Thieme

41. Jahrestagung der Deutschen Arbeitsgemeinschaft zum Studium der Leber

Datum/Ort:
14.–15. Februar 2025, Klinikum rechts der Isar der Technischen Universität München

Tagungspräsident:
Prof. Dr. Percy A. Knolle

Inhalt

Lecture Session I
BASIC HEPATOLOGY (FIBROGENESIS, NPC) 14/02/2025, 01.10pm – 01.55pm, Lecture Hall

L1.01 Extracellular matrix protein 1 (ECM1) balances liver regeneration by interfering with HGF/c-Met-ERK-MYC and TGF-β-SMAD signaling pathways

Autorinnen/Autoren Ye Yao[1], Yujia Li[1], Chenjun Huang[2], Seddik Hammad[1], Laura Danielczyk[1], Chunfang Gao[3], Matthias Ebert[4], Honglei Weng[1], Steven Dooley[1], Sai Wang[5]

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Objective: Extracellular matrix protein 1 (ECM1) is crucial for liver homeostasis and negatively correlates with chronic liver disease (CLD) progression. However, its role in acute liver injury and regeneration (LR) remains unclear. This study investigates ECM1's impact on LR and its underlying mechanisms.

Design: Ecm1-tdTomato mice were administered adeno-associated virus 8 (AAV8)-ECM1 seven days before 70 % partial hepatectomy (PHx). Hepatic gene expression was analyzed with RNA sequencing. Functional assays were done with hepatocytes, mouse liver tissue and patient samples.

Results: ECM1 is downregulated during LR after PHx. Interference with ECM1 downregulation by AAV8-ECM1 delays proliferation and liver mass gain at days 2 and 4, but catches up by day 8, as indicated by the liver-to-body weight ratio and immunostaining of PCNA and Ki67. Mechanistically, in early-stages of LR (days 0–4), downregulation of ECM1 is required for efficient HGF/c-MET/ERK/MYC signaling to mediate cell cycle progression, including CyclinA2, B1, B2, and Birc5 expression. In the late stage (days 4–8), overexpression of ECM1 inhibits latent TGF-β activation, therefore interfering with TGF-β-induced cell cycle kinase inhibitors p15, p16, p18, and p19, required for regeneration termination, which finally restores the liver mass. Additionally, Myc overexpression in hepatocytes rescues ECM1 mediated proliferation inhibition. In liver

tissue of patients, ECM1-positive hepatocytes display reduced nuclear Myc expression.

Conclusion: ECM1 regulates liver regeneration by modulating HGF/c-MET/ERK/MYC and TGF-β/SMAD pathways. We hypothesize that for patients requiring liver regeneration, ECM1 downregulation benefits hepatocyte proliferation and liver function restoration. However, its inhibitory effect on TGF-β signaling should also be considered.

L1.02 Korrektur der Morbus Wilson Punktmutation H1069Q in iPSCs mittels CRISPR/Cas9 Genom-Editierung

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Morbus Wilson (MW) ist durch toxische Kupferansammlungen, hauptsächlich in der Leber und im zentalen Nervensystem, gekennzeichnet. Die Punktmutation H1069Q ist die häufigste Mutation des Kupfertransporters ATPase7B in westlichen Populationen. Ein Ziel dieser Studie war es zu prüfen, ob eine CRISPR/Cas9-vermittelte Genkorrektur in MW-induzierten pluripotenten Stammzellen (iPSCs) deren Fähigkeit zur Differenzierung in hepatozytenähnliche Zellen (HLCs) beeinträchtigen oder hemmen kann. Ein weiteres Ziel bestand darin, das Potenzial der HLCs zur Wiederherstellung der Kupferresistenz zu bewerten, was auf die Funktionalität von ATPase7B hinweist. In dieser Studie wurden Harnepithelzellen von MW-Patienten, die die heterozygote Mutation H1069Q/N1270S tragen, mittels transienter Transfektionsmethoden zu iPSCs umprogrammiert. Zur Einleitung der homologiegerichteten Reparatur wurden iPSCs mit dem Plasmid PX459.H1069Q und einer Reihe einzelsträngiger Oligo-DNA-Nukleotide transfiziert. Einzelne iPSC-Klone wurden mittels Sanger-Sequenzierung analysiert. In 46 % aller analysierten iPSC-Klone wurde die H1069Q Mutation erfolgreich korrigiert. Die zweite Mutation N1270S war nicht betroffen. Die korrigierten iPSC-Klone wurden in HLCs differenziert und mittels real-time-RT-PCR auf hepatozytenspezifische Markergene untersucht. Mittels MTT-Tests wurde die Zellvitalität bzw. -proliferationsrate von ATP7B-korrigierten und unkorrigierten HLCs nach Inkubation in toxischen Kupferkonzentrationen bestimmt. Die korrigierten HLCs zeigten eine Hochregulierung hepatozytenspezifischer Markergene (ATP7B, Albumin, AFP, TTR, TF, HNF4α, MDR1, CAR1, APOA1) sowie eine verbesserte Resistenz gegenüber hohen Kupferkonzentrationen. Zusammenfassend zeigt diese Studie, dass die CRISPR/Cas9-Technik bei iPSCs hocheffizient ist und ihre Fähigkeit zur Differenzierung in HLCs nicht beeinträchtigt. Diese Technologie verfügt über ein bemerkenswertes therapeutisches Potenzial zur Korrektur des ATP7B-Gens und trägt somit zu neuen Therapieansätzen für MW bei.

L1.03 Modeling Ischemic-Type Biliary Lesions in Human Cholangiocyte Organoids

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Ischemic-type biliary lesions (ITBL) is a significant and challenging biliary complication following liver transplantation, characterized by nonanastomotic strictures on cholangiogram and usually leading to graft failure or mortality. While risk factors such as ischemia-, bile salt toxicity- and immune response-induced injury have been identified, the precise cellular and molecular mechanisms underlying bile duct injury in ITBL remains unexplored. This knowledge gap stems from the lack of relevant primary models that recapitulate in vivo conditions. Using human liver or bile biopsies-derived cholangiocyte organoids (intrahepatic cholangiocyte organoids, IHCO or bile cholangiocyte organoids, BCO) as a model, we demonstrated both cholangiocyte organoids derived from healthy donor closely resemble primary cholangiocytes in terms of key biliary marker expression, tubular morphogenesis and functional properties. In contrast, organoids emerged from ITBL livers or bile develop only cystic spheres, failing to generate branching duct network resembling in vivo architecture. Cells in ITBL-organoids exhibited aberrant apical-basal polarity, reduced expression of cholangiocyte transporters and enzymes, and diminished responsiveness to hormone stimulation. Our findings provide cellular and functional insights into the extensive biliary injury observed in ITBL patients. Further studies will be focused on how bile duct epithelial damage in donor livers leads to post-transplant cholangiopathies

Lecture Session II
CLINICAL HEPATOLOGY, SURGERY, LTX
14/02/2025, 03.15pm – 04.00pm, Lecture Hall

L2.01 Multimodal assessment of the skin-nerve-axis identifies specific patterns in patients with cholestatic liver disease-associated pruritus

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Background: Chronic pruritus is a common symptom in cholestatic liver diseases, significantly affecting quality of life and posing treatment challenges. Although potential pruritogens have been identified, the mechanisms that activate sensory nerve fibers in the skin remain unclear. This study assessed biological, neuroanatomical, microbial, and neurofunctional parameters in cholestatic patients with and without pruritus.

Methods: 61 patients with cholestatic liver diseases (PBC, PSC, and other chronic cholestasis) completed validated questionnaires, including mean itch intensity on a numeric rating scale (NRS). Skin punch biopsies were analyzed for intraepidermal nerve fiber density (IENFD), bile acid subspecies, and skin microbiome composition. Sensory nerve function protocols, transcutaneous si-

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nusoidal electrical stimulation targeting C-fibers, and microneurography were used to measure peripheral C-nerve activity.

Results: Patients were divided into high-pruritus (NRS ≥ 3) and low-pruritus (NRS < 3) groups. Both groups were comparable in age, gender, laboratory markers, and disease stage. Selective C-fiber stimulation induced dose-dependent itching in high-pruritus patients, while low-pruritus patients reported pain sensations, similar to healthy controls. IENFD was significantly reduced in cholestatic patients, particularly in those with high pruritus ($p < 0.001$). Bile acid subspecies analysis was successfully established with a subset of biopsies. Skin microbiome beta-diversity showed no differences between groups. A higher proportion of functionally altered C-fibers was recorded via microneurography in the high-pruritus group (59 %) compared to the low-pruritus group (36 %).

Conclusion: Cholestatic patients with pruritus display disrupted sensory nerve anatomy and function, suggesting that an altered skin-nerve axis plays a crucial role in the pathophysiology of cholestatic pruritus.

L2.02 HOPE treatment prior to organ transplant alters key immune modulators in patients receiving liver transplantation

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Background: Hypothermic oxygenated machine perfusion (HOPE) is recognized as a powerful strategy to protect allografts from ischemia-reperfusion injury. While its benefits on early graft function have been demonstrated in several trials, its specific impact on immune regulation post-transplant remains unexplored. This study aimed to investigate how HOPE influences key immune modulators in patients undergoing liver transplantation.

