lower strata of the forest and displays a temporal mid-domain effect.

We gratefully acknowledge the support of the German Centre for Integrative Biodiversity Research (iDiv) Halle-Jena-Leipzig funded by the German Research Foundation (FZT 118).

Poster 167

The Ubiquitin Proteasome System in Dilated and Ischemic Cardiomyopathy

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Aims:
Dilated (DCM) and ischemic cardiomyopathies (ICM) are associated with cardiac remodelling, where the ubiquitin proteasome system (UPS) holds a central role. We characterized the UPS in heart tissue of cardiomyopathy patients.

Methods and Results:
Myocardial tissue from ICM (n=23), DCM (n=28) and control (n=14) patients were used to quantify ubiquitinylated proteins, the E3 ubiquitin ligases muscle atrophy F-box (MAFbx) and muscle RING finger 1 (MuRF1) by Western blot. The proteasomal and enzyme activity of NADPH oxidase were determined fluorometrically. Proteasomal activity was comparable for the chymotrypsin- (p=0.71) and caspase-like activity (p=0.93) between the groups. The trypsin-like activity was decreased by trend in ICM (0.8±0.1µU/mg) compared to DCM (1.1±0.1µU/mg) and control (1.0±0.1µm/mg; p=0.06). Decreased ubiquitin expression in both cardiomyopathies (ICM vs. control: p <0.01; DCM vs. control: p<0.01) as well as less ubiquitin-positive deposits were detected in ICM-damaged tissue (ICM: 4.2%±0.6%, control: 6.3%±0.4%, p=0.02). No differences were observed for the ubiquitin-linkage specific K63 (p=0.71), expression of MuRF1 (p=0.62), NADPH oxidase activity (p=0.63) and AIF-positive cells (p=0.50). Statistical trends were detected for a reduced MAFbx expression (p=0.07) and multi-ubiquitination of proteins as well as for increased K48 ubiquitin-linkage in the DCM-group (p=0.07).

Conclusion:
Different expression of E3 ligases and UPS activation markers were observed in DCM- and ICM-damaged myocardial tissue, suggesting differential involvement of the UPS in the pathologies underlying DCM and ICM.

Poster 168

Lens - The system behind the LIFE Data Portal

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With the Lens system we provide a platform for researchers to discover datasets in medical studies. As Lens uses CDISC's ODM standard, studies can provide their clinical data and metadata for public or restricted access by importing well-known ODM XML files into their Lens system. After the import, the metadata is available in a data dictionary which allows full text search backed by Elastic Search. The data on the other hand is indexed in a database allowing millisecond fast case count queries over millions of datapoints. The case count queries help researchers to find cohorts for their scientific problems. A modern user interface allows researchers to browse the data dictionary and to specify queries in an intuitive manner. A set of feature toggles and other parameters allows studies to customize and brand the Lens system for their own needs. In LIFE we use Lens to provide the LIFE Data Portal. Another instance backs the Leipzig Health Atlas Data Portal. We provide a Helm chart to deploy Lens on Kubernetes cluster.

Poster 169

Identification of promising targets for tolerance induction following heart transplantation

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Introduction:

Tolerance-inducing cell subsets following heart transplantation(HTx) can be found among dendritic cells(DCs) and regulatory T cells(T_{regs}).At present, it is unknown which cell subsets change during tolerance induction and maintenance.Therefore, pre-HTx and long-term HTx(LT-HTx) patients were investigated for their immunological tolerance-inducing profile.

Methods:

Heparinized whole blood samples of n=20 patients with end-stage heart failure(pre-HTx) and n=20 LT-HTx patients without rejection episodes were analyzed for DC cell subsets expressing BDCA1, 2, 3, 4 and for the T_{reg} subsets expressing CD39, CD62L, CD120b and CD147.Percentages and mean fluorescence intensities(MFIs) of the cell subsets were documented.The cytokine profile of IL2,IL4,IL10,IFNg,IL17A,IL34 and IL35 was detected by multiplexing.

Results:

Single DC subsets showed changes between pre-HTx and LT-HTx patients: BDCA2$^+$ and 4$^+$ plasmacytoid DCs were increased (%BDCA-2+ p=0.029; %BDCA4+ p=0.017) in LT-HTx patients compared to pre-HTx patients.The percentage of total Tregs and the highly suppressive CD62L$^+$ subset was higher in pre-HTx patients compared to LT-HTx patients (%T_{regs} p=0.003, %CD62L$^+$ p=0.013).LT-HTx patients showed a more balanced cytokine level.The tolerance-mediating cytokine IL34 plasma level was higher in LT-HTx patients (36.9±25.8pg/ml) compared to pre-HTx patients (21.0±21.0pg/ml).

Conclusion:

BDCA-2$^+$ and -4$^+$ plasmacytoid DCs, CD62L$^+$ and CD39$^+$ T_{regs} and an increased IL34 plasma level seem to be the adjustment screws to obtain transplant tolerance and will serve as targets for the development of new tolerance-inducing strategies.

Poster 170

Preserved Mitochondrial Function After Elective Cardiac Arrest Induced by Cyclosporin Supplementation to a Cardioplegic Solution

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Introduction:
Mitochondrial permeability transition pore (mPTP) opening plays a crucial role in cell death during ischaemia-reperfusion injury (IRI). Cyclosporine A (CsA) inhibits mPTP opening. This study aimed to establish whether CsA treatment reduces IRI after elective cardiac arrest (ECA).

Methods:
Landrace pigs (50-60kg) were subjected to midline sternotomy and cardiopulmonary bypass at 34°C followed by 90min of cardiac arrest during which they were randomly allocated to receive either a single shot of standard cold HTK-Bretschneider solution (HTK; n=6) or HTK-Bretschneider plus 1.2mg/L CsA (HTK/CsA; n=6) followed by 30min of reperfusion. Myocardial biopsies were harvested at baseline, during ischemia and 45min following reperfusion. Cytometric, histochemical and mitochondrial respiration analyses were performed on each of these samples.

Results:
After Reperfusion dp/dt min was significantly increased in HTK/CsA compared to HTK (-1366±247 vs. -848±304; p=0.012). There was a slight decrease in cells with an intact mitochondrial membrane potential during ischemia and following reperfusion in HTK (from 17.6±5.2% to 14.4±3.8%) and HTK/CsA (from 25.0±18.5% to 16.0±7.0%) (p=0.552). Basal respiration was preserved in HTK/CsA-treated but not in HTK-treated hearts following reperfusion (8.2±1.3 vs. 3.8±1.4 pmol O2•S-1•mg-1 wW; p=0.045). There was no significant difference in IHC experiments.

Conclusions:
CsA as an adjunct to HTK preserves mitochondrial function and leads to a faster recovery of cardiac function after ECA. Further investigations are warranted to determine the viability of this treatment on the cellular level.

Poster 172

CoCu: a new short questionnaire to evaluate diet composition and culture of eating in children and adolescents

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Background & Aims:
The aim of this project was to develop and validate a short nutrition questionnaire (CoCu) for children and adolescents that assesses the composition of diet and the culture of eating. We investigated associations of what and how children eat with their age, gender, and social background.

Methods:
The „diet composition“ part contains 14 questions about the number of portions of different food products children eat per week or per day. The food products were based on food groups assessed in a Food Frequency Questionnaire (FFQ). The „culture of eating“ part asks five questions on how children eat (e.g., number of meals). The questionnaire was completed by 741 10-to 19-year-old children (self-report) and 863 parents of 2-to 9-year-old children (parent-report) in the framework of the LIFE Child study. In a subsample (n=212 for the parent-report and 188 for the self-report), retest reliability was assessed by correlating answers given at two consecutive study visits. In another subsample of the self-report (n=105), the validation of the questionnaire was assessed by comparing answers in CoCu with answers in a more detailed FFQ.

Results:
The analyses revealed significant positive correlations between responses given at two consecutive study visits as well as significant positive correlations between CoCu and FFQ. Furthermore, children‘s composition of diet as well as their eating culture differed significantly depending on child age, gender, and social background.

Conclusions:
CuCo presents a useful tool to assess children‘s and adolescents‘ diets in a time-efficient and economic way.

Poster 173

Risk factors and prognostic markers of arterial hypertension from childhood to adulthood

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Background:
Arterial hypertension (HT) is associated with obesity, metabolic (dyslipidemia, hyperinsulinemia) and vascular changes (endothelial dysfunction, atherosclerosis). However, there is uncertainty in regard to the development of HT and long-term consequences of associated risk factors among children and adolescents.

Methods:
We compared cross-sectional and longitudinal data from the „Leipzig Atherobesity Childhood Cohort“, comprising 332 ambulatory blood pressure monitoring recordings of normal-weight (BMI-SDS ≤ 1.28) and overweight (BMI-SDS > 1.28) individuals aged 6 - 25 years. Additionally, we assessed metabolic parameters, endothelial dysfunction (reactive hyperemia index, RHI) and subclinical vascular changes (intima media thickening, IMT).

Results:
9% of overweight children between 6 -8 years had systolic HT, increasing up to 58% in the group of 18 - 21 year-olds. During childhood, systolic blood pressure was independently associated with peak insulin levels after correction for BMI-SDS, sex, age and height, whereas no BMI-independent correlation was found for glucose and cholesterol levels, or IMT and RHI. Regarding the long-term outcome, HT and overweight during childhood revealed a significant association with HT in adulthood. Whereas 71% of children with HT remained hypertensive in adulthood, 24% of normotensive children had HT when grown up (OR 8.0). Also, 56% of overweight and 12.5% of normal-weight children had HT in adulthood (OR 26.2).

Conclusions:
HT and overweight during childhood are major risk factors for HT during early adulthood.

Poster 174

Left atrial appendage regional wall movement analysis using tissue velocity imaging

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Purpose:
Impaired function of the left atrium (LA) and/or left atrial appendage (LAA) cannot only be observed in patients with atrial fibrillation (AF) but also in patients with sinus rhythm (SR). The present study intends 1) to describe several risk factors which are associated with impaired LA-/LAA function 2) to describe a new approach for the evaluation of LAA function by regional LAA wall motion analysis using tissue velocity imaging (TVI).

Methods:
In 1164 patients the following echocardiographic parameters were assessed: left ventricular ejection fraction (LV-EF), LA volume index (LA-VI), LV end-diastolic filling pressure (E/E'), LAA flow (LAA-FV) and tissue velocities (LAA-TV). Regional LAA wall motion analysis was performed in the medial and lateral LAA region. LAA-TV medial > LAA-TV lateral was hypothesized to be highly suggestive for impaired LAA function.

Results:
At the time of TEE investigation, 781 patients had SR and 383 had AF. In patients with AF, LAA-TV medial > LAA-TV lateral could be measured in 88% (n=340/383) of the patients. In patients with SR, LAA-TV medial > lateral could be observed in 30% (n=227/781) of these patients. However, diagnosis of paroxysmal AF has been confirmed in half of SR patients with LAA-TV medial > lateral (n=108/227).
Further, patients with AF had significantly lower LV-EF, LA-EF, LAA-FV/-TV and higher LA-VI and E/E' than patients with SR.

Conclusion:
Regional LAA wall motion analysis seems to be a feasible new approach for the evaluation of LAA function. Impairment of LAA function may be considered, if LAA-TV medial > LAA-TV lateral is observed.

Poster 175

Ist der Zusammenhang zwischen Schlafdauer und Übergewicht/ Adipositas nur eine Frage des Sozialstatus?

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Hintergrund:
Viele Studien haben bereits einen Zusammenhang zwischen Übergewicht und Schlafdauer im Kindes- und Jugendalter gezeigt. Es ist ebenfalls bekannt, dass sowohl Übergewicht als auch Schlafdauer von Kindern vom Sozialstatus ihrer Familien abhängen. Unklar ist jedoch, inwieweit sich Zusammenhänge zwischen Übergewicht und Schlafdauer in Abhängigkeit vom Sozialstatus der Familien unterscheiden.

Methoden:
Daten von 1537 Teilnehmern (1 - 14 Jahre) der Leipziger LIFE Child-Studie wurden ausgewertet. Die Schlafdauer wurde mittels Fragebogen erfasst und der BMI wurde von geschultem Studienpersonal gemessen. Der soziale Status wurde durch einen Index angegeben, der Einkommen, Bildung und berufliche Stellung der Eltern berücksichtigt. Zusammenhänge zwischen Schlafdauer (abhängige Variable) und Übergewicht (unabhängige Variable) wurden mittels multipler linearer Regression geschätzt. Dabei wurde insbesondere die Interaktion zwischen sozialem Status (hoch vs. gering) und der Gewichtsgruppe (normal vs. übergewichtig) betrachtet.

Ergebnisse:
Übergewichtige Kinder schlafen kürzer als normalgewichtige Kinder. Die signifikante Interaktion zwischen Gewichtsgruppe und sozialem Status zeigte jedoch, dass dieser Zusammenhang nur in sozial schwächeren, nicht aber in sozial bessergestellten Familien zu beobachten war.

Diskussion:
Die Ergebnisse lassen vermuten, dass Kinder aus sozial schwächeren Familien bestimmten Einflussfaktoren ausgesetzt sind, die das gemeinsame Auftreten von Übergewicht und kurzer Schlafdauer begünstigen.

Poster 176

Karrier - A Kubernetes Docker Cloud Distribution for Medical Informatics

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With Karrier we build a turnkey Kubernetes distribution for running medical applications and scientific workloads. At the LIFE Research Center we run EDC applications, the LIFE Reseach Database and the LIFE Data Portal on top of Karrier. Additionally we host demontrators of the Leipzig Health Atlas and the Bridgehead of the German Biobank Alliance inside Karrier. Karrier runs on top of common enterprise virtual environments like VMWare vSphere. We provision Karrier with help of the infrastructure-as-code toolset HashiCorp Terraform and track changes to the clusters with the version control system Git. We reach fault tolerance and high availability within a datacenter by using multiple virtual machines for each component like the load-balancers, the control plane and the worker nodes. As security is very important in medical applications, we control the access to the clusters by system of short lived certificates which are signed by our secure enclave implemented by HashiCorp Vault. By using Karrier we were able to implement continous delivery pipelines for our own applications to support an agile software development process.

Poster 177

AgeWell.de - a pragmatic multicentric cluster-randomized controlled prevention trial against cognitive decline in older primary care patients

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Adipositas
Biomedizin / Translationale Regenerative
Biophysik und Bioanalytik
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Computergestützte Chirurgie
Immunologie und Infektiologie
Klinische Studien
Molekularbiologie
Molekulare Neurobiologie
Systemische Neurobiologie
Psychologie und Kognition
Klinische Onkologie / Palliativmedizin
Zivilisationserkrankungen
Molekulare Onkologie
Klinisches Imaging

Background:
In the absence of treatment options, identification of effective prevention strategies acts as a key element to counteract the dementia epidemic. Due to the complex nature of dementia, trials targeting multiple risk factors should be particularly effective. So far, only few such multi-component trials have been launched, but yielding promising results. In Germany, comparable studies are lacking. AgeWell.de will be conducted as the first multi-component prevention trial in Germany.

Methods:
Study design: multi-centric, cluster-randomized controlled multi-component prevention trial. Participants: 1,152 community-dwelling GP patients (60-77 years) with increased dementia risk, recruited at 5 study sites across Germany. GP practices will be randomized to intervention A (nutritional counseling, physical activity, cognitive training, optimization of medication, management of vascular risk factors, social activity; if necessary, interventions targeting grief and depression) or B (general health advice on the intervention components and GP treatment as usual). We hypothesize that over the 2-year follow-up period, intervention group A will benefit significantly from the intervention in terms of preserved cognitive function/delayed cognitive decline (primary outcome) and other secondary outcomes (e.g. quality of life, social activities, depressive symptomatology).

Discussion:
Compared to previous trials, AgeWell.de covers an even broader set of interventions suggested to be beneficial for the intended outcomes. The findings will add substantial knowledge on modifiable lifestyle factors to prevent/delay cognitive decline.

Poster 178

RNAi-mediated knockdown of neuropilin-1/-2 and GIPC1 in pancreatic carcinoma leads to tumor cell inhibition in vitro and in vivo.

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Pancreatic ductal adenocarcinoma (PDAC) is a more common cancer type and presents with a 5-year survival rate of less than 4%. The poor success rate of chemotherapy or surgery shows the necessity of novel treatment strategies like targeted therapies, specifically interfering with oncogenic pathways relevant e.g. in migration, invasion or proliferation. Neuropilin-1/-2 (NRP1, NRP2) are transmembrane glycoproteins with relevance in tumorigenesis and angiogenesis. Overexpression has been found in various tumor entities including PDAC and correlated with aggressive phenotype and therapy resistance. Important for neuropilin signaling is the adapter protein GIPC1 (GAIP interacting protein C-terminus/Synectin). Thus, we have focused on these three targets as potential new targets against PDAC.RNA interference (RNAi) is a powerful strategy for the specific knockdown of any selected target gene, mediated by small interfering RNAs (siRNAs). In this project, we have extensively analyzed the effects of RNAi-based transient GIPC1, NRP1 and NRP2 knockdown on the molecular and cellular level. In a broad panel of PDAC cell lines, we observed reduced cell viability, induction of apoptosis, decreased proliferation due to cell cycle inhibition, and ROS activation. In some cases, combined knockdown of two target genes in parallel led to enhanced tumor cell inhibition. Most importantly, treatment with nanoparticle-formulated siRNAs against these targets led to tumor growth inhibition in a xenograft mouse model, especially in the case of the NRP2.Our data suggest that GIPC1, NRP1 and NRP2 are new promising targets in pancreatic cancer therapy.

Poster 179

Carnosine increases the efficiency of treatment with temozolomide and x-irradiation of primary glioblastoma cell cultures

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Objective:
Glioblastoma (GBM) has a poor prognosis even under standard therapy, combining surgery, temozolomide (TMZ) and irradiation (Rx). It was demonstrated before that the dipeptide carnosine (Car) reduces viability of GBM cells in vitro. We investigated whether Car increases the response of primary GBM cells to standard therapy.

Materials and Methods:
Primary GBM cell cultures from 5 patients were incubated in medium with ot without compounds (Car and/or TMZ) and irradiated. 7 days after irradiation, viability of cells was determined by measuring ATP in cell lysates (ACL) and dehydrogenase activity in living cells (DHA).

Results:
Car reduced cell viability in all cell cultures, achieving a maximum effect at 30 mM (up to 55.6±6.5% (ACL) and 51.0±7.9% (DHA)). TMZ treatment was less effective in the 2 cell cultures with unmethylated MGMT promoter compared to the 3 others (maximum effect at 300 μM: 22.4±3.2% (ACL) and 40.2±6.2% (DHA)). The combination of Car with TMZ was more effective than treatment with Car or TMZ treatment alone in all cells. Radiation alone reduced cell viability and an additive effect of all Car concentrations at all radiation doses employed was observed. Finally, the combination of Car with TMZ and Rx revealed maximum reduction of viability (up tp 4.3±0.7% (ACL) and 20.0±2.7% (DHA); all p 0.05).

Conclusion:
Here we demonstrate that, in all cell cultures derived form glioblastoma, carnosine increases the efficiency of standard therapy composed of x-irradiation and temozolomide by a factor of ~1.54±0.90. Therefore, carnosine my be considered as an adjuvant to standard therapy.

Poster 180

Brown adipocytes impair chemosensitivity in non-small cell lung cancer cells in the context of cancer cachexia

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Background:
Lung cancer patients often experience cancer cachexia (CC) in the course of their progressive disease. CC is associated with reduced quality of life and shorter patient survival. Brown adipose tissue (BAT) and its derived adipokines may play a crucial role in the development of cancer cachexia and resistance to chemotherapy in lung cancer patients. We aimed to find out whether BAT-derived supernatants reduce chemosensitivity in non-small cell lung cancer (NSCLC) cells.

Methods:
Four NSCLC cell lines (H322, A549, PC9, H1650) were subjected to culture media derived from undifferentiated and differentiated BAT. NSCLC cells were treated with cisplatin, gefitinib or osimertinib for 72 hours, respectively. Proliferation via colorimetric MTT assay and apoptosis via flow cytometric annexin V FITC assay were investigated after chemotherapeutic treatment of each NSCLC cell line cultured with conditioned BAT-medium. BAT-derived supernatants were searched for potentially relevant adipokines via enzyme-linked immunosorbent assay.

Results:
All NSCLC cell lines cultured with BAT-derived media showed reduced chemotherapy efficacy as compared to control media. Strongest BAT-specific effects were found in A549 and PC9 cells treated with cisplatin or gefitinib. Conditioned BAT media protected A549 and H1650 cells from cisplatin-induced apoptosis. The BAT-derived adipokines irisin, betatrophin, and fibroblast growth factor 21 were released into the supernatants of BAT.

Conclusions:
BAT-derived supernatants reduce chemosensitivity in NSCLC cells. BAT might induce tumor progression potentially via specific adipokine signaling.

Poster 181

Peptide transporters PEPT2, PHT1 and PHT2 are overexpressed in glioblastoma and mediate the cellular uptake of carnosine.

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The naturally occurring dipeptide carnosine (β-alanyl-L-histidine) inhibits the growth of glioblastoma (GBM) cells. Here, we investigated the expression of proton-coupled oligopeptide transporters (POTs) in GBM and their contribution to the uptake of carnosine.

The expression of four POTs identified in humans (PEPT1, PEPT2, PHT1 and PHT2) was examined on the level of mRNA in primary GBM cell cultures, GBM cell lines, tumor tissue and healthy brain. High performance liquid chromatography coupled to mass spectrometry was used to verify the functional activity of the transporters by quantifying carnosine uptake in the presence of competitive inhibitors and after siRNA-mediated knockdown of potential transporters in LN405 cells.

In tumor tissue, the expression of PEPT2, PHT1 and PHT2 was significantly increased compared to healthy brain. Although PEPT2 expression decreased during cultivation to healthy brain levels, PHT1 and PHT2 were also significantly overexpressed in cultured GBM cells compared to normal brain. PEPT1 mRNA was not detected in any sample. Uptake of carnosine was significantly reduced in the presence of β-alanyl-L-alanine, competitive inhibitor of all POTs and in the presence of L-histidine, only substrate of PHT1 and PHT2. Furthermore, siRNA-mediated knockdown of PEPT2, PHT1 and PHT2 resulted in significantly decreased carnosine uptake.

Our results indicate that PEPT2, PHT1 and PHT2 contribute to the uptake of carnosine in GBM cells and may play a role in drug interactions and therapeutic efficacy. In general, overexpression of these transporters could be valuable for targeted tumor diagnostics and therapy.

Poster 182

D,L-methadone does not increase the anti-neoplastic effect of radio- and chemotherapy in glioblastoma cell culture

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Objective:
Standard therapy of Glioblastoma (GBM) consists of surgery and radio-chemotherapy using temozolomide (TMZ) resulting in median survival of only 14.6 months. Recently, the opioid D,L-methadone emerged as a potential drug for treatment of GBM. Despite the lack of further evidence, an increasing number of cancer patients request treatment with D,L-methadone. Here, we investigated whether D,L-methadone in combination with standard therapy may be beneficial for GBM treatment.

Methods:
Cultures of GBM cells and fibroblasts were treated with increasing concentrations of D,L-methadone in combination with either X-irradiation, TMZ or both. Cell viability was determined by measuring ATP concentrations (ACL) and dehydrogenase activity (DHA).

Results:
Concentrations of D,L-methadone up to 1 µM did not significantly reduce viability of GBM cells, but a concentration of 1 µM D,L-methadone reduced fibroblast viability significantly ($p < 0.05$) to 87.5% ± 6.1% (DHA) compared to the untreated control. At concentrations of 10 µM and 30 µM of the opioid – which are known to be toxic plasma concentrations in humans - GBM cell viability was significantly diminished to 82.4% ± 8.4%; $p<0.05$ and 53.4 ± 6.8 %; $p<0.005$ (DHA), respectively. No synergic effect was observed at any D,L-methadone concentration with any combination of treatment.

Conclusion:
D,L-methadone reduces glioblastoma cell viability in culture only at physiologically toxic concentrations. Moreover, no synergistic effect is observed. Therefore, recommending D,L-methadone for glioblastoma treatment does not seem plausible, according to our data.

Poster 183

Inhibition of tumor cell migration by subtoxic concentrations of bosutinib and dasatinib

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The prognosis of malignant tumors is to a great extent determined by the ability of cancer cells to form metastases. Interference with the biological processes regulating cellular motility could provide the basis for novel treatment options complementing the classic cytoreductive approaches. Src- and abl-dependent signaling pathways are critically involved in the regulation of cellular adhesion and motility. Thus, we postulated that the dual src and abl inhibitors bosutinib and dasatinib inhibit the promigratory phenotype of cancer cells. To test this hypothesis, we made use of a panel of human cancer cell lines and determined the antiproliferative effect of bosutinib and dasatinib via WST-1 assay and quantitation of apoptosis induction. Furthermore, we evaluated the impact of the inhibitors on cellular motility using in vitro wound healing assays, transwell migration assays, colony spread assays, and analyses of spheroid outgrowth. In most cell lines, bosutinib and led to a pronounced growth inhibition at concentrations > 1 µM. Dasatinib induced antiproliferative effects in most cases already at concentrations > 100 nM. More importantly, bosutinib and dasatinib severly decreased the migratory potential in most investigated cell lines, even in non-toxic concentrations. Of note, their was no clear association between the sensitivity of tumor cells against the antiproliferative and the antimigratory effects of the inhibitiors. These findings suggest that bosutinib and dasatinib have potential anti-migratory properties even at low concentrations and might be a useful complementation in treatment regimens of solid cancers.

Poster 184

Charakterisierung von Histon-Deacetylasen in ösophagealen Adenokarzinomzelllinien

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Das Adenokarzinom des Ösophagus zeigt im Verlauf der letzten Jahrzehnte insbesondere in der westlichen Welt eine steigende Inzidenz. Diese Tumorentität entsteht meist auf dem Boden eines Barrett-Ösophagus, einer durch eine gastroösophageale Refluxkrankheit verursachten Metaplasie. Durch multimodale Therapiekonzepte konnte in den letzten Jahren ein 5-Jahresüberleben von ca. 55% erreicht werden.

Histon-Deacetylasen (HDACs) können epigenetisch durch die Deacetylierung von Histonen in die Genexpression von Zellen eingreifen, sind jedoch in dieser Tumorentität noch wenig erforscht.

Für die Untersuchungen der Einflüsse von HDACs und HDAC-Inhibitoren wurden zwei verschiedene Zelllinien ausgewählt, die Adenokarzinomzelllinie OE19 sowie ein Cisplatin-resistenter Subklon (OE19FB).

Mittels Proliferationsassay wurde das Ansprechen der beiden Zelllinien auf das Chemotherapeutikum Cisplatin vergleichend getestet. Diese Behandlung zeigt eine deutlich stärkere Hemmung der Proliferation bei der Zelllinie OE19 (OE19 IC_{50} von 22,8µM, OE19FB IC_{50} von 60,7µM).

Um den Effekt von HDAC-Inhibitoren auf die Expression von Genen mit Einfluss auf die Zellzykluskontrolle zu untersuchen, erfolgte eine Analyse der Expression der Marker p21, p53, MDM2 und DNMT1 unter Behandlung mit den Inhibitoren Vorinostat und DDK137. Insbesondere eine Behandlung mit DDK137 führt zu einer deutlich erhöhten mRNA-Expression von p21, während sowohl Vorinostat als auch DDK137 in einer Herunterregulation von p53, MDM2 und DNMT1 resultieren.

Weiterhin ist zu klären, ob die Wirkung der HDAC-Inhibitoren die Chemosensitivität der Zellen gegenüber Zytostatika erhöht.

Poster 185

CXCL11 promotes tumor progression by the biased use of the chemokine receptors CXCR3 and CXCR7

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The chemokine, CXCL11, is highly expressed in different solid tumors and controls tumor growth, metastasis, and lymphocyte infiltration. Although of potential clinical interest, it is presently unknown whether these tumor-promoting activities involve the CXCL11 receptors, CXCR3 and/or CXCR7. This issue is further intrigued by the fact that CXCR3 exists in the two functionally divergent splice variants, CXCR3A and CXCR3B, which exert pro- and anti-tumorigenic influences, respectively.

To unravel the role of the various CXCL11 receptors in tumor progression, we have now defined their role in CXCL11-induced chemotaxis of the tumor cell lines, A549, C33A, DLD-1, MDA-231, and PC-3.

CXCL11-induced cell migration was either sensitive to the CXCR3 antagonist, AMG487 (DLD-1), the CXCR7 antagonist, CCX771 (C33A and PC-3), or both (A549, MDA-231). Moreover, in C33A and PC-3 cells, but not in the other tumor cells, pharmacological activation and inhibition of CXCR3B prevented and potentiated CXCL11-induced cell migration, respectively. Both immunocytochemistry and Western blot analysis finally revealed that the observed cell type specific organization of CXCL11 system is not the result of differences in expression levels or subcellular location of CXCL11 receptors. Our findings imply that therapeutic use of CXCR3 antagonists in cancer patients requires exact knowledge of the organization of the CXCR3 system in the respective tumor.

Poster 186

Selective degradation of polo-like kinase 1 by a hydrophobically tagged inhibitor of the polo-box domain

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Protein-protein interactions are crucial regulatory events in both physiological and pathological processes within the cell. In that regard, the direct control of a misregulated protein of interest with a small molecule is a promising but challenging approach in drug discovery. The selective degradation of a target protein via the proteasomal pathway can be utilized by hydrophobic tagging (HT) of bioactive compounds, which mimics a partially denatured state of the protein. In this study, we present the first application of hydrophobic tagging to an existing small-molecule inhibitor of a protein-protein interaction. We developed Poloxin-2HT by fusing an adamantyl tag to Poloxin-2, an inhibitor of the polo-box domain (PBD) of the protein kinase Plk1, which is a key regulator of mitosis and thus a promising target for tumor therapy. Compared to the untagged PBD inhibitor Poloxin-2, Poloxin-2HT selectively reduced the protein levels of Plk1 over Plk2 and Plk3 in HeLa cells and had a significantly stronger effect on cell viability and the induction of apoptosis. Moreover, the change in cellular phenotype validates that Poloxin-2HT targets Plk1 in living cells. Our work demonstrate hydrophobic tagging of selective inhibitors of protein-protein interactions as a novel strategy to target and selectively degrade disease-relevant proteins.

Poster 187

The influence of autophagy modulators and carnosine on apoptosis in glioblastoma

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There is mounting evidence that apoptosis and autophagy are complexly connected and share common mediators. Here we investigate, whether treatment of glioblastoma (GBM) cells with carnosine, which inhibits GBM growth, in combination with inhibitors or inducers of autophagy (AP) results in enhanced apoptosis.

Cells from two GBM lines and six different patient derived GBM cell cultures were exposed (24 h and 48 h) to bafilomycin A1 (BafA1; inhibitor of AP; 100 nM), rapamycin (Rap; inducer of AP; 100 nM), carnosine (50 mM) or one autophagy modulator combined with Car. Apoptosis was monitored by determining Caspase 3 and Caspase 7 (Csp3/7) activities.

Csp3/7 activities were induced in T98G cells after 24 hours incubation in carnosine. Inhibition of autophagy in T98G cells via BafA1 resulted in increased activity of Csp3/7 after 24 hours of incubation which was further increased after 48 hours. Combining BafA1 and carnosine synergistically increased Csp3/7 activities in T98G.

The effect of both compounds was observed to have a similar tendency in six individually examined patient derived GBM cell cultures, but not in U87 cells.

In both cell lines and in primary cultures Rap reduced activation of Csp 3/7.

In summary, the present study investigated the innovative approach of therapeutically application of AP modulators with other anti-neoplastic drugs in GBM therapy.

AP inhibition by BafA1 led to the activation of Csp3/7 which was synergistically potentiated by carnosine. Consequently, activity of Csp3/7 was impaired by the activator of AP Rap without additive effect.

Poster 188

Transcriptional expression of the proliferation marker Ki-67

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Ki-67, the protein encoded by the human gene MKI67, is the most frequently used proliferation marker in pathology for cancer diagnostics. Although Ki-67 has been widely employed as a diagnostic tool for more than two decades, the cellular function and the regulation of the gene expression remained largely unknown. Only recently, it was discovered that Ki-67 serves as a chromosome separator during mitosis and an organizer of heterochromatin. Ki-67 protein levels vary throughout the cell cycle with an expression maximum in G_2 phase. In G_0 Ki-67 is not expressed. Our experiments demonstrate that MKI67 mRNA levels also fluctuate in a cell cycle-dependent manner preceding expression of the protein. This observation suggests that Ki-67 expression is controlled on the transcriptional level. Indeed, we show that MKI67 expression is mainly regulated via two CHR transcriptional elements together with a CDE promoter site. Remarkably, all three sites are involved in transcriptional repression as well as activation of MKI67 through binding of the DREAM and MMB transcription factor complexes, respectively. This promoter structure represents a novel type of MuvB target genes. Therefore, we identify the mechanism of MKI67 cell cycle-dependent transcriptional regulation and explain the long observed expression pattern of the Ki-67 proliferation marker.

Poster 189

Predicting corticobasal syndrome and alien/anarchic limb syndrome from magnetic resonance imaging

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Alien limb phenomenon is a rare syndrome associated with a feeling of non-belonging and disowning toward one's limb. In contrast, anarchic limb phenomenon leads to involuntary but goal-directed movements. Alien and anarchic limb phenomena are frequently observed in corticobasal syndrome (CBS), an atypical parkinsonian syndrome characterized by rigidity, akinesia, dystonia, cortical sensory deficit, and apraxia.

The structure-function relationship of alien/anarchic limb was investigated in multi-centric structural MRI data. Whole-group and single-subject comparisons were made in 25 CBS and eight CBS-alien/anarchic limb patients vs. healthy controls. Support vector machine classification was used to see if CBS with and without alien/anarchic limb could be distinguished by structural MRI patterns.

Whole-group comparison of CBS and healthy controls revealed asymmetric frontotemporal atrophy. CBS with alien/anarchic limb syndrome vs. healthy controls showed frontoparietal atrophy adjacent to the supplementary motor area and cingulate cortex contralateral to the side of the affected limb. Classification of patients with CBS yielded accuracies of 79%. CBS-alien/anarchic limb syndrome was differentiated from patients with CBS with an accuracy of 81%. Predictive differences were found in the cingulate gyrus spreading to frontomedian cortex, postcentral gyrus, and temporoparietoocipital regions.

This study presents the first MRI-based group analysis on alien/anarchic limb syndrome in CBS. Results pave the way for individual clinical syndrome prediction and allow understanding the underlying neurocognitive architecture.

Poster 190

Brain functional networks remodeling in corticobasal syndrome – a multimodal MRI study

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The clinical diagnosis of corticobasal syndrome (CBS) is a challenge for physicians. The implementation of in vivo imaging markers could improve the diagnostic accuracy. We aimed to investigate the neural correlates of CBS using T1-weighted and resting-state functional MRI and to test their diagnostic value in single-subjects. Nineteen CBS patients (age 67.0±6.0 years; mean±SD) and 19 healthy controls (age 66.5±6.0) were recruited from the German FTLD Consortium. Changes in brain functional connectivity and structure were assessed, respectively, with eigenvector centrality mapping plus seed-based analysis, and voxel-based morphometry. Additionally, support vector machine classification was used to test the diagnostic potential of MRI markers. A decrease in brain interconnectedness was observed in the right central operculum, middle temporal gyrus and posterior insula, while increases were detected in frontal areas, namely in medial superior-frontal gyrus, anterior cingulum and in caudate nuclei. Pervasive gray matter density reductions were found in CBS patients compared to controls, particularly affecting the bilateral insula, putamen, and thalamus. The support vector machine classification showed that both connectivity and structural data significantly distinguished CBS and controls, respectively with an accuracy of 76% and 79%. The combination of MRI-markers via multiple kernel learning lead to an accuracy of 84%. Our results support the use of multimodal MRI markers to assist the clinical diagnosis of CBS – a further step towards the implementation of MRI-based diagnostics in clinical practice.

Poster 191

Extended Standardized Echocardiography in Pre-Participation Screening of Athletes

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Echocardiography is an important part of the investigation of competitive athletes being required by some of the sports federations. Therefore, a standardized protocol for consistent exclusion and monitoring of cardiac abnormalities is necessary. As competitive athletes should have a normal cardiac morphology and function, following issues were evaluated. Firstly, we introduce an extended standardized transthoracic investigation. Secondly, we describe unusual findings inside our cohort and following consequences. Examinations following to the presented proposal have been performed since 2017. It contains the proposed transthoracic investigation in adults according to European recommendations, as well as additional sports-specific documentations. Successful image acquisition and parameters which are crucial for the diagnosis of relevant diseases were analyzed retrospectively. So far, 54 male athletes have been analyzed. In three patients suspect results with referring to potential sudden cardiac death causes were found. Bicuspid aortic valve was found in two athletes, one of them with additional indicators for hypertrophic cardiomyopathy. One athlete presented regional deformation abnormalities due to myocarditis. These findings immediately implicated medical therapy and frequent control investigations. Echocardiographic investigation requires a high level of accuracy, especially in sports-medicine. Therefore, the standardized examination should be extended with respect to image acquisition as well as additional analyses by post processing to ensure comparable quality of data inside various sport-medical facilities.

Poster 193

Monitoring of ventilation delay with Electrical Impedance Tomography

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Unilateral diaphragmatic paresis can have different causes and leads to a severe reduction of respiratory functions. It often occurs because of diseases or nerve damage, but is sometimes also found in patients who underwent a recent shoulder surgery. For postoperative analgesia, an Interscalene Brachial Plexus Block (ISB) effectively reduces pain. ISB can, however, also affect the phrenic nerves and thus impair diaphragmatic function for hours after surgery. Recognizing and correctly diagnosing the resulting dyspnea can be challenging, especially in the presence of chronic lung diseases such as COPD.

A novel method is the visualization of pulmonary ventilation through Electrical Impedance Tomography (EIT). It enables the real-time monitoring of the lung's impedance change, which are closely correlated with pulmonary ventilation. Yet, subtle ventilation differences are difficult to detect using the pure image data or the collected left-to-right-impedance distribution. That's why others proposed to analyze temporal impedance (ventilation) changes in different image regions using a Regional Ventilation Delay (RVD) map. Unfortunately a slow inflation maneuver is required for RVD analysis, restricting its use. We propose a similar approach without the need of a special ventilation maneuver, where parameter extraction is done by identifying times of complete inspiration and expiration. Additionally, the method has the potential for detection and monitoring of other complications of mechanical ventilation such as pneumothoraces, pendelluft or breath stacking.

Poster 194

Detektion von Wurzelkaries mittels quantitativer lichtinduzierter Fluoreszenz (QLF)

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Aufgrund der hohen Prävalenz der Wurzelkaries gewinnt deren Diagnostik zunehmend an Bedeutung. Bisher hat sich neben der klinischen Beurteilung keine Detektionsmethode für Wurzelkaries etabliert. Ziel der Studie war es, die Methode der quantitativen lichtinduzierten Fluoreszenz (QLF) zur Detektion von Demineralisationszuständen der Wurzeloberfläche zu evaluieren.

In die Untersuchung wurden 12 Probanden mit 46 freiliegenden Wurzeloberflächen einbezogen. Zunächst erfolgte eine klinische Bewertung mit Hilfe der ICDAS-Klassifikation und anschließend QLF-Aufnahmen mit der QRayCam durch drei kalibrierte Untersucher. Dieses Procedere wurde nach 14 Tagen wiederholt. Nachfolgend wurden die QLF-Aufnahmen randomisiert und dreifach durch die kalibrierten Untersucher hinsichtlich der Demineralisation (ΔF) und des Läsionsvolumens (ΔQ) analysiert. Die Korrelation zwischen klinischer Bewertung und QLF-Analyse wurde mit dem Rangkorrelationskoeffizienten nach Spearman-Rho (r) ermittelt, die intra- und interindividuelle Reliabilität durch den Intraklassenkorrelationskoeffizienten (ICC).

Mit der QLF lässt sich über ΔF eine metrische Quantifizierung von unterschiedlichen Demineralisationszuständen auf Wurzeloberflächen ermitteln ($p < 0{,}01$).

Die QLF ermöglicht die Detektion und Differenzierung von Wurzelkariesläsionen und kann ergänzend zur klinischen Bewertung für prospektive Verlaufskontrollen von Demineralisationszuständen freiliegender Wurzeloberflächen empfohlen werden.

Poster 195

Quantitiative Perfusionsmessung von Lebergefäßen: Bewertung einer softwarebasierten Perfusionsanalyse im Vergleich zum etablierten Spektraldopplerverfahren.

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Einleitung:
Chronische Lebererkrankungen führen zu einer Veränderung der Leberdurchblutung. Die Duplex-Sonographie ist das Standardverfahren zur Beurteilung der Leberperfusion (LP). Die zusätzliche Verwendung des Spektraldopplers (SD) ermöglicht eine Perfusionsmessung (PM) basierend auf der mittleren Flussgeschwindigkeit. Ein neues softwarebasiertes Analyseverfahren erlaubt eine pixelgenaue Perfusionsanalyse (pPA).

Ziel:
Vergleich der pPA mit dem etablierten SD.

Methodik:
Die Pfortaderperfusion gesunder Probanden und von Patienten mit chron. Lebererkrankung wurde mittels SD (Toshiba Aplio500) standardisiert präprandial untersucht. Unmittelbar im Anschluss erfolgte die pPA (PixelFlux, Chameleon-Software). Bei den Probanden erfolgte eine weitere PM nach definierter Nahrungsaufnahme, die regelhaft zu einer Zunahme der LP führt.

Ergebnis:
20 Probanden (23 Jahre, BMI 21,5 kg/m^2) und je 10 Patienten mit NAFLD (58 Jahre; 30,3 kg/m2) und Leberzirrhose (67 Jahre; 26,5 kg/m^2) wurden untersucht. Die PM beider Verfahren korrelierten stark ($r=0.515$, $p<0,001$, $n=40$) und wiesen keinen Unterschied in der Quantifizierung des Flussvolumens im Portalvenenstamm auf (Abb. A/B). Beide Verfahren zeigten einen Anstieg der postprandialen LP (Medianer Blutfluss prä/post [cm^3/min]: SD 718/1708 ($p<0,001$); pPA 834/1783 ($p<0,001$)).

Schlussfolgerung:
Die pPA korreliert gut mit dem Referenzverfahren SD und ist geeignet Änderungen der LP zu quantifizieren. Durch die pixelgenaue Erfassung der laminaren Blutströmungen könnte mittels pPA eine exaktere Messung des Flussvolumens gelingen. Hierzu sind weiterführende Studien mit invasiven Goldstandard notwendig.

Poster 196

Characterization of high and low gradient severe aortic stenosis in relation to secondary echocardiographic parameters

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Purpose:
echocardiographic parameters, e.g. mean pressure gradient (mPG) and aortic valve opening area (AVA), can be incongruent in patients with severe AS. The aim of the present study was to characterize additional parameters, e.g. left ventricular hypertrophy (LVH), LV end-diastolic pressure (LVEDP) and systolic pulmonary artery pressure (sPAP) in patients with severe AS.

Methods and Results:
373 patients (mean age 78±10 years; 49.8% male) with severe AS (AVA < 1cm²; peak flow velocity of the aortic valve > 4 m/s) were divided into two groups by their mPG (low gradient (LG): mPG < 40mmHg (n=279); high gradient (HG): mPG ≥ 40mmHg (n=94)).In addition, patients were divided by indexed stroke volume (SVi) into low flow (LF) AS: SVi < 35 ml/m² (n=184) and normal flow (NF) AS: SVi ≥ 35 ml/m² (n=189). LVH > 13mm, E/E' > 13 and sPAP > 30 mmHg were considered as pathological. LVH was documented in 47.7% of LG-AS and in 86.2% of HG-AS patients. Increased E/E' was found in 75.3% and in 73.4% of LG- and HG-AS. Elevated sPAP was observed in 76.7% of LG-AS and 88.3% of HG-AS. 53.2 % of HG-AS patients showed pathological measurements for all three additional parameters compared to 31.6% of LG-AS patients. Normal values for all three additional parameters were only found in 3% of LG-AS and 2% of HG-AS patients.

Conclusions:
Patients with HG-AS more often exhibit LVH and an increased sPAP. 97% of patients with severe AS exhibit at least one of the additional parameters (LVH, E/E' or sPAP) in pathological ranges. This analysis sets the stage for follow-up studies to determine the prognostic importance of these echocardiographic parameters.

Poster 197

Treatment of functional mitral regurgitation by the Carillon® Mitral Contour Device – an echocardiographic analysis of acute effects

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Purpose:
Functional mitral regurgitations (FMR) are associated with increased morbidity/mortality in heart failure patients. Older age and comorbidities are most striking characteristics of patients who were denied surgical treatment.

Methods:
Transthoracic echocardiography (TTE) was performed in 30 patients (age 76±9 years, 8 males) with moderate or severe FMR before and at discharge after implantation of the Carillon® device. The following parameters were assessed: mitral valve diameter ($Diam_{MV}$), tenting area, vena contracta, velocity-time-integral ratio, regurgitant fraction (RF), regurgitant volume (RV) by 2D-PISA and by volumetric approach and effective regurgitant orifice area (EROA).

Results:
Mean RF was reduced from 49±11% to 34±13% ($p<0.001$), mean RV from 33±13ml to 25±12ml ($p<0.001$) and mean EROA from 0.24±0.1cm^2 to 0.19±0.1cm^2 ($p<0.05$). No significant differences were obtained for both approaches of RF and RV assessment. Significant decreases were also noted for mean values of tenting area, vena contracta and VTI ratios. Mean $Diam_{MV}$ was reduced from 3.8±0.5cm to 3.5±0.5cm ($p<0.001$).
In detail, a significant RF reduction was achieved in 25 (83%) FMR patients. In patients with sinus rhythm (SR) (n=16) higher RF reduction (20±12%) was observed than in patients with atrial fibrillation (n=14) (10±12%).

Conclusion:
Acute effects of the Carillon® device on mitral valve morphology and function can be documented by TTE. TTE enables a quantitative approach of analyzing the interventional success obtained by the Carillon® device in patients with FMR. The therapeutical benefit seems to be higher in SR patients.

Poster 198

Simulation study on Electrical Impedance Lung Imaging with partial access to the thorax

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In prehospital emergency scenarios such as car crashes with trapped patients, the emergency physician needs to check the patient's vital state before taking further actions. Lacking alternatives that can be applied outside the hospital, physicians use auscultation for the examination of lung function. However, when executed in a noisy environment, this method is often not sufficient enough to allow for a proper analysis of respiratory functions.

An alternative non-invasive monitoring of lung function is achievable by employing Electrical Impedance Tomography (EIT). The current focus of the method's application is on lung monitoring in the intensive care unit as support and observation of mechanical ventilation.

In this simulation study, the potential use of EIT in prehospital emergency scenarios is examined. Existing EIT devices require a full enclosure of the thorax by the electrodes for the imaging process. However, in emergency scenarios this full enclosure may not be possible for trapped or injured patients.

Therefore, the imaging device must be able to handle a reduced number of electrodes, placed on only a part of the patient's thorax. To simulate this in a set of real animal EIT data, parts of the measured voltages are deleted. The modified data sets are then reconstructed and compared to the original image, reconstructed with the full data. The first results of this study show a reduction in the image quality and problems in the interpretability of the images even for a small number of reduced electrodes. In future work, different stimulation pattern need to be developed, to handle only partial access to the thorax.

Poster 199

MRI Single Image In-Plane Super Resolution Using Deep Learning

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Bridging the gap between MRI and histology there is a need for increased resolution of MRI images. In this work we combined a mixed-scale dense convolutional network [1] and a structure preserving loss function [2], to increase the in-plane resolution of in-vivo MRI images with sub-millimeter resolution using dictionary learning.

To assess the performance of our network we compared basic image quality metrics (PSNR and SSIM) against the well known SRCNN [3]. Both networks were trained with data from the publicly available 'atlasing of the basal ganglia' (ATAG) consortium dataset [4].

Despite having 20 times fewer parameters our architecture can reconstruct high-resolution images in comparable quality and learns to better preserve high-frequency details than networks trained with L2-loss. The reduced number of parameters allows training with fewer datasets.

Preliminary experiments show that the architecture in general is working well and comparable to SRCNN even without any optimization of hyper-parameters. This is a promising approach to faster in-vivo imaging by increasing the resolution in a post-processing step.

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Poster 200

Radiosynthesis and preliminary biodistribution studies of the first ^{18}F-labeled MCT1/MCT4 lactate transport inhibitor in mice

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Anaerobic glycolysis in tumor cells stimulates the conversion of pyruvate to lactic acid. Monocarboxylate transporters 1 and 4 (MCT1/MCT4) are integral plasma membrane proteins that transport lactic acid and are highly expressed in non-hypoxic regions of human cancers (e.g. colon, brain, breast, and kidney). Inhibition of MCT1/MCT4 results in intracellular lactate accumulation, acidosis and cell death. In the current study, the first ^{18}F-labeled MCT1/MCT4 inhibitor was developed for potential in vivo imaging of MCT expression in cancer.

The MCT1 and MCT4 inhibitory activity of FACH was estimated by [^{14}C] lactate uptake assays. A protected mesylate precursor was developed for labeling. Radiosynthesis of [^{18}F]FACH was achieved by a two-step reaction, starting with the radiofluorination using [^{18}F]TBAF followed by protective group removal via hydrolysis under optimized reaction conditions. [^{18}F]FACH was separated by semi-preparative HPLC, purified and formulated in 10% EtOH in saline. The in vivo metabolism and the biodistribution of [^{18}F]FACH were investigated in female CD-1 mice.

FACH showed high MCT1 and MCT4 inhibitory activity (IC_{50} = 11.0 and 6.5 nM). [^{18}F]FACH was obtained with 39 ± 3% radiochemical yield (n = 10) after deprotection of the intermediate with TFA in CH_3CN at r.t. for 15 min. The organ distribution pattern of [^{18}F]FACH in healthy mice corresponds to the specific expression of MCT1 and MCT4 in kidney, lung, pancreas and liver.

The high uptake of [^{18}F]FACH in kidney and other peripheral MCT-expressing organs suggests the suitability of the radiotracer for further PET studies of solid tumors expressing MCTs.

Poster 201

Ligamental compartments and their relation to the passing spinal nerves are detectable with MRI inside the lumbar neural foramina

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Purpose:
Intraforaminal ligaments (IFL) in lumbar neural foramina (NF) and their relation to the lumbar spinal nerves (SN) are addressed.
Method: Giemsa- and PAS-stained plastinated body slices of 15 lumbar spines have been made and compared to MRI and CT data acquired of the same fresh specimens. We have dissected one fixed lumbar spine to discuss our results with previous literature.

Results:
In the NF very thin medial IFL touch the SN. As a second compartment intermedial vertical IFL are seen. A third lateral horizontal compartment of IFL is formed by thick cranial and caudal ligaments. Both without direct contact to the SN. From medial to lateral, the IFL thicken. All compartments are 3D-reconstructed. If compartments of the IFL have no direct contact to the SN seen in the slices, a connection has been noticed after dissection.

Conclusion:
Manual dissection seems to be inappropriate for a detailed study of the IFL. The lateral and intermedial compartments beeing free of the SN may play a role in power transmission and protecting the SN, while the thin medial IFL may lead and hold the SN passing the NF under physiological conditions. From the topography we conclude that the IFL are relevant in all cases of foraminal stenosis. Any herniation in the NF presses IFL to the SN. Therefore, we think the IFL themselves could also cause neurogenic claudication in case of their non-physiological turnover. “Occult” stenosis seems to be related to changing IFL. Diagnosis of IFL seems to be possible using MRI.

Leipzig Research Festival for Life Sciences 2019

Das 15. Research Festival Leipzig 2019, das von der Medizinischen Fakultät und der Fakultät für Lebenswissenschaften gemeinsam veranstaltet wird, soll allen »Life Science« WissenschaftlerInnen und ÄrztInnen aus Leipzig und dem Umland die Möglichkeit eröffnen, ihre Forschungsergebnisse in Form von Postern zu präsentieren und mit anderen Arbeitsgruppen zu diskutieren.

Für die Unterstützung der Veranstaltung danken wir:

Medizinische Fakultät der Universität Leipzig
Fakultät für Lebenswissenschaften der Universität Leipzig
Biotechnologisch-Biomedizinisches Zentrum (BBZ), Leipzig
Fraunhofer Institut für Zelltherapie und Immunologie, Leipzig
Innovation Center Computer Assisted Surgery (ICCAS), Leipzig
Integriertes Forschungs- und Behandlungszentrum AdipositasErkankungen (IFB), Leipzig
Max-Planck-Institut für Kognitions- und Neurowissenschaften Leipzig
Research Academy Leipzig
Sonderforschungsbereich 1052 ›Mechanismen der Adipositas‹, Leipzig
Universitätsklinikum Leipzig

ISBN: 978-3-00-061805-5