## ORAL SESSION 1: Immunology on 13th June (11:00 - 12:00)

### (O1) Production of nature-identical Bet v 1 and Ara h 2 using a plant – based transient expression system

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In-vitro allergy diagnostic tests are frequently performed with recombinant allergens which are produced in bacterial or yeast expression systems. Plant-based expression systems, such as the virus-driven Nicotiana benthamiana system, offer alternatives to obtain post-translational modifications(PTMs) and correct conformation of plant-derived allergens as natural-like recombinant (r) products. We selected two major allergens, a non-modified allergen, birch pollen Bet v 1, and an allergen with PTMs, peanut Ara h 2. Agrobacterium tumefaciens, contains a Ti plasmid enabling the delivery of T-DNA into plant cells. We used two tobacco mosaic virus (TMV)-based provectors that harboured T-DNAs encoding either Bet v 1 or Ara h 2 on a 3'-module or viral proteins on a 5'-module. A third provector delivered the phiC31 integrase for recombining the 3'- and 5'-modules. N. benthamiana plants were infiltrated via syringe without a needle using a suspension of agrobacteria transformed with the three provectors. Synthesis of Bet v 1 or Ara h 2 mRNAs was achieved within 10 days after successful recombination of the subgenomic promoter and allergen sequences. Recombinant allergens, including a C-terminal hexa-histidine tag, were purified using Ni-NTA loaded beads. The highest expression yield was 50 mg per kg fresh leaf. The purified allergens were confirmed by mass spectrometry sequencing and tested for obtained PTMs. rBet v 1 and rAra h 2 reacted with monoclonal antibodies and IgE from allergic patients' sera. We established the usefulness of the deconstructed TMV-based vector system for expressing two major allergens in N. benthamiana plants. This method offers a favorable alternative for complex plant-derived allergen production over bacterial or yeast expression systems. Further objectives included biochemical and immunological characterizations of the recombinant allergens. Supported by the Austrian Science Fund doctoral program W1248-B30.

## (O2) Hepatocyte-intrinsic Ifnar1 signaling modulates hepatic metabolism and adaptive immunity

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Viral infections induce inflammatory processes involved in antiviral defense, tissue damage and repair, as well as metabolic reprogramming. In this study, we employed a model of chronic viral infection to investigate the systemic interplay between inflammation and metabolism. Integration of longitudinal changes of transcriptomes and proteomes of the liver identified antiviral response programs as well as global metabolic alterations, with lipid and amino acid pathways being most prominently affected. Conditional ablation of Ifnar1 in hepatocytes revealed type I interferon (IFN-I) signaling as a central regulator of hepatic metabolism, modulating systemic metabolite levels. Specifically, IFN-I signaling targeted the urea cycle through transcriptional repression of the enzymes Otc and Ass1, resulting in increased arginine and decreased ornithine concentrations in the serum. Pharmacological targeting of the urea cycle revealed immunosuppressive effects on T cells and ameliorated hepatic immunopathology. These findings shed light on the complex inter-organ crosstalk during systemic inflammation and establishes IFN-I-induced modulation of the hepatic urea cycle as an endogenous mechanism of immunoregulation.

## (O3) Cutaneous microbiome dynamics in allogeneic hematopoietic stem cell transplantation

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Background: The success of allogeneic hematopoietic stem cell transplantation (HSCT) remains limited due to severe side effects, such as infections and graft-versus-host disease (GVHD). Dysbiosis of intestinal microbes has already been linked to an increased risk of GVHD development and poor outcome. Even though cutaneous inflammation presents the earliest and most common manifestation of GVHD, the role of the skin microbiome in this setting remains elusive.
Methods: We obtained patient material (peripheral blood, skin scales, stool and skin biopsies) at 5 time points before myeloablative conditioning and up to one year after HSCT (n = 20). The cutaneous and intestinal microbiome is analysed with 16S rRNA and whole metagenome sequencing. In vivo interactions of bacteria with immune cells are monitored by combining monoclonal antibodies with fluorescent in situ hybridization (FISH). Bacterial numbers/[upmm2] and distance calculations from CD45[up+] and HLA-DR[up+] cells are assessed via StrataQuest Analysis Software.
Results: Primary 16S rRNA sequencing of the cutaneous microbiome up to one year after HSCT shows a clear disturbance of the initial bacterial composition at the day of transplantation (day 0) up until 14 days later, which is not reconstituted at later time points (day 100& 365) and remains permanently altered. 16S rRNA FISH stainings in skin of the same patients also revealed a significant decrease in bacteria/[upmm2] on day 0 and 14. Surprisingly, bacterial numbers reached baseline levels at day 100 after transplantation, arguing for a change in repopulation of bacteria rather than overall count.
Conclusion: This study gives us the possibility to examine interactions of microbes with immune cells in the skin over time after reset of the immune system and re-population of bacteria species post-transplantation.

## (O4) Investigating oncogenic functions of STAT5B in innate(-like) lymphocytes

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STAT5B is a master regulator of development, survival and function of innate and innate-like lymphocytes (including natural killer (NK) and NKT cells). Gain-of-function mutations in the SH2 domain of human STAT5B, especially STAT5B-N642H, are associated with aggressive forms of CD56+ T cell and NK cell lymphomas/leukemias. We previously described a mouse model expressing human (hSTAT5B-N642H under the Vav-1 promoter, which develops severe CD8+ T cell neoplasia. However, innate lymphocytes have not yet been investigated in this model and we aim to explore the ability of hSTAT5B-N642H to serve as an oncogenic driver in innate lymphocyte neoplasms. We hypothesized that alterations affecting innate lymphocytes are masked by the CD8+ T cell disease established in hSTAT5B-N642H mice. Therefore, we transplanted CD3-depleted bone marrow into immune-deficient recipients and observed an enhanced expansion of hSTAT5B-N642H compared to non-mutant hSTAT5B NK cells, which was however overruled by T cell expansion. To circumvent T cell disease, we transplanted hSTAT5B or hSTAT5B-N642H bone marrow depleted of T cells, stem cells and lymphoid progenitors. Interestingly, recipient mice transplanted with these hSTAT5B-N642H cells developed a disease characterized by expansion of CD3+NK1.1+NKp46+CD1d-independent NKT cells, which was serially transplantable and responsive to JAK1/2 inhibitor treatment. Taken together, we demonstrate that Vav1-driven hSTAT5B-N642H expression allows for the transformation of innate-like lymphocytes upon removal of transformed CD8+ T cells. Our novel NKT cell disease model, which closely resembles aggressive human CD56+ T-cell large granular lymphocyte (T-LGL) leukemia, will allow to explore new therapeutic approaches and study underlying mechanisms of STAT5B-driven leukemogenesis. Further research is ongoing to investigate if and how mutant STAT5B contributes to NK cell transformation and how hyperactive STAT5B signaling affects lymphocyte function.

## ORAL SESSION 2: Malignant diseases on 13th of June (13:45 - 14:45)

### (O5) Chromatin mapping and single-cell immune profiling define the temporal dynamics of ibrutinib drug response in chronic lymphocytic leukemia

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## (O6) Examining the Function of PDGFRB in Anaplastic Large Cell Lymphoma

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Anaplastic large-cell lymphoma (ALCL) is an aggressive non-Hodgkin T-cell lymphoma commonly diagnosed in children and young adults. A majority of ALCL tumours harbour the translocation t(2;5)(p23;q35), resulting in the fusion of Nucleophosmin (NPM) to the Anaplastic lymphoma kinase (ALK) gene. The oncogenic fusion protein (NPM-ALK) is constitutively expressed and contributes to the pathogenesis of 70% of ALCL cases. Recent studies from our lab identified AP-1 transcription factors as downstream effectors of NPM-ALK, which directly up-regulate platelet derived growth factor receptor beta (Pdgfrb) expression in lymphocytes. Strikingly, therapeutic inhibition of PDGFRB with Imatinib resulted in rapid and sustained remission in late-stage therapy-resistant ALCL patients. In this study, we set out to determine the underlying mechanisms and the nature of PDGFRB signalling in ALCL. To elucidate the associated PDGFRB signalling pathways in ALCL, we have developed a mouse model which yields a deletion of PDGFRB in CD4+ T cells expressing the human NPM-ALK oncogene (NPM-ALK_PDGFRB). NPM-ALK_PDGFRB mice have significantly prolonged survival rates and reduced tumour growth, due to increased apoptosis. NPM-ALK_PDGFRB tumours exhibit a decrease in lymphatic vessels, which is accompanied by a decrease in tumour dissemination. Moreover, in vivo deletion of PDGFRB results in a decrease in the signal transducer and activator of transcription 5 (STAT5) and NPM-ALK signalling pathways dampening tumour aggressiveness. Manipulation of PDGFRB levels in vitro, via CRISPR/Cas9 mediated knockout or overexpression, in primary tumour cell lines mirrors the changes in signalling pathways observed in the tumours in vivo.

In summary, expression of PDGFRB results in increased tumour burden via modulation of both the NPM-ALK oncogene and the STAT-signalling pathway. Our data therefore supports the oncogenic role of PDGFRB and opens new avenues for therapeutic intervention in ALCL treatment.

## (O7) A protective role of myeloid mTORC1 in colitis and colorectal cancer

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The gut is responsible for digestion, absorption and metabolism of dietary nutrients. It has the highest cell turnover of any tissue. Stomach, small and large intestine present a strikingly different anatomy and function and little is known how the colon maintains homeostasis. A dysregulation in cellular turnover or the immune cell compartment can promote inflammatory bowel diseases (IBDs), which are the main risk factors for generating colitis-associated colorectal cancer (CRC). The mammalian target of rapamycin (mTOR) has a central role in the effector functions of immune cells and both mTOR complexes are involved in CRC formation. Little is known about the cell-specific mTOR functions in macrophages during CRC. In our mouse model, mTORC1 is constitutively active in macrophages by deletion of the gene Tsc2 (Tsc2fl/flLyz2cre/+ mice). These Tsc2-deficient macrophages tend to be of the anti-inflammatory M2 type and are significantly more abundant in the colon compared to control mice. Interestingly, these mice present a reduced tumor development after the AOM/DSS-induced colitis-associated CRC. In fact, during an acute DSS-induced colitis model, reduced weight loss and colon shrinkage with a concomitant reduced erosion area are observed together with reduced proinflammatory cytokine production. We performed a metabolomic analysis on whole colon samples of mice at steady state and during colitis and noticed significantly increased levels of some essential amino acids, polyamines and histamine. In conclusion, mTORC1 activity in macrophages promotes tissue homeostasis by modulating the metabolic environment and helps to protect during colitis. This study identifies metabolic cues that help to better understand the role of macrophages in the colon during homeostasis and disease.

## (O8) The role of clinical joint inflammation and acute phase response on structural progression of patients with psoriatic arthritis

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Psoriatic arthritis (PsA) belongs to the group of the seronegative spondylarthropathies and is associated with psoriasis. Disease activity can be measured clinically (eg, swollen joint count, SJC) and systemically (eg, C-reactive protein, CRP). The aim of our study is to determine the contribution of clinical and systemic inflammation on structural progression of PsA patients. We analyzed patient data from the IMPACT 2 trial (infliximab, INF vs. placebo, PLC), obtained modified Sharp-van-der-Heijde Scores from X-rays (baseline, after one year) and levels of CRP and SJC. We computed radiographic progression, and time-averaged SJC (taSJC) and CRP (taCRP) values. In a logistic regression model, we assessed the impact of taCRP, taSJC, and their interaction, on structural progression. We divided patients depending on their taCRP and taSJC levels into active (+) or inactive (-) subgroups and tested whether radiographic progression was different in taCRP+ vs. taCRP- and taSJC+ vs. taSJC- (Mann-Whitney U test). As INF patients showed no structural progression (-1.16±3.96), we focused our analyses on PLC patients (progression: 0.74±2.98, n=76). TaSJC, taCRP, and their interaction, were associated with progression (OR taSJC: 1.24, CI 95 %: 1.04-1.47, p=0.016; OR taCRP: 6.08, CI 95%: 1.12-33.0, p=0.036; interaction term: p=0.097). Progression was higher in taSJC+ patients compared to taSJC- patients (1.05±3.21 and 0.56±2.30, respectively; p=0.016), as well as numerically higher without statistical significance in taCRP+ vs. taCRP- patients (1.14±3.23 and 0.05±2.37, respectively; p=0.532). There was evidence that SJC activity plays a role in CRP- patients (p=0.076), whereas CRP activity seems to be of less importance SJC- patients (p=0.643). To conclude, in patients with PsA, both clinical and systemic inflammation have impact on structural progression; in patients without systemic inflammation, clinical joint activity may be considered as a risk factor for progression.

## ORAL SESSION 3: Cell Communication in Health and Disease on 13th of June (17:30 - 18:00)

### (O9) Molecular imaging of the antigen recognition dynamics in CD8+ cytotoxic T-cells

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Cytolytic T-cells (CTLs) can detect with their low affinity T-cell antigen receptors (TCRs) the presence of even a single antigenic peptide-loaded MHC molecule I (pMHCI) among thousands of structurally related yet non-stimulatory pMHCs (Purbhoo et al. 2004). How they achieve this is not clear but appears to depend at least in part on the special binding conditions within the special constraints of the immunological synapse, the area of contact between a T-cell and an antigen presenting cell. Here receptors and their ligands are not only pre-oriented, but they are often enriched in specific membrane domains and also subjected to cellular forces. To relate these cell biological parameters to T-cell antigen sensitivity in a more comprehensive manner we are monitoring TCR-pMHC binding in nascent synapses with the use of molecular imaging modalities. We confront TCR transgenic CTLs with a glass-supported lipid bilayer (SLB) functionalized with pMHCI, adhesion and co-stimulatory molecules. This allows us to conduct (single molecule) measurements in noise-attenuated Total Internal Reflection (TIRF) mode, to control for ligand composition and density to quantitate their specific influence on TCR-pMHCI binding and TCR-proximal downstream signaling. We also plan to assess the role of CD8 co-receptor engagement with the use of pMHCI mutants, which are deficient in CD8 binding. In this fashion we expect to gain novel insights into cell biological and molecular processes underlying the phenomenal sensitivity of CTLs towards antigen.

## (O10) Exploring trained immunity in pulmonary infection

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Trained immunity refers to the ability of innate immune cells to undergo cellular alterations in response to endogenous or exogenous stimuli. These alterations occur on a genetic, epigenetic and metabolic level and enhance immune responses to subsequent pathogenic challenges. In order to exploit trained immunity therapeutically, it is necessary to investigate the underlying mechanisms in the context of disease. Bacterial pneumonia remains a leading cause of morbidity and mortality worldwide, and is most commonly caused by Streptococcus pneumoniae. During the early phase of infection, innate host defense is primarily mediated by alveolar macrophages AMs), the tissue-resident macrophages of the lung. In order to investigate whether AMs can be trained for enhanced immune activity, we intranasally administer a viral TLR agonist to wild type mice, isolate AMs six days later and asses their immune responses upon ex vivo challenge with heat-inactivated S. pneumoniae. Additionally, we aim to dissect the cellular mechanisms of trained AM responses by genetic, epigenetic and metabolic profiling. In order to test whether in vivo training can protect from pneumonia, we infect trained and naïve mice with live S. pneumoniae and assess the pulmonary bacterial load and tissue damage. We could demonstrate that in vivo training enhances the phagocytic capacity and inflammatory cytokine production of AMs upon ex vivo bacterial challenge. Furthermore, trained AMs displayed a distinct lipid and metabolic profile, which may be responsible for their enhanced immune responses. Importantly, training reduced the pulmonary bacterial burden during subsequent in vivo S. pneumoniae infection. In conclusion, our data suggest that AMs can be trained to protect from pneumonia. Our ultimate goal is to understand the mechanisms of trained AM immunity in order to promote the development of novel therapeutic strategies to treat pulmonary infections by exploiting innate immune function.

## ORAL SESSION 4: Medical Physics on 14th of June (10:00 - 10:30)

### (O11) Flexible size-adaptable multi-turn multi-gap coaxial RF coils (MTMG-CCs) for Magnetic Resonance Imaging (MRI)

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In MRI, flexible radio frequency (RF) coils form-fitted to the region of interest and size-adapted for the target anatomical site provide an SNR-optimal setup for MR signal detection. Auto-resonant structures like coaxial RF coils with one gap in both the outer and inner conductor provide high mechanical flexibility but are restricted to a single coil size, determined by the target resonance frequency (f0) and the properties of the cable. In this work, we combine the concepts of multi-turn multi-gap transmission line resonators and coaxial RF coils, and evaluate the extended range of possible coil sizes that can be achieved with realistic cable parameters. We proposed an equivalent RLC-circuit for MTMG-CCs which allows to numerically determine the resonance frequency as a function of the following parameters: coil diameter d0, characteristic cable impedance Z0, cable diameter d1, dielectric permittivity _r and the number of turns and gaps (nt, ng).
For experimental validation on the bench, we measured the resonance frequency of 27 coils with d0=6/9/12 cm, nt=1-3 turns and ng=1-3 that were fabricated out of one cable type (d1=2.5mm, _r=2.1, Z0=50Ω). Calculated f0 values deviate up to ±11.3% from measured ones. Targeting 1H-MRI at common B0 field strengths and considering realistic cable parameters, the achievable range of MTMG coaxial coil diameters starts at ≈3 cm and is almost continuous up to 60/60/49/38/35 cm for B0 values of 1.5/3/7/9.4/10.5 T, respectively. As a general outcome, the use of multiple turns and/or gaps provides additional degrees of freedom for RF coil design and enlarges the coaxial coil diameter range that can be achieved for a given frequency as compared to the single-turn single-gap case.
The combination of the MTMG and coaxial coil principles allows designing light and ultra-flexible coils with an optimised diameter, which are highly beneficial to many clinical MRI applications where anatomical inter-subject variability is strong.

## (O12) Comparison of Motion Compensation techniques for cardiac PET imaging

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Aim: In this study, we aim to improve the image quality of cardiac PET aquisitions by introducing corrections for the cardiorespiratory motion at different stages of the PET-image reconstruction (before, during or after image-reconstruction (IR)).
Materials/Methods: Three motion correction (MoCo) techniques were compared: (1) MoCo before IR (Projection Based Motion Compensation [P-MoCo]), (2) Motion-Compensated during IR [MCIR] and (3) motion correction after IR (Reconstruct-Transform-Average [RTA]). The proposed methods were compared head-to-head for both simulations and patient examinations. All simulations were performed using a well-established model (Extended Cardiac-torso [XCAT] phantom). P-MoCo is a sinogram-based approach limited due to loss of information when moving from image-to-sinogram space. To test the applicability range of P-MoCo, simplistic axial (1D) and anterior-posterior (2D) respiratory motion models as well as complex 3D cardio-respiratory motion models were evaluated in the XCAT phantom. Additionally, the three MoCo methods were considered for two patients. Myocardium-to-background ratios (MBR) were used to evaluate the performance of the MoCo approaches.
Results: For XCAT phantom data, increased MBR values (with respect to the static images without MoCo) of 36.2/34.4/9.4 % (P-MoCo), 44.0/42.4/35.2 % (MCIR) and 39.1/37.7/28.6 % (RTA) were observed for 1D/2D/3D motion models, respectively. In the patient datasets, P-MoCo and RTA lead to mean±SD increased MBR (with respect to the static images without MoCo) of 28.5±7.3 % (P-MoCo) and 20.6±6.8 % (RTA), with similar noise properties to those observed for the static image-reconstructions.
Conclusion: P-MoCo yields to comparable results as image-based methods like MCIR or RTA for respiratory motion models but cannot handle complex cardio-respiratory motion in three dimensions. Further, P-MoCo provides similar results to RTA for respiratory MoCo of cardiac PET patient data.

## ORAL SESSION 5: Public Health and Neuroscience on June 14th (12:00 - 13:00)

### (O13) Monitoring evidence on overall survival benefits of anti-cancer drugs approved by the European Medicines Agency between 2009 and 2015

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Objective: The introduction of fast-track licensing strategies increases the approval of anti-cancer drugs with ambiguous benefit-risk profiles. Thus, in many instances there is lacking evidence about overall survival (OS) at the time of marketing authorization. Our objective was to monitor and characterize therapies with ambiguous benefit-risk profiles and identify any post-approval updates on median OS after at least three years of approval by the European Medicines Agency (EMA).
Methods: We included all originator anti-cancer drugs with initially ambiguous benefit-risk profiles that received marketing authorization by the EMA between Jan 1, 2009 and May 31, 2015. Our monitoring timeframe was at least three years after EMA-approval. To identify study updates, the following three sources were included: clinicaltrials.gov, EPARs, and PubMed.
Results: In total, we identified 102 eligible approval studies. Out of these, a negative difference in median OS or no information was available in 43 (42.2%) instances. During monitoring, 11 updates with accessible information on median OS could be identified. Including monitoring results there are still 32 remaining therapies (31.4%) where no or negative information (n=27 [26.5%] and n=5 [4.9%], respectively) regarding median OS is present at least three years after EMA approval.
Conclusion: One-third of oncology drugs with ambiguous benefit-risk profiles fail to demonstrate a survival benefit even after several years of marketing authorization. Systematic and transparent post-approval monitoring mechanisms will be of high relevance to assure a clinically relevant patient benefit, since the trend towards faster access to medicine with uncertain benefit is increasing rather than declining.

## (O14) Identification of brain areas related to a complex task with [18F]FDG-functional PET in comparison to fMRI and arterial spin labeling

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With functional PET (fPET) task specific changes in glucose metabolism can be quantified in a single measurement. However, until now only simple tasks targeting primary sensomotoric regions have been conducted. Therefore, we aimed to identify brain areas during complex task performance and variations in the cognitive load. 22 healthy subjects were scanned once in a hybrid PET/MRI. To measure changes in glucose metabolism the radiotracer [18F]FDG was administered. The paradigm consisted of an adapted version of Tetris including two complexity levels. Each complexity level was conducted twice and separated by a rest condition. During the scan PET emission data was acquired simultaneously with arterial spin labeling(ASL). Functional MRI was recorded after the PET scan with shorter task and rest blocks and an additional control condition. Task-specific changes were estimated for all 3 modalities and compared with the Dice coefficient. Additionally, the differences between complexity levels were investigated. We found significant task-specific activation($p<0.05$ FWE-corrected) with fPET, fMRI and ASL in the dorsal attention network, namely intraparietal sulcus and frontal eye field as well as supplementary motor area and the occipital cortex. The Dice coefficient showed a good overlap between all modalities(0.49 to 0.55). Significant differences between complexity levels were detected in fPET and fMRI ($p<0.05$ to 0.001) but not in ASL. We could demonstrate that brain regions involved in complex task performance can be detected not only with conventional methods such as fMRI and ASL, but also with fPET. Hence, task-specific changes in glucose metabolism can be reliably estimated even if the target regions are unknown a priori. Furthermore, fPET showed a high sensitivity to detect slight variations in cognitive task load induced by different complexity levels, unlike ASL. Thus, fPET is a promising tool to investigate brain regions related to higher order cognitive functions.

## (O15) Evaluation of [11C]tariquidar as a PET tracer to measure ABCB1 and ABCG2 transport activity in the liver

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ABCB1 and ABCG2 are two efflux transporters which mediate the secretion of many drugs or drug metabolites from the liver into bile. Changes in hepatic ABCB1 and ABCG2 transport activity (caused by e.g. disease, drug-drug interactions or genetic polymorphisms) may lead to alterations in the plasma clearance of drugs, which may cause severe side effects. In this study we evaluated the suitability of PET imaging in combination with the model ABCB1/ABCG2 substrate [11C]tariquidar = [[up11]C]tariquidar to measure hepatic ABCB1/ABCG2 transport activity in humans and in mice. [11C]Tariquidar PET scans were carried out in 5 healthy volunteers without and with a concurrent i.v. infusion of unlabeled tariquidar (225 mg/h). In addition, FVB wild-type and transporter knockout mice (Abc1a/b(-/-) = Abc1a/b[-/-], Abcg2(-/-) = Abcg2[-/-] and Abc1a/b(-/-)Abcg2(-/-)) underwent two consecutive [11C]tariquidar PET scans with i.v. pre-treatment with unlabeled tariquidar (15 mg/kg). A previously developed 3 compartment PK model was used to determine the rate constants defining the hepatobiliary kinetics of [11C]tariquidar. The co-administration of unlabeled tariquidar caused a significant ($p<0.05$) reduction in k3 = k[down3] (rate constant describing transfer of radioactivity from liver to bile) in humans. In mice, pre-treatment with unlabeled tariquidar significantly reduced k3 in wild-type, Abc1a/b(-/-) and Abcg2(-/-) mice, while in Abc1a/b(-/-)Abcg2(-/-) mice there were not significant changes in k3 between scans. Moreover, in the baseline scans, k3 was significantly lower in Abc1a/b(-/-)Abcg2(-/-) mice as compared to wild-type mice, but unaltered in Abc1a/b(-/-) mice and Abcg2(-/-) mice. These results suggest that [11C]tariquidar PET can be used to measure hepatic ABCB1 and ABCG2 transport activity in humans and in mice. Our data point that there is a mutual functional compensation between ABCB1 and ABCG2 in the hepatobiliary excretion of dual substrate drugs.

## (O16) HRV (Heart Rate Variability) as a non-invasive measurement method for per-formance diagnostics and training control

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The aim of this study is to determine whether non-invasive heart rate variability (HRV) recordings can be used to monitor training exercises and to estimate athletic performance. A central question which needs to be addressed, in this context, is if analysis of the HRV is a valid method to estimate over-training, athletic condition and athletic performance. Recently, condition and performance have been evaluated with lactate test procedures and spirometry. Several tests were conducted to determine the relationship of data from lactate test samplings, spirometry and HRV recordings. Four groups of professional athletes, ball sports (n=15), martial arts (n=17), endurance sports (n=8) and hobby athletes as a control group (n=6) underwent a standardized treadmill or bicycle ergometer step test with increasing load rates, for example 2 km/h or 20-50 Watt every 3.5 minutes, synchronized with standardized series of lactate test sampling, spirometry and ECG recording. Additionally, a physical and anthropometric evaluation was part of the testing procedure. An inclusion criterion for all athlete groups was a minimum training frequency of an hour, five days a week focussing on continuous performance improvement. There is evidence that detailed real-time or offline analysis of ECG data allows conclusions on actual individual athletic performance without the need of complex instrumentation and laboratory environment. The decreasing variability in the heart rate correlates significantly with the increase in lactate concentration in the blood in all testing groups (mean correlation of all subjects r=0.7902; SD=0.073). During physical stress certain frequency bands of the regular HRV analysis (0.0033 - 0.4 Hz) decrease until a certain point in time, where the variation of the beat-to-beat interval reaches an individual minimum. By using these frequency components, conclusion regarding activites of symphatetic and paraymphatetic pathways can be drawn.

## ORAL SESSION 6: Molecular Mechanisms of Cell Biology on June 14th (16:45 - 17:45)

### (O17) Engineering young extracellular matrix environment for enhanced bone regeneration during aging

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Regeneration of bone defects in elderly patients is limited due to the decreased function of bone forming cells and compromised tissue physiology. It was previously shown that the regenerative activity of stem cells from aged tissues can be enhanced by young systemic and tissue microenvironments. The aim of our project is to investigate the extracellular matrix (ECM) derived from placental tissue, as well as ECM engineered from human induced pluripotent stem cells (hiPSCs) for improved bone regeneration during aging. hiPSCs-ECM was engineered from hiPSC-derived mesenchymal-like progenitors (hiPSC-MPs) and characterized before and after decellularization using immunofluorescent stainings. The effects of the engineered ECMs on bone regeneration were tested using human bone marrow stromal cells (hBMSCs) of different ages. The human placenta substrate (HPS) was isolated using different Tris-NaCL buffers, characterized using SDS-PAGE and tested using human umbilical vein endothelial cells (HUVECs) for formation of vascular networks. Cultivation of hBMSCs on the hiPSC-ECM reproducibly accelerated hBMSC growth and significantly increased early markers of osteogenesis (ALP activity, collagen deposition) in young and aged hBMSCs. However, matrix mineralization and increased gene expression levels of the late osteogenic markers BSP and OPN were only detected in aged BMSCs cultured on hiPSC-derived ECM in osteogenic medium. HPS was successfully isolated from placenta tissue and exhibited a similar pattern but more durable vascular networks from HUVECs as compared to control cultures on Matrigel® matrix. Our studies suggest that aged BMSCs activity can be rejuvenated in the presence of hiPSC-engineered ECM and that HPS has the potential to support vascular network formation. Tissue engineering strategies employing young ECM materials could potentially enhance bone regeneration in elderly patients.

## (O18) Multi-scale profiling of lung adaptation after transplantation

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Lung transplantation (LTx) is the ultimate, life-saving treatment for patients with end-stage respiratory failure. Despite recent medical advances, mortality rates after lung transplantation remain high (20-45% over the first 5 years) when compared to other solid organ transplants. This outcome is due to chronic lung allograft dysfunction (CLAD), which is clinically defined as a persistent decrease in forced expiratory volume in 1 second (FEV1). To this date, the precise mechanisms leading to CLAD remain elusive and no specific treatment is available. The aim of our study is to acquire multi-omics information by conducting bacterial 16S rRNA gene sequencing, fungal ITS sequencing, lipidomics, metabolomics and flow cytometry from donor and recipient broncho-alveolar lavage fluid samples. The assembled dataset will hopefully enable us to identify key players in lung allograft dysfunction and to predict individual patient trajectories towards CLAD.
Analysis of flow cytometric data revealed that the relative proportion of alveolar macrophages showed an increase with time after LTx. Consistently, multivariate analysis of 16S, lipidomic and metabolomic datasets revealed time after LTx as the most powerful explanatory variable for each of the datasets. Furthermore, microbial diversity and richness showed robust correlations with time after LTx. Individual donor microbiomes were highly predictive of recipient microbiomes early after LTx, whereas influence of the donor microbiome decreased with time, indicating that the lung microbiome adaption occurs in an individualized fashion. Tantalizingly, machine learning techniques showed predictive power of the microbiome for FEV1 dynamics after sample collection, suggesting an influence of the lung microbiome on transplant function. Current efforts are focused on integrating different datasets to enable early identification of patients at risk for developing CLAD.

## (O19) Fibrocytes and neutrophil extracellular traps at the culprit lesion site in myocardial infarction: a role for monocyte chemoattractant protein 1

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Leukocyte-mediated inflammation is crucial in ST-segment elevation myocardial infarction (STEMI). We recently observed that neutrophil extracellular traps (NETs) are increased at the culprit lesion site CLS, promoting the activation and differentiation of fibrocytes, cells with mesenchymal and leukocytic properties. Fibrocyte migration is mediated by monocyte chemoattractant protein (MCP)-1 recognized via C-C chemokine receptor type 2 (CCR2).
We investigated the interplay between fibrocyte function, NETs and MCP-1 in STEMI.
CLS and femoral blood of STEMI patients (n=50) was drawn during percutaneous coronary intervention. We characterized CCR2 expression of fibrocytes by flow cytometry. MCP-1 and NET marker citrullinated histone H3 (citH3) were measured by ELISA. Fibrocytes were treated in vitro with MCP-1. Human coronary arterial endothelial cells (hCAECs) were stimulated with isolated NETs, and MCP-1 was measured by ELISA and qPCR. The influence of MCP-1 on NET formation in vitro was assessed using isolated neutrophils.
Fibrocytes accumulated at the CLS in STEMI. Fibrocyte CCR2 expression was decreased compared with femoral control. MCP-1 and citH3 were increased at the CLS. CLS MCP-1 was correlated positively with fibrocyte accumulation, and negatively correlated with CCR2 expression. In vitro, MCP-1 decreased fibrocyte CCR2. NET stimulation of hCAECs induced MCP-1. MCP-1 attenuated ionomycin-induced NETosis.
Fibrocyte accumulation at the CLS appears to be mediated by MCP-1. NETs induce endothelial MCP-1, promoting a chemotactic gradient for fibrocyte migration. The inhibitory effect of MCP-1 on NETosis might serve as a negative feedback loop, limiting inflammation.

## (O20) In depth analysis of the microenvironmental influence on human blood-brain barrier integrity in cerebral ischemia

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The blood-brain barrier (BBB) is damaged during ischemic insults such as stroke or traumatic brain injury. As the exact mechanisms of BBB disruption during cerebral ischemia are still unknown and accessibility to human data is limited, the necessity to develop in-vitro models resembling in-vivo conditions is evident. Recently, we have established a BBB model based on human induced pluripotent stem cells (hiPSC) reflecting several properties of the in-vivo phenotype such as high paracellular tightness, transporter protein expression and functionality (Appelt-Menzel et al., Stem Cell Reports, 2017). In 2016, Page et al. (Page et al., Fluids Barriers CNS, 2016) showed the applicability of a hiPSC-based BBB model for simulating cerebral ischemia by oxygen/glucose deprivation (OGD) for 24 hours. This time span does not resemble physiological conditions. In order to shorten exposure time, we investigated whether co-cultures with human primary astrocytes and pericytes or the rat glioma cell line C6 influence barrier breakdown. OGD treatment of 6, 7, 9 and 17 hours was applied to analyze time-dependent BBB damage. Barrier breakdown was assessed by TEER (transendothelial electrical resistance) and permeability studies with the paracellular marker fluorescin as well as with a high-throughput qPCR chip (Fluidigm®), western blotting and immunohistochemistry. Thereby, we defined the optimum duration of OGD treatment for a reasonable barrier breakdown between 6 and 7 hours, indicating the pivotal role of microenvironmental cells on barrier damage. Interestingly, mono-cultures of hiPSC-derived endothelial cells exposed to OGD showed an increase in barrier properties. A comprehensive analysis of expression level changes of tight junction proteins, SLC- and ABC-transporters indicates a complex regulatory network underlying BBB breakdown in cerebral ischemia. In conclusion, we were able to improve the applicability of our hiPSC-derived BBB model for research on cerebral ischemia.