Methods: A single-center study of 100 patients receiving liver transplantation at the University Hospital RWTH Aachen between 2019 and 2024 was conducted. Of these, 38 received HOPE-treated donor livers, while 62 received livers with standard preservation treatment. Soluble immune markers, including T-cell immunoglobulin mucin domain-containing protein 3 (sTIM-3), sCD163 and programmed death ligand 1 (sPD-L1), were measured in patients` serum before surgery (baseline), within 24 hours post-surgery (POD1) and one week after surgery (POD7).

Results: Patients who received HOPE-treated livers experienced significantly fewer postoperative complications ($p = 0.04$). Post-surgery, these patients exhibited significantly lower sTIM-3 concentrations, a marker involved in T-cell activation, suggesting reduced immune activation. The macrophage activation marker sCD163 was also significantly reduced in the HOPE group. Conversely, sPD-L1, known to inhibit T-cell activation and to promote immune tolerance, was elevated in the HOPE-treated patients, potentially contributing to improved graft tolerance.

Conclusion: Our findings demonstrate that HOPE treatment has an immediate impact on the host immune response in patients following liver transplantation. The observed changes in sTIM-3, sCD163, and sPD-L1 provide early insights in immunemodulatory effects of HOPE and its potential to improve post-transplant outcomes by influencing key immune pathways.

L2.03 Right ventricular contractility predicts clearance of ascites after transjugular intrahepatic portosystemic shunt (TIPS)

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Background and aims: One major drawback of TIPS implantation is deterioration of cardiac function probably due to unrecognized cirrhotic cardiomyopathy (CCM). Reduced left ventricular global longitudinal strain (LV-GLS) has been shown to be associated with development of acute and chronic liver failure (ACLF) and reduced prognosis. However, as right ventricular function may primarily be affected by increased blood shunting due to TIPS implantation, we hypothesized that reduced right ventricular global longitudinal strain (RV-GLS) may be associated with (I) ascites persistence and (II) with development of ACLF and (III) reduced prognosis.

Methods: 144 patients with TIPS implantation due to recurrent ascites and RV-GLS measurement in pre-TIPS echocardiography were included in this study (NCT05782556). Primary endpoint was ascites persistence, ACLF after TIPS and transplantation-free survival.

Results: Median RV-GLS was -21.3 [-24.6-(-17.7)] % before TIPS implantation. RV-GLS was significantly associated with ascites persistence after TIPS implantation (sHR 1.16 [1.09-1.23], $p < 0.001$) adjusted for the FIPS score. RV-GLS was significantly worse (indicating less contractility) in patients with cardiac decompensation within 6 months after TIPS implantation (-17.7 % vs. -21.8 %; $p = 0.002$; sHR 1.15 [1.05-1.25], $p = 0.003$). Further, RV-GLS was also associated with the development of post-TIPS ACLF within 6 months (sHR 1.20 [1.11-1.29], $p < 0.001$) and with reduced transplantation-free survival (HR 1.25 [1.03-1.54], $p = 0.025$) adjusted for the FIPS score.

Conclusions: RV-GLS is an important predictor for ascites persistence and cardiac decompensation after TIPS implantation that my trigger ACLF and higher mortality. Therefore, RV-GLS may be a helpful additional tool for risk stratification in these patients.

Lecture Session III
METABOLISM (INCL. MASLD)
14/02/2025, 05.50pm – 06.35pm, Lecture Hall

L3.01 Interaktion zwischen metabolischen Faktoren und Genetik am Beispiel Alpha-1-Antitrypsin-Mangel

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Einleitung und Ziel: Ziel dieser Studie ist es, die Einflüsse von Diabetes und Body-Mass-Index (BMI) auf den Alpha-1-Antitrypsin-Mangel (AATM)-assoziierten Leberphänotyp sowie die Entwicklung hepatischer Endpunkte zu analysieren.

Methodik: Diese multizentrische Kohorte umfasst 1.890 Individuen mit schwerem AATM (Pi * ZZ), von denen 928 nach mind. 6 Monaten ein Follow-up erhielten. Hepatische Endpunkte wurden definiert als Lebertransplantation, leberbedingte Todesfälle und erste hepatische Dekompensation. Der Vergleich mit Individuen ohne (Pi * MM) sowie mit heterozygotem AATM (Pi * MZ) erfolgte mittels UK Biobank.

Ergebnis: Bei Baseline waren 67 Pi * ZZ Teilnehmende Diabetiker, 621 übergewichtig (BMI 25.0-29.9 kg/m2) und 305 adipös (BMI ≥ 30 kg/m2). Diabetiker wiesen im Vergleich zu Nicht-Diabetikern signifikant häufiger erhöhte ALT-, AST-, GGT-Werte auf (27-61 % vs. 13-24 %). Fortgeschrittene Fibrose war unter Diabetikern fünfmal häufiger (OR 4.7-5.4). In den normalgewichtigen Pi * ZZ-lern waren erhöhte Leberwerte selten (9-20 %), häufiger bei übergewichtigen (16-31 %; OR 1.9-2.4) und adipösen (23-37 %, OR 2.4-3.0). Fortgeschrittene Leberfibrose war fast fünfmal häufiger in adipösen (12 %, OR 4.3-4.8) und fast dreimal häufiger in übergewichtigen Individuen (8 %, OR 2.4-3.0). Während eines medianen Follow-ups von 4 Jahren erlebten 55 Pi * ZZler einen Leberendpunkt. Diabetiker und adipöse Teilnehmende wiesen ein erhöhtes Risiko für einen Leberendpunkt auf (HR = 3.8-6.2, p < 0.001). In der Pi * MZ- und Pi * MM-Kohorte waren die ORs für erhöhte Leberwerte, fortgeschrittene Fibrose und Leberendpunkte bei Diabetikern kleiner und bei Übergewicht und Adipositas vergleichbar zur Pi * ZZ-Kohorte.

Schlussfolgerung: Diabetes und Adipositas sind Genotyp-unabhängig mit erhöhten Lebersurrogatmarkern und einem erhöhten Risiko für eine Dekompensation verbunden, die prozentuale Auswirkung ist unter Pi * ZZ Individuen jedoch am prägnantesten. Diese Daten ermöglichen eine personalisierte Versorgung und Beratung.

L3.02 MLKLK219R Mutation Protects Against Diet-Induced MASLD but is Attenuated by Alcohol Consumption

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Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a complex clinical problem with significant societal and individual consequences. Up to date it has not been possible to clearly define molecular targets in order to treat MASLD in a comprehensive manner. The role of necroptosis in the pathogenesis of MASLD remains a topic of debate. Previous studies have yielded contradictory results when the necroptosis executioner, mixed lineage kinase domain-like pseudokinase (MLKL), was deleted in mice fed a high-fat/caloric diet. MLKL-/- mice showed either a complete rescue from diet-induced obesity, steatosis and liver damage or no protection at all. We show here, that MLKLK219R knock in mice, which are unable to execute necroptosis, despite the continued expression of the full-length protein, exhibit a protection from Western diet-induced MASLD. As such, they showed reduced weight gain, attenuated steatosis, reduced hepatitis and an increased glucose tolerance. Moreover, MLKLK219R mice showed decreased fat depots, but the lipid metabolism showed no differences compared to WT mice. In line, in vitro experiments revealed impaired differentiation and lipid storage of primary adipocytes isolated from inguinal white adipose tissue (iWAT) from MLKLK219R mice. Interestingly, the additional alcohol consumption, which represents an additional cardiometabolic risk factor for MASLD, partially attenuated the protective effects seen in the dietary model alone. MLKLK219R mice still showed differences in terms of body weight gain, steatosis, hepatitis and glucose tolerance, but liver inflammation was more prevalent.

Together, these results suggest a complex interplay between diet, necroptosis and additional metabolic risk factors in the pathogenesis of MASLD.

L3.03 A 5:2 intermittent fasting regimen ameliorates MASH and fibrosis and blunts HCC development via hepatic PPARα and PCK1

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DOI 10.1055/s-0044-1800996
The role and molecular mechanisms of intermittent fasting (IF) in metabolic dysfunction-associated steatohepatitis (MASH) and its transition to hepatocellular carcinoma (HCC) are unknown. Here, we identified that an IF 5:2 regimen prevents MASH development as well as ameliorates established MASH and fibrosis without affecting total calorie intake. Furthermore, the IF 5:2 regimen blunted MASH-HCC transition when applied therapeutically. The timing, length, and number of fasting cycles as well as the type of MASH diet were critical parameters determining the benefits of fasting. Combined proteome, transcriptome, and metabolome analyses identified that peroxisome-proliferator-activated receptor alpha (PPARα) and glucocorticoid-signaling-induced PCK1 act co-operatively as hepatic executors of the fasting response. In line with this, PPARα targets and PCK1 were reduced in human MASH. Notably, only fasting initiated during the active phase of mice robustly induced glucocorticoid signaling and free-fatty-acid-induced PPARα signaling. However, hepatocyte-specific glucocorticoid receptor deletion only partially abrogated the hepatic fasting response. In contrast, the combined knockdown of Ppara and Pck1 in vivo abolished the beneficial outcomes of fasting against inflammation and fibrosis. Moreover, overexpression of Pck1 alone or together with Ppara in vivo lowered hepatic triglycerides and steatosis. Our data support the notion that the IF 5:2 regimen is a promising intervention against MASH and subsequent liver cancer [1].
https://www.cell.com/cell-metabolism/fulltext/S1550-4131(24)00135-9
References
[1] Gallage et al. Cell Metabolism. 2024;

Lecture Session IV
TUMORS
15/02/2025, 09.10am – 09.55am, Lecture Hall

L4.01 Hepatocarcinogenesis and metabolic control of immunosuppression by ATF6a-driven ER-stress

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DOI 10.1055/s-0044-1800997
Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer-related mortality with limited therapy. While endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) are implicated in HCC, the role of the UPR-transducer activating transcription factor 6 alpha (ATF6α) remains unclear. In sharp contrast to the well-characterized role of ATF6α as an adaptive response to ER-stress, we here demonstrate that chronic ATF6α-activation is a hitherto unknown immune-metabolic master regulator in driving liver cancer: We establish ATF6α-activation in human chronic-hepatitis and HCC, unexpectedly associated with tumor-progression and correlated with reduced patient-survival. Chronic, hepatocyte-specific activation of ATF6α in mice induced early onset liver injury with ER-stress, DNA-damage, and hepatocyte-proliferation. Aged mice with hepatocyte-specific ATF6α-activation developed spontaneous liver-cancer due to oncogenic signaling in hepatocytes and an immunosuppressive microenvironment. Targeting Atf6 via germline, hepatocyte-specifically or by therapeutic hepatocyte-delivery of antisense-oligonucleotides dampened HCC in distinct preclinical liver-cancer models. Here, we identify chronic ATF6a-activation to drive ER-stress, bridging aberrant liver metabolism with immunosuppression in hepatocarcinogenesis.

L4.02 Association of the Genetic Variant VEGFA rs3025039 with Incidence and Prognosis of Cholangiocarcinoma

Autorinnen/Autoren Justus Pein[1], Saskia Niklisch[1], Deniz Uluk[1], Paul Horn[1], Carolin Victoria Schneider[2], Linda Hammerich[1], Cornelius Engelmann[1], Frederik Schliephake[1], Florian Roßner[1], David Horst[1], Johann Pratschke[1], Frank Tacke[1], Isabella Lurje[1], Georg Lurje[1]
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DOI 10.1055/s-0044-1800998
Background: Patients with cholangiocarcinoma (CCA) have a dismal prognosis, even when amenable to resection. We investigated genetic single-nucleotide polymorphisms (SNP) for their role in postoperative CCA prognosis, the susceptibility to CCA and in the tumor microenvironment.
Methods: Patients undergoing surgical CCA resection at Charité – Universitätsmedizin Berlin were genotyped for a SNP-panel including EGF, HIF1A, IL1B, VEGFA and ICAM1. Influence of the variants on population-based CCA susceptibility was investigated in UK Biobank. The role of intratumoral VEGFA expression and co-expression with other pathways was analyzed in an external iCCA dataset (Dong L.,Cancer Cell,2022).
Results: Of 221 patients undergoing CCA-surgery, 130 (58.8 %) had intrahepatic and 91 (41.2 %) perihilar CCA. Patients with the low-expression VEGFA T-allele (n = 56/221, 25.3 %) had longer cancer-specific survival in the full cohort (mean 88 months, 95 %CI 71.7-104.5 vs. 67 months, 95 %CI 51.4-82.4, p = 0.007), and both longer cancer-specific and overall survival in the intrahepatic subgroup (83 months, 95 %CI 63.5-103.8 vs. 48 months, 95 %CI 36.9-59.8, p = 0.040; 52 months, 95 %CI 37.1-67.4 vs. 29 months, 95 %CI 23.1-36.3, p = 0.028, respectively). Lower intratumoral VEGFA expression (159/244, 65.2 %) was associated with long-term mortality (2-year mortality 25.2 % vs. 43.5 %, log-rank p = 0.001). Multivariate analysis confirmed prognostic independence in both datasets. Simultaneously, carriers of the T-allele had a higher risk of CCA in the community-based UK Biobank (OR, 1.27, 95 %CI 1.08-1.49, p = 0.003).
Conclusion: Both the presence of the low-expression VEGFA variant (rs3025039T) and low VEGFA expression identify subgroups of patients with mitigated oncologic and overall prognosis, while presence of the rs3025039T was associated with increased risk of CCA.

L4.03 Activating Mucosal-Associated Invariant T (MAIT) cells for next generation immunotherapy of liver cancer

Autorinnen/Autoren Benjamin Ruf[1], Patrick Huang[2], Chi Ma[3], Mohamed-Reda Benmebarek[3], Rajiv Trehan[3], Kylynda Bauer[3], Yuta Myojin[3], Tim Greten[3], Firouzeh Korangy[3]
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DOI 10.1055/s-0044-1800999
Introduction: Mucosal-associated invariant T (MAIT) cells represent up to 30-40 % of T cells in the liver and they play a crucial role in the regulation of immunity and inflammation. We have recently shown that MAIT cells can contribute to anti-tumor activity in mice when activated and expanded with a prototypic activating MAIT T cell receptor ligand, 5-OP-RU. The aim of this work was to resolve the underlying mechanisms of MAIT-mediated anti-tumor immunity.
Methods: Syngeneic mouse models of orthotopic primary liver cancer and liver metastases were used to study anti-tumor activity of MAIT cells. A series of pharmacological depletion experiments and genomic conditional knockout mouse strains were used to identify additional effector immune cells and hu-

moral factors that mediate this effect. Single-cell RNA sequencing and high-dimensional flow cytometry provided crucial clues to underlying mechanisms.
Results: Combination immunotherapy of 5-OP-RU and CpG induced a strong systemic in vivo expansion and activation of MAIT. We show that MAIT cells are potent mediators of this anti-tumor activity across various models of liver cancer in vivo when activated by 5-OP-RU/CpG. Additional pharmacological depletion experiments and genomic conditional knockout mouse strains helped to identify effector cells and co-stimulatory effector molecules as critical components required for MAIT-induced tumor suppression.
Conclusion: MAIT cells play an important role in tumor immunology and represent an attractive new target for immunotherapy. Finely tuned, context-dependent mechanisms determine MAIT cell function in vivo. Targeted by treatment with MAIT ligand 5-OP-RU, they recruit a network of anti-tumor effector cells for liver cancer control.

Lecture Session V
VIRAL HEPATITIS AND IMMUNOLOGY
15/02/2025, 11.40am – 00.25pm, Lecture Hall

L5.01 A liver-tissue rheostat limits T cell receptor signaling and impairs function of virus-specific CD8 T cells in chronic viral hepatitis

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DOI 10.1055/s-0044-1801000

While acute hepatitis B virus (HBV) infections are controlled by a robust, antiviral CD8 T cell response, CD8 T cells are scarce and dysfunctional in chronic HBV infections. Here we demonstrate that the underlying mechanisms responsible for the functional inhibition of CD8 T cells during persistent hepatic infections is driven by the microenvironment of the liver.
To analyze antigen-specific immunity, we utilized a preclinical model system based on hepatotropic, recombinant adenoviruses to transfer the HBV genome into hepatocytes, thereby inducing acute-resolving or persistent infections. Subsequently, we conducted analysis on these tissues by using confocal microscopy and by isolating antigen-specific CD8 T cells and subjecting them to analysis by flow cytometry and RNA sequencing. Using in vitro co-cultures, we could further investigate interactions between hepatic cells and CD8 T cells.
In persistent viral infections antigen-specific CD8 T cells establish a close contact with liver sinusoidal endothelial cells (LSEC). These CD8 T cells revealed elevated protein kinase A (PKA) phosphorylation, increased activity of cAMP responsive element modulator (CREM) and consequently impaired T cell receptor signaling causing loss of effector function. Pharmacological blockade of the adenylyl-cyclase-cAMP-PKA axis as well as knockdown of adenylyl cyclase in T cells rescued the dysfunctional CD8 T cells. Co-culture of CD8 T cells with LSECs in vitro phenocopied increased PKA phosphorylation and revealed molecule exchange from LSECs to CD8 T cells.
Thus, close contact with LSECs during persistent, hepatotropic infections curbs the function of antigen-specific effector CD8 T cells in a rheostat-like fashion via the adenylyl cyclase-cAMP-PKA axis.

L5.02 Non-Selective Beta Blockers Reduce Inflammatory Bystander CD8 + T Cell Activation in Decompensated Cirrhosis

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DOI 10.1055/s-0044-1801001

Background & Aims: Liver cirrhosis is linked to immune dysfunction, involving both immunodeficiency and systemic inflammation. We have recently shown that bystander-activated CD8 + T cells contribute to this inflammation. Non-selective beta blockers (NSBBs) are used in cirrhosis to lower portal pressure and reduce decompensation risk. However, evidence suggests that NSBBs have also anti-inflammatory effects.
Methods: Thus, we analyzed the impact of NSBBs on CD8 + T cells in patients with decompensated cirrhosis (n = 31). Ex vivo phenotypic and in vitro functional analyses of blood and ascites CD8 + T cells were performed in matched patients on NSBB therapy (n = 18) compared to those without (n = 13).
Results: Ex vivo, CD8 + T cells expressed adrenergic beta receptors (ABR1 and ABR2). In vitro, propranolol reduced the frequency of bystander-activated (CD69 + CXCR6 +) CD8 + T cells and inhibited the production of pro-inflammatory cytokines upon IL12/15/18 stimulation, without affecting antigen-specific responses upon CMV peptide stimulation. Ex vivo phenotypic analysis confirmed the in vitro findings, showing reduced innate activation marker expression and lower frequencies of bystander-activated CD8 + T cells in patients on NSBB therapy compared to those without. Notably, plasma and ascites NSBB levels from selected patients negatively correlated with bystander CD8 + T cell frequencies.
Conclusions: Our study suggests that propranolol suppresses bystander-activated CD8 + T cells in decompensated cirrhosis while maintaining antigen-specific functions, highlighting NSBBs as a potential strategy to mitigate systemic inflammation in cirrhosis.

L5.03 New treatment targets in autoimmune hepatitis: detection using integrative omics and target validation in a proof of concept phase II clinical trial

Autorinnen/Autoren Jan Philipp Weltzsch[1], Yang Xu[1], Christoph Kilian[1], Babett Steglich[1], Christina Weiler-Normann[1], Michael Dudek[2], Laura Liebig[3], Malte Wehmeyer[1], Marcial Sebode[1], Johannes Hartl[1], Silja Steinmann[1], Ida Schregel[1], Ludwig Horst[1], Marius Böttcher[1], Joseph Tintelnot[1], Adrian Sagebiel[1], Ruba Al Shonikat[1], Jonas Wagner[1], Guido Rattay[1], Varshi Sivayoganathan[1], Ning Song[1], Nico Kaiser[1], Kolster Manuela[1], Maria Bono Merino[4], Alena Laschtowitz[5], Sören Alexander Weidemann[1], Christian F. Krebs[1], Victor Puelles[1], Eva Tolosa[1], Stefan Bonn[1], Norbert Hübner[6], Percy Knolle[2], Lorenz Adlung[1], Johannes Herkel[1], Christoph Schramm[1], Nicola Gagliani[1], Ansgar Wilhelm Lohse[1]
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DOI 10.1055/s-0044-1801002

Standard immunosuppression for autoimmune hepatitis (AIH) is non-specific with corticosteroids as drug of choice for remission induction. An improved understanding of the underlying pathophysiology is needed and could enable a tailored therapeutic approach and avoid side effects associated with standard therapy.
We combined systems and experimental immunology to map the cellular and molecular network involved in AIH and substantiated these findings by targeting tumor necrosis factor alpha (TNF), a key component of this network, in a clinical trial. Our computational models and functional experiments indicate that IL-15, produced by dendritic cells and macrophages, primes the cytotoxic activity of liver-resident CD8 T cells. The full activation of this cytotoxic pathway is driven by TNF released from clonally expanded, tissue-resident CD4 T cells. In response to TNF, hepatocytes from patients with AIH upregulate adhesion molecules for CD8 T cells and MHC class II molecules, making them susceptible to damage caused by both CD8 and CD4 T cells, perpetuating the inflamm-

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atory cycle. As a validation, we performed an open-label, proof-of-concept phase II trial using infliximab, a monoclonal antibody against TNF, as induction therapy of newly diagnosed, untreated AIH. We observed a rapid treatment response with 90 % ALT reduction within 24 weeks from baseline with this entirely steroid-free treatment. These findings provide a detailed and unified view of the cellular and molecular mechanisms underlying AIH, and identify TNF as a treatable target.

Poster Visit Session I
BASIC HEPATOLOGY (FIBROGENESIS, NPC)
14/02/2025, 12.30pm – 01.00pm

P1.01 Role of SOCS2 in Chemokine Signalling and its Impact on Hepatocellular Carcinoma Cells

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DOI 10.1055/s-0044-1801003

Background and Aims: Hepatocellular carcinoma (HCC) is a primary liver cancer characterized by tumor development. In Pakistan, HCC is the eighth most common cancer and the seventh leading cause of liver cancer deaths. Research highlights that HCC is closely associated with chronic inflammation. The Suppressor of Cytokine Signaling (SOCS) genes, particularly SOCS2, play a crucial role in cellular responses to extracellular signals, primarily through the janus kinase (JAK), signal transducer and activator of transcription (STAT) pathways. SOCS2 modulates cytokine responses, thereby maintaining homeostasis. This study, therefore, aims to investigate the role of SOCS2 in chemokine signaling pathways, and its impact on HCC cell proliferation and migration.
Methods: Human liver cell line HepG2 was used in the current study. HepG2 cells were transfected with pEGFP-C2-SOCS2 plasmid to overexpress SOCS2. The differential expression of cytokines (e.g., IL-6, IL-1β), and chemokines (e.g., CXCR4, CXCL6, CXCL12, CXCL14, CCL20), as well as JAK2 and STAT3, was determined through qPCR. HEK293 cells were used as control cells. Assays were performed to analyze the impact of SOCS2 overexpression in HCC cells.
Results: Findings of the study revealed that SOCS2 significantly suppressed the expression of STAT3, cytokines IL-6 and IL-1β, and chemokines CXCR4, CXCL6, CXCL12, and CCL20. Additionally, SOCS2 inhibited the migration and proliferation abilities of HCC cells compared to the control cells.
Conclusion: The study concludes that SOCS2 significantly reduces the expression of inflammatory mediators in HepG2 cells, thereby suppressing HCC progression.

P1.02 Amelioration of dyslipidemia and hepatic fibrosis by quercetin in comparison with silymarin

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DOI 10.1055/s-0044-1801004

Dyslipidemia leads to chronic liver injury which in turn causes fibrosis, cirrhosis and liver failure. Quercetin, a flavonoid has been reported to have a therapeutic benefit in liver diseases. This study is designed to explore the effects of quercetin on dyslipidemia and hepatic fibrosis, comparing it with silymarin. Forty male wistar rats were divided into control, diseased and two treatment groups. Thioacetamide (TAA) was used to induce disease in the diseased and treatment groups through intraperitoneal injections twice a week for 6 weeks. The treatment groups received daily doses of quercetin and silymarin for the same duration. Results indicated that both quercetin and silymarin modulated the levels of cholesterol, triglycerides, H.D.L., L.D.L. and V.L.D.L. compared to the diseased group. Gene analysis indicates that SMO, PTCH, SOCS3, IHH, SHH, HHIP, and Gli-3 were found to be statistically significant upregulated in diseased group, while remained stable in the treatment groups. Sudan black staining revealed abnormal deposition of phospholipids in the diseased group, but mild accumulation were observed in the quercetin and silymarin administered groups. In conclusion, quercetin demonstrated preventive potential by effectively stabilizing lipid profile, regulating gene expression related to fibrosis pathways and reducing abnormal lipid accumulation in the hepatocytes, with effects are comparable to those of silymarin.

P1.03 Die geschlechtsspezifische Regulation des Estradiol-Signalwegs in der portalen Hypertension

Autorinnen/Autoren Fabian Schachteli, Sabine Klein, Robert Schierwagen, Maximilian Joseph Brol, Jonel Trebicka, Frank Erhard Uschner
Institut University Hospital Muenster
DOI 10.1055/s-0044-1801005

Hintergrund: Die Leberzirrhose betrifft überwiegend männliche Patienten (60-70 %) und führt zu klinischen Symptomen (z.B. Bauchglatze), die durch Änderungen des Hormonstatus ausgelöst werden. So vermittelt Estradiol über den nukleären Estrogenrezeptor (ER) α u.a. fibrotische und metabolische Effekte. Der G-Protein gekoppelte Estrogen-Rezeptor (GPER) kann dagegen über kurzfristige Änderungen des Estradiol-Spiegels vasodilatativ und kardioprotektiv wirken, wurde aber bisher in der Leberzirrhose nicht untersucht.
Methodik: Die Induktion der Leberzirrhose erfolgte mittels Gallengangsligatur in männlichen (M), weiblichen (W) und weiblichen, ovariektomierten (W-OVX) Ratten. Ein Teil der Ratten (M; W-OVX) erhielt zusätzlich eine Estradiol-Einmalgabe. Anschließend erfolgte die Bestimmung der Estradiol-Konzentration, der mRNA und Protein-Expression der Estradiol-Rezeptoren und des NO-Signalweges, sowie eine invasive hämodynamische Messung und ex vivo Aortenringkontraktionen.
Ergebnisse: In (W-OVX) Ratten zeigte sich eine verminderte hepatische GPER Expression sowie eine reduzierte Aktivität des NO-Signalweges. Im extrahepatischen Gefäßsystem induzierte die OVX jedoch eine vermehrte GPER und ERα Expression im Vergleich zu (W)-Ratten. Dies führte zu einem erhöhten hepatisch portal-venösen Widerstand mit reduziertem systemischen Widerstand im Vergleich zu weiblichen Ratten ohne OVX, während die Aorta aus (W-OVX)-Ratten ex vivo eine erhöhte Kontraktilität zeigte. Die Gabe von Estradiol in (W-OVX) Ratten führte zu einer signifikanten Reduktion des portal-venösen Widerstands und des Portaldrucks im Vergleich zu W-OVX-Ratten ohne Estradiol. Interessanterweise konnte kein Einfluss von Estradiol auf die Rezeptorexpression oder Hämodynamik in (M)-Ratten beobachtet werden.
Diskussion: Ein chronischer Estradiol-Mangel führt im Tiermodell geschlechtsspezifisch zu einer Verschlechterung der portalen Hypertension, welche durch eine Estradiol-Gabe behoben werden kann. Die Beeinflussung des GPER-Signalweges könnte eine Therapie der portalen Hypertension darstellen.

P1.04 Rare but there: Novel approaches to discover hepatic mast cell functions in liver fibrosis

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DOI 10.1055/s-0044-1801006

Mast cells (MCs) are myeloid cells with immune modulatory properties. Upon activation they release pro-inflammatory mediators such as proteases and cytokines. It has been suggested that MCs may contribute to the development of liver fibrosis. However, investigating hepatic MC biology in mice is challenging due to low MC numbers and lack of suitable detection techniques. Here, we evaluated whether the expression strength of MC markers correlates with the degree of liver fibrosis in mice and aimed to determine the frequency and localization of hepatic MCs. We applied both a toxic (DEN/CCl4 treatment) and a genetic (Mdr2-/- mice) liver fibrosis model in C57BL/6 mice and found a significant correlation between fibrosis grade and expression of several established mast cell markers. This correlation was corroborated in patients with fibrosis and HCC as determined by using publicly available transcriptomics datasets. We used FACS to purify and isolate MCs from fibrotic mouse livers and verified MC signatures by qPCR analysis of MC-specific gene expression. Hepatic MCs were predominantly negative for Mast-Cell-Protease 5 (Mcpt5) and occurred at a low frequency (approximately 1-2 % of leucocytes). Using Molecular Cartography of fibrotic liver sections, we determined the spatial localization, expression signature, abundance (approximately 2 cells/mm2) and cellular environment of murine hepatic MCs .

In summary, we demonstrated the existence of MCs in murine fibrotic livers and defined an MC expression signature that correlates with the strength of fibrosis. These findings will help to study MC biology in liver disease more effectively in the future.

P1.05 Insulin determines TGF-β-induced epithelial-to-mesenchymal transition through FOXO1 cellular translocation

Autorinnen/Autoren Rui Liu[1], Rilu Feng[1], Chenhao Tong[1], Tao Lin[1], Stefan Munker[2], Matthias Ebert[3], Steven Dooley[1], Hua Wang[4], Honglei Weng[1]

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DOI 10.1055/s-0044-1801007

Background and Aims: It remains unknown why TGF-β easily induces epithelial-to-mesenchymal transition (EMT) in vitro, but is rarely detectable in vivo. This study scrutinizes the key role of FOXO1 in the TGF-β-induced EMT in hepatocytes, cholangiocytes and liver cancer cells.

Methods: Expression of FOXO1, EMT phenotype proteins such as SNAIL1 and E-cadherin, as well as phosphorylation of SMAD2/3 were examined by immunohistochemistry in liver tissue of patients. TGF-β-induced EMT and the role of insulin on EMT were investigated in cultured hepatocytes, cholangiocytes, HCC- and cholangiocarcinoma cells.

Results: Immunohistochemical staining shows robust SMAD2/3 phosphorylation in liver cells, including hepatocytes, cholangiocytes and cancer cells. However, the same cells maintain E-cadherin expression and do not express SNAIL1. In cultured hepatocytes, cholangiocytes and liver cancer cells, TGF-β stimulation induces expression of core EMT transcription factors SNAIL1 and SNAIL2, which subsequently leads to loss of E-cadherin expression upregulation of mesenchymal markers such as collagen and vimentin. SNAIL1 and SNAIL2 transcription requires both TGF-β-induced p-SMAD2/3-SMAD4 and FOXO1, which form a complex and bind to the promoters of SNAILs. Notably, insulin concentrations in medium of liver cells rapidly reduce to very low levels within 48h. Mechanistically, adding insulin into the culture medium inhibits TGF-β-induced SNAIL1/2 transcription, subsequent E-cadherin loss and EMT through phosphorylation and nuclear exclusion of FOXO1.

Conclusion: Given a key role of insulin in the regulation of systemic homeostasis, insulin depletion is an impossible mission in mammals. The presence of insulin impedes EMT of liver cells through phosphorylating FOXO1 in mammals.

P1.06 Cell type-specific role of CD44 in liver regeneration

Autorinnen/Autoren Sophia Bernatik[1], Franziska Ihli[1], Birgit Kohnke-Ertel[1], Fabian Delugré[1], Tanja Derowski[1], Simone Jörs[1], Carolin Mogler[2], Fabian Geisler[1], Roland Schmid[1], Ursula Ehmer[1]

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DOI 10.1055/s-0044-1801008

Background: CD44, a cellular adhesion molecule involved in liver regeneration and fibrosis, shows increased expression after liver injury. In cholestatic injury, it localizes around ductular reactions (DR) near the portal triad, while exhibiting a distinct pattern in hepatocytes during liver damage. However, its functional role in liver regeneration across different injury models remains uncertain.

Methods: This study investigated CD44's role in both acute and chronic liver injury using Cd44-/- (KO) mice compared to wildtype C57BL/6J mice in different liver damage models. Acute liver injury of hepatocytes was induced with a choline-deficient, ethionine-supplemented (CDE) diet, while acute bile duct injury was targeted using a DDC diet. Chronic cholestasis was modeled in Mdr2-/;Cd44-/- and Mdr2-/- mice. Liver tissue samples were collected and analyzed for CD44 expression and the proliferation marker KI67.

Results: In CDE diet-induced acute injury, CD44-deficient mice showed significantly lower number of proliferative (KI67 +) cells and decreased hepatocyte proliferation ($p = 0.0175$). In chronic cholestatic injury, a significant difference in DR proliferation ($p = 0.0421$) was observed between Mdr2-/-; Cd44-/- and Mdr2-/- mice after 3 months, with no change in hepatocyte proliferation. YAP (yes-associated protein) seems to be upregulated by CD44 in cholestatic injury models ($p = 0.0131$), potentially explaining the increased proliferation in DR. However, in the CDE diet model, targeting hepatocyte damage, Cd44 knockout does not affect YAP expression.

Conclusion: These findings highlight the cell type-specific and possibly injury-dependent role of CD44 in liver regeneration. We further aim to identify differential mechanisms mediating CD44-dependent cell proliferation.

P1.07 High copper levels induce inflammation and oxidative stress in a cell culture model of Wilson's disease

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DOI 10.1055/s-0044-1801009

The trans-Golgi network compartment acts as one of the major hubs controlling intracellular copper flux by hosting the copper transporter ATP7B. Dysfunctions in hepatocytes leads to cellular copper accumulation, culminating in autophagy, disruption of mitochondrial activity and cell death. Our aim was to compare the cellular responses to copper in wild type (WT) and ATP7B knockout

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(KO) hepatoma cells (HepG2) and investigating the effect of high copper levels on oxidative stress and inflammatory processes.
The response of HepG2-WT and HepG2-ATP7B-KO cells to CuCl2 was investigated through cell viability (CCK8 Assay) and transcriptional changes. Oxidative stress induction was assessed by GSH/GSSG ratio after CuCl2 treatment. NFκB and AP1 promoter activity was determined in vitro after CuCl2 treatment using the luciferase reporter and LEGENDPlexTM assay.
Multiple component analysis of GEO data (GSE107323) identified gene expression patterns in ATP7B-KO cells that are associated with autophagy, ion transport and cell intrinsic immunological signals (NFκB and AP1). Quantitative PCR partially validated the expression of selected genes. CuCl2 treatment resulted in upregulation of luciferase reporter activity in NFκB and AP1 promoter assays leading to secretion of TNF, IL1B and IL8. Oxidative stress, determined by decreased GSH/GSSG ratio and increased H2O2 levels was observed 24 h after CuCl2 treatment.
Inflammation is a self-defensive reaction that aims to eliminate or neutralise harmful stimuli and restore tissue integrity. The present data showed that in addition to metal ion transport and autophagy, processes involved in inflammation and oxidative stress were induced by high copper in an ATP7B-KO cell culture model.

P1.08 Proteomic profiling of FFPE liver specimens of biliary atresia patients

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DOI 10.1055/s-0044-1801010
Biliary atresia (BA) is a progressive, obstructive bile duct disease with neonatal onset and represents the leading cause of pediatric liver transplantation. The pathogenesis of BA is poorly understood and effective medical treatments are lacking.
Here, we characterized routine diagnostic formalin-fixed, paraffin-embedded (FFPE) liver specimens from BA patients (n = 14) using liquid chromatography-tandem mass spectrometry (LC-MS/MS), comparing them to control liver tissue samples with no overt histopathological changes (n = 7).
We identified over 5,000 proteins (protein groups), with more than 250 differentially abundant proteins (DAPs) based on log2 FC ± 1 and q-value < 0.05 thresholds. Network and enrichment analyses (STRING database) of increased DAPs revealed terms and pathways related to “actin filament organization” (GO), “extracellular space” (GO), “lysosome” (KEGG), “neutrophil degranulation,” “innate immune system” (Reactome Pathways), and “degradation pathway of sphingolipids” (WikiPathways), among others. Decreased DAPs were associated with enrichment terms, such as “alpha-amino acid metabolic process” (GO), “mitochondrial matrix” (GO), and “tyrosine metabolism” (KEGG).
Our data so far suggest that FFPE-LC-MS/MS may provide deeper insights into the molecular alterations in BA. We are currently expanding our analyses to other neonatal cholestatic liver diseases (e.g. PFIC) to identify disease-specific proteomic signatures. These may help to improve tissue-based diagnostics and enhance our understanding of the respective disease mechanisms, potentially leading to better therapeutic options.

P1.09 Intestinal Barrier Disruption in Liver Cirrhosis: Bacteria-mediated Cell Junction Degradation and p53-Mediated Paraptosis in Spontaneous Bacterial Peritonitis

Autorinnen/Autoren Karsten Gülow[1], Claudia Kunst[2], Rebecca Seitz[2], Nele Hahn[2], Julia Huber[2], Celina Macek[2], Martha Ernst[2], Carina Steindl[2], Patricia Mester-Pavel[2], Arne Kandulski[2], Christoph Brochhausen[3], Martina Mueller-Schilling[2]
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DOI 10.1055/s-0044-1801011
Background: Bacterial translocation from the gut to the abdominal cavity is critical in developing spontan bacterial peritonitis (SBP), a severe complication of liver cirrhosis. Cirrhosis patients have a reduced mucus layer, allowing direct contact between bacteria and intestinal epithelial cells. This interaction degrades cell junctions, causes tissue damage, and induces cellular stress (Haderer et al., 2022). We investigated bacterial effects on cell-cell junctions and examined the role of p53 family proteins—key regulators of cellular stress – in bacteria-induced paraptosis, a regulated form of cell death.
Methods: HCT-116 cells in 2D and 3D models, along with patient-derived organoids, were co-cultured with Escherichia coli strains (E. coli O6 or SBP-ascites isolates). Protein levels of occludin, E-cadherin, p53, and p73 were assessed by Western blot. The effects of bacteria on different p53 isoforms were studied using HCT-116 reporter cells with an exon-specific reporter system (Truong et al., 2021). Cell death kinetics and morphology were analyzed by flow cytometry and electron microscopy.
Results: Co-culture with E. coli caused significant occludin and E-cadherin degradation in both 2D and 3D models, with variations depending on bacterial strain and duration. While p53 isoforms associated with cell death increased, oncogenic isoforms were downregulated. This downregulation correlated with the induction of paraptosis, characterized by mitochondrial swelling and chromatin condensation. Furthermore, paraptosis kinetics were modulated by p53 family proteins.
Conclusion: Understanding these molecular mechanisms is essential for developing targeted therapies for SBP, focusing on bacteria-induced cell junction degradation, p53-mediated stress responses, and regulated cell death in the intestinal epithelium.

P1.10 Cell type specific decoding of TGF-β2 production, signaling and outcome in the dynamics of cholestatic liver disease

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DOI 10.1055/s-0044-1801012
In healthy and diseased livers, TGF-β2 is expressed in cholangiocytes and proliferating bile ducts with upregulation upon tissue damage and inflammation. How TGF-β2 and its downstream signaling pathways contribute to disease progression remains elusive. Here, we explored TGF-β2 expression dynamics, target cells and outcome with cell type specific resolution in patients with primary sclerosing cholangitis (PSC). Liver specimens from PSC patients were analysed by HE and IHC. Localization of TGF-β2 and TGFβR3 was determined via RNAscope. In silico analyses of 3 databases were performed to uncover upstream regulators of TGF-β2 expression including transcription factors. Cytokines, bile acids, and stressors were experimentally investigated in the human cholangiocyte cell line MMNK1 at mRNA and protein level using pharmacological inhibition of the respective signaling pathways. In PSC patients , TGF-β2 and TGFβR3 is predominantly located in non-parenchymal cells in periportal regions, indicating activated myofibroblasts and LSEC. Bioinformatic predictions of TGF-β2 promoter binding sites reveale d, among others, CREB1 as candidate for TGF-β2 induction. Bile acids including LCA, and combinations of

UCDA, CDA, DCA induced TGF-β2 in cholangiocytes. Cell stressors as H_2O_2 upregulated TGF-β2 in MMNK1. FXR inhibition with GW4064 blunted TGF-β2 expression induced by LCA or H_2O_2. Spatial transcriptomics in PSC livers are performed to comparative profile TGF-β2 signaling activation. This study provides a cell type-resolved analysis of TGF-β2 and TGF-βR3 expression in tissue of PSC patients. New potential target sites of TGF-β2-driven disease progression were determined suggesting inhibition of TGF-β2 expression by inhibiting bile acid or H2O2 function may provide a therapeutic

P1.11 A Biliary Organoid Approach to Study the Transition from Primary Sclerosing Cholangitis to Cholangiocarcinoma

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DOI 10.1055/s-0044-1801013

Background: The pathomechanisms underlying cholangiocarcinoma (CCC) from primary sclerosing cholangitis (PSC) remain unclear. There is an urgent need for innovative models to study the malignant transformation of PSC to CCC. 3D cell culture models, such as organoids, have shown great potential in studying PSC and CCC. We have established a novel protocol to generate organoids from bile and bile duct biopsies and now aim to apply this model to investigate PSC/CCC.

Methods: Bile fluid and bile duct biopsies from patients with PSC, CCC, and non-PSC/CCC were used to generate organoids. Organoids derived from bile fluid were characterized to determine their cellular origin using cholangiocyte- and hepatocyte-specific markers, which were analyzed by qPCR, Western blot, and immunofluorescence.

Results: Organoids were successfully generated from bile duct biopsies across different patient groups (control, PSC, CCC). Additionally, a novel protocol was developed for generating organoids from bile fluid, offering a less invasive alternative to biopsy collection. A panel of markers (Epcam, Cytokeratin-19, and Sox9) confirmed that the cells within the organoids are cholangiocytes.

Conclusion: Understanding the pathophysiological mechanisms driving the progression of PSC to CCC is critical for early diagnosis and the development of novel therapies. We successfully established a biliary organoid model, including a new method of generating organoids from bile fluid, which is less invasive. This model provides a platform for further research into PSC-CCC transformation and holds potential for creating highly personalized, patient-specific therapeutic approaches.

P1.12 NF-κB reactivation in TAK1LPC-KO mice induces lethal cholemic nephropathy

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Hepatocellular carcinoma (HCC), the common end-stage of chronic liver diseases, arises almost exclusively in the context of chronic hepatic inflammation. The transcription factor NF-κB serves as an important regulator of these inflammatory processes, although its role in hepatocarcinogenesis remains controversial. Conditional deletion of TAK1 (TGF-β-Activated-Kinase-1) in liver parenchymal cells (LPC; TAK1LPC-KO) in mice is characterized by the inactivation of NF-κB and concomitant activation of spontaneous hepatocyte apoptosis and cholangiocyte necroptosis. This activation of spontaneous cell death leads to cholestasis, liver inflammation, liver regeneration and eventually drives hepatocarcinogenesis. While apoptosis and necroptosis exert differential effects on cholestasis and hepatocarcinogenesis in TAK1LPC-KO mice, the impact of inactivated NF-κB signaling on disease progression remains unclear.

To investigate the impact of reactivating NF-κB signaling in TAK1LPC-KO mice, we genetically expressed a constitutively active form of the NF-κB-inducing kinase IKK2 (IKK2ca) with TAK1LPC-KO mice (TAK1LPC-KO/IKK2LPC-ca). NF-κB reactivation in TAK1LPC-KO mice abolished hepatocyte apoptosis and, consequently, prevented the strong compensatory cell proliferation and concomitant hepatocarcinogenesis. In contrast, hepatic NF-κB reactivation was unable to prevent cholangiocyte necroptosis, and in fact, it exacerbated the observed ductopenia. This is probably also due to the loss of compensatory proliferation by inhibiting apoptosis. Despite a robust transdifferentiation of hepatocytes into Sox9-positive progenitors, mature bile ducts could not be restored, resulting in lethal cholemic nephropathy.

P1.13 ATF3 modulates the extracellular microenvironment and inflammation pathways, protecting the mouse liver from carbon tetrachloride (CCl4)-induced fibrosis

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Introduction Liver fibrosis is a pathological process characterized by the excessive proliferation of connective tissue within the liver. Hepatic stellate cells (HSCs) are very important in fibrogenesis and are regulated by liver macrophages. Activating transcription factor 3 (ATF3) is critical in various inflammatory processes; however, its specific role in macrophage-mediated mechanisms of liver fibrosis remains largely unexplored.

Methods We investigated the role of ATF3 in liver fibrogenesis using mice with bone marrow macrophage-specific ATF3 knockout (ATF3-Δmyel). Mice were treated with intraperitoneal injections of CCl4. Immunohistochemistry (IHC) was used to assess the infiltration of different macrophage populations in liver tissue. Furthermore, we analyzed effector molecules and signaling pathways associated with the differences in fibrosis between the two groups.

Results Our data showed that liver fibrosis is more severe in ATF3-Δmyel mice. Based on our IHC results we found that the proportion of liver resident macrophages versus monocyte-derived macrophages changed. We observed a decrease in the expression of Kupffer cell in the ATF3-Δmyel group, at the same time, the expression of monocyte-derived macrophages increased. By analyzing potential effector molecules, we found that the liver tissue of the ATF3-Δmyel group had higher expression of chemokines. Pathway analysis showed that it was mainly the TGF-β/Smad pathway that seemed to be affected.

Discussion We were able to show the strong influence of ATF3 on macrophages and liver fibrosis. ATF3 has a crucial impact on recruitment and inflammatory activation of bone marrow-derived macrophages, thereby altering the severity of liver fibrosis.

Key words Liver fibrosis; macrophage; ATF3

P1.14 ALR induces EGF-receptor transactivation and impairs classical IL-6 signaling by activation of sheddase ADAM17

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ALR (Augmenter of Liver Regeneration), an anti-apoptotic and anti-inflammatory co-mitogen, is released upon and supportive for liver regeneration. Molecular details of how ALR addresses proliferation and inflammation are rare. Hepatoma cell lines were treated with recombinant human ALR (rALR) and/or specific inhibitors, followed by analysis of respective signaling pathways using immunoprecipitation, Western Blot, qRT-PCR and ELISA techniques. We present evidence for 1) rALR, irrespective of direct receptor binding, phosphorylates EGFR at cytoplasmic sites and subsequently activates downstream mediators Erk1/2 and Akt. 2) rALR abates IL-6-induced STAT3 phosphorylation and thereby reduces STAT3 target gene expression e.g. involved in inflammation (ICAM-1) and iron homeostasis (hepcidin, Transferrin-receptor, ZIP14). 3) rALR attenuates IL-6-induced STAT3 phosphorylation independent of EGFR activation and involvement of cytoplasmatic regulatory proteins (SOCS1/3, PIAS, JAK1/2, SHP1/2). 4) rALR enhances membrane tethered mature ADAM17/TACE expression thereby increasing its sheddase activity and subsequently release of membrane-bound EGFR ligands such as TGFα and soluble IL-6R subunit α (sgp80) from IL-6R. 5) rALR induces a G-protein coupled receptor (GPCR) and consequently phosphorylation of src, which in turn activates sheddase ADAM17. In conclusion, rALR activates sheddase ADAM17/TACE via GPCR and src, thereby releasing TGFα as well as sgp80. TGFα binds to and activates EGFR and its downstream signaling pathways (MAPK, PI3K/Akt) responsible for cell proliferation. Reduction of functional IL-6 receptor complex by IL-6R shedding leads to reduced STAT3 target gene expression with consequences for inflammation. ALR triggers ADAM17 thereby inducing EGFR trans-signaling and IL-6R shedding, and potentially other ADAM17 targets including their subsequent pathways.

P1.15 TGF-β-SMAD axis plays an essential role in the regulation of LPC proliferation and performing hepatocyte function in acute liver failure

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Background and Aims: Liver progenitor cells (LPCs) performing vital liver function can rescue patients with acute liver failure (ALF) from death. To date, key signaling controlling LPC proliferation and initiating liver functional gene expression remains largely unknown. This study investigates the crosstalk between TGF-β and EGF signaling in LPC proliferation and performing liver functional gene transcription.
Methods: LPC proliferation was examined in DDC-fed mice. Cell type specific spatial transcriptomics was performed on 80 regions of interest selected based on CK7 + LPCs, CK8 + /18 + hepatocytes and CD68 + macrophages from 4 ALF patients. Crosstalk between EGF and TGF-β signaling was investigated in LPC line HepaRG cells.
Results: TGF-β inhibits LPC proliferation through impeding G1-S phase transition. Accordingly, LPC proliferation is remarkably increased in DDC-fed SMAD7 transgenic mice, in which TGF-β-induced p-SMAD3 is inhibited, compared to those from wild-type mice. In ALF patients, immunohistochemistry revealed the existence of p-SMAD2 in robustly proliferative LPCs. Spatial transcriptomics demonstrate remarkable activation of both EGF receptor- and TGF-β-dependent genes, which might be driven by EGF and TGF-β from surrounding macrophages. In vitro, EGF prevails TGF-β-dependent proliferative inhibition through impeding SMAD3 binding to the c-MYC promoter. Interestingly, SMADs and c-MYC synergistically promote transcription of vital liver functional genes such as APOA and TF in LPCs.
Conclusions: TGF-β-SMAD signaling physiologically controls LPC proliferation. In ALF, TGF-β-dependent anti-proliferative effect is overtaken by macrophage-derived EGF signaling in activated LPCs. TGF-β-SMAD synergies EGF-c-MYC axis to regulate LPCs to perform hepatocyte function, which is essential for ALF patients' survival.

P1.16 Disease stage dependent efficacy of systemic apical sodium dependent bile acid transporter (ASBT) inhibition in mice with cholemic nephropathy

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Cholemic nephropathy (CN) is a severe complication of cholestasis-associated liver diseases with an unmet need for therapy. Recently, we identified the molecular mechanism of CN and showed that systemic ASBT inhibitors (ASBTi) almost completely prevented CN. However, it is not clear if ASBTi could also be used for therapy or if they are only effective in prevention. Here, we studied the therapeutic effect of ASBTi in CN. ASBTi was administered twice daily for four weeks into bile duct-ligated mice (BDL) mice at four distinct CN stages: (I) an early stage with predominantly proximal tubular epithelial cell (TEC) death events (BDL day 3); (II) leaky peritubular capillaries and tubular dilatation stage (BDL week 3); (III) fibrosis stage (BDL week 6); and (IV) an advanced stage with glomerular cysts and reduced ASBT expression (BDL week 9). ASBTi caused massive urinary excretion and systemic reduction of bile acids at all disease stages. Recovery of the BDL-induced body weight loss and improvement of kidney damage biomarkers and survival were observed when ASBTi was applied up to stage III. RNA-sequencing revealed amelioration of BDL-induced gene

expression changes by ASBTi at all stages with larger effect size at early stages. Histological analysis revealed significant reduction of replacement proliferation of TEC, cystic dilatation of renal tubules, capillary leakiness, and renal fibrosis when therapy was initiated up to stage III. Significant reduction of glomerular cysts was observed even when therapy started at stage IV. In conclusion, ASBTi showed a long therapeutic time-window in CN with stage-dependent effect size.

P1.17 Cross-cellular interactions between hepatocytes and cholangiocytes: The role of NF-κB pathways in hepatocarcinogenesis

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The transition from chronic injury to cancer in the liver is driven by responses of the microenvironment to distinct forms of liver cell death. Recently, we demonstrated that deletion of Traf2 and Caspase-8 in liver parenchymal cells activates canonical and non-canonical NF-κB pathways and sensitises towards necroptosis, converting hepatocytes into a sublethal state. This enabled the prolonged release of NF-κB-dependent alarmins and cytokines, thereby promoting ductular reaction, immune activation and hepatocarcinogenesis. Consequently, complete inactivation of NF-κB in hepatocytes and cholangiocytes accelerated the execution of necroptosis and converted necroptosis into a hypo-reactive cell death form, preventing initiation of hepatocarcinogenesis. Further analysis was conducted to elucidate the specific function of canonical vs. non-canonical NF κB in mediating liver injury and liver cancer development. For this purpose, we targeted additionally IKK2 or IKK1 as central activating kinases of both NF κB pathways as well as the NF κB subunits itself via p65 or NF κB2. Our results suggest an essential function of the non-canonical NF-κB signalling pathway in cholangiocytes, since its inactivation affects not only the ductular reaction but also the development of hepatocellular carcinoma. Moreover, if necroptosis and NF-κB are only active in one of the two cell compartments, which was confirmed through hepatocyte or cholangiocyte-specific knockout lines, neither inflammation nor carcinogenesis will occur. This implies the existence of a cross-cell control mechanism between hepatocytes and cholangiocytes, depending on cell death responses during hepatocarcinogenesis.

P1.18 Gender-specific development of liver injury and necroinflammation over time after hepatic ischaemia-reperfusion in a mouse model

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DOI 10.1055/s-0044-1801020

Introduction Ischaemia and reperfusion injury (IRI) are still one of the main problems after liver transplantation. Although many new findings on the pathomechnism of IRI have been elucidated over the past decades, little is known about how the course of the injury compares between the genders.

Methods In a hepatic IRI mouse model, we used 8-12 week old males and females of the C57BL6 strain. Part oft the liver was clamped for 45 min (or 90min) and reperfused after defined times (0 min, 20 min, 1 h, 2 h, 6 h, 24 h). Serum and liver tissue were analysed (ALT and AST; immunohistochemistry of CD3, Gr-1, NKp46 cells). Furthermore, cell death signalling pathways were analysed by rtPCR and Western blot.

Results We have seen significant increases in serum ALT in both genders after reperfusion at early time points. Females showed higher ALT levels at 1h post-reperfusion (400 U/l vs. 200 U/l), while in males higher ALT levels were detected at 48h (86 U/l vs. 37 U/l). CD3 + T cells were found to be higher in the female animals (2.6 vs. 7.8 cells/hpf), while no sex-specific differences were found in NKp46 + and Gr-1 + cells. In addition, we detected gender-specific differences in cell death activation (GPX4, ACSL4, PARP).

Discussion The early phase of hepatic ischaemia and reperfusion appears to develop differently in male and female mice. In particular, T cell-mediated necroinflammation and cell death appears to be significantly different, which may be important for the post-transplantation outcome.

P1.19 Efficacy of Software-Based Analysis of Mouse Liver Samples to Assess Cell Death

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DOI 10.1055/s-0044-1801021

Introduction Histopathological assessment of histological samples is a major challenge in terms of reliability and validity. Inter-rater differences in knowledge and training can vastly alter the scoring outcome of histological samples. The emergence of software utilizing neural networks in image analysis therefore offers great opportunity to approach this issue by offering software-based analysis methods aimed at improving histopathological analysis. We present a novel approach of delineating regions in mouse liver samples affected by cell death.

Material & Methods We introduced hepatic ischemia in a mouse model, followed by different times of reperfusion (0h, 20min, 1h, 2h, 6h, 24h and 48h). Liver tissue slides were stained with hematoxylin and eosin and digitalized. We then imported the digitalized slides into QuPath. In a first step, we used a neural-network-based pixel classifier to differentiate between areas affected by cell death and healthy areas within the sample. In a second step, we trained a second pixel classifier to further stratify the areas affected by cell death into three categories (early cell death, moderate cell death, extensive cell death).

Results Both the algorithm differentiating between healthy regions and regions experiencing cell death as well as the algorithm aimed at further stratifying the stages of cell death show high correlation with results obtained by human raters.

Conclusion Software-based histopathological image analysis using neural networks shows great promise in obtaining valid and reliable results for research. However, future research is necessary to make algorithms more robust to differences in staining and morphological abnormalities.

P1.20 Cellular cytokinesis, hyperplasia and hypertrophy define critical phases for liver regeneration efficiency

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Adult liver consists of hepatocytes with multiple ploidy classes. Quantifying ploidy and nuclearity distributions aids in developing models predicting regeneration efficiency after surgery.

Mice were subjected to 2/3 partial hepatectomy (PHx) and observed between 0.5 to 90 days. 3D reconstructed images were generated from liver tissue slices co-stained with antibodies to visualize sinusoidal networks, pericentral hepatocytes, S-phase, and cell nuclei. The 3D quantification of polyploidy, nuclearity and proliferation using TiQuant was mathematically modeled using a state-transition framework integrated into a 3D spatiotemporal liver regeneration model.

In healthy murine liver, more than 85 % of hepatocytes display nuclear polyploidy, with about 75 % being binucleated. Following PHx, about 50 % of binucleated hepatocytes are lost within 24 hours, indicating cytokinesis occurs without altering DNA content. From postoperative days 2 to 7, fewer nuclei per cell and increased DNA content suggest that DNA synthesis followed by cytokinesis is the primary regeneration mechanism. In later stages of regeneration, an increase in liver mass indicates that hypertrophy appears to be the predominant process. Mathematical models suggest that cytokinesis regulate the transition between mono- and binucleated cells during regeneration.

In conclusion, the process of liver regeneration can be divided in three phases: Cyokinesis without DNA synthesis, DNA synthesis followed by cytokinesis and hypertrophy to foster mass recovery. The percentage of binucleated hepatocytes is a predictor of the initial regeneration efficacy based on cytokinesis. This mechanism can be modeled using a state-transition framework integrated into a 3D spatio-temporal liver regeneration model, which simulates tissue-scale regenerative capacity.

P1.21 Comparative evaluation of standard machine learning models for liver fibrosis detection

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Background: Liver fibrosis progressing to cirrhosis is common in chronic liver disease, often leading to severe complications. Early detection is crucial, but current serological markers are inadequate. This prompted the analysis of explainable machine learning models to improve fibrosis detection.

Materials and Methods: We analyzed 655 patients who underwent liver biopsies, with clinical and laboratory parameters extracted retrospectively. Machine learning models, including tree-based models as well as classical and deep learning methods, were used for binary and three-stage liver staging. Independent validation was conducted on 302 patients from an independent hospital. Models were trained, hyperparameter-tuned, and tested on the collected data, demonstrating robust performance in fibrosis classification.

Results: The accuracy of machine learning models for predicting moderate liver fibrosis, severe fibrosis, and cirrhosis using blood markers was robust, with accuracies reaching up to 88.46 %, 92.31 %, and 82.69 % respectively. The tree-based models, LightGBM, XGBoost, and Random Forest, performed best across various classification tasks with an accuracy range of 82.69 % to 92.31 % for binary classification, and an accuracy of 76.95 % for three-stage classification, significantly outperforming FIB-4. SHAP analysis of the best ensemble models identified platelets, MCV, and INR, as the most influential biomarkers, with models using only these parameters achieving comparable performance to those using the full set of biomarkers for the cirrhosis classification (ACC max. 86.52 %).

Conclusion: Machine learning models can significantly improve the prediction of liver stages compared to serum-based tests alone. Platelets, MCV, and INR are considerably more important than previously thought.

P1.22 Using X-Ray Microscopy to Visualize 3D Architecture of Native Spheroid and Organoid Samples

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Introduction Organoid and spheroid cell cultures have revolutionized in-vitro research allowing for the creation of three-dimensional cell constructs that have the potential of closely mimicking conditions in-vivo. However, three-dimensional cell constructs cannot be visualized sufficiently by histology as only two-dimensional slices can be observed and further sample deterioration may occur in preparation. A novel approach to this issue is using X-ray tomography allowing for three-dimensional visualization and further segmentation of the sample without sample destruction.

Material & Methods Extrahepatic biliary organoids as well as hepatic spheroids were cultivated, and paraffin embedded. 5mm cylinders were cut and mounted for measurement using the ZEISS VersaXRM-500 Xradia micro-CT. Measurement consisted of an overview image of the sample allowing for a spatial identification of samples within the cylinder. Based on the overview, high resolution images were obtained. High resolution images were then reconstructed, and three-dimensional volumes of samples were obtained. Those were further segmented using a region-growing segmentation algorithm to obtain quantitative information about the sample volume.

Results Tissue slices obtained using X-ray tomography highly correlated with histological slides. Three-dimensional reconstruction allowed for the appreciation of morphological features of both organoids and spheroids, giving a clear indication of sample structure and spatial configuration.

Conclusion X-ray microscopy offers a novel approach to analyzing three-dimensional cell culture samples. Using unstained samples, it allows for high spatial resolution allowing for the appreciation of three-dimensional features without the need for the destruction of the samples which can still be used for histological analysis.

Poster Visit Session II
CLINICAL HEPATOLOGY, SURGERY, LTX
14/02/2025, 02.20pm – 03.15pm

P2.01 Assessment of Liver Fibrosis using Shear Wave Elastography in Comparison to FibroScan and Histology

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Chronic liver diseases can lead to fibrosis and eventually to cirrhosis. The extent of liver damage is crucial for therapy planning and prognosis. Liver damage can be measured by transient elastography (FibroScan) as a validated method for non-invasive quantification of liver stiffness, while shear wave elastography (SWE) is a newer ultrasound technique.

Our study included 214 patients with different liver diseases or with healthy livers. Liver stiffness was determined by both techniques, additionally, liver biopsy was performed in 33 patients. The aim of this study was to assess the value of SWE in comparison to FibroScan for determining different stages of fibrosis, and to correlate histology with SWE results.

The data showed a high correlation between the measurements from FibroScan and SWE (r = 0,925, "p < 0,001"). For SWE, cut-off-values were determined for detecting significant fibrosis (8,42 kPa) and cirrhosis (12,7 kPa) with high sensitivity and specificity. Moreover, the subgroup analysis of the biopsied patients showed that the overall histological grading (ρ = 0,909, "p < 0,001"), as well as the classification of advanced fibrosis or cirrhosis (ρ = 0,866, p = 0,05), positively correlated with the results of SWE.
The study illustrates that SWE is a reliable method for assessing liver stiffness, which can be integrated into modern ultrasound devices in order to take advantage of SWE, which is less susceptible for interfering factors such as ascites and obesity as compared to FibroScan.

P2.02 Microbial detection in peritonitis may be faster by automated molecular methods, but less sensitive, which also depends on cause of peritonitis

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Background Bacterial peritonitis is a serious infection, associated with high mortality in cirrhosis. Outcome is better the faster appropriate antibiotic treatment is given, but a wide variety of bacteria, antibiotic resistance and time consuming conventional microbiological work-up hamper rapid treatment. We aimed to clarify if a commercial automated multiplex PCR application (Unyvero IAI) might improve microbial diagnosis.
Methods We retrospectively analyzed patients with bacterial peritonitis on the background of cirrhosis or peritoneal dialysis (PD), in whom both conventional microbiological culture and the Unyvero IAI PCR application were performed, with respect to sensitivity and time to positive result.
Results Our patient cohort comprised 43 patients with peritonitis, n = 24 and n = 19 on the background of peritoneal dialysis (PD) and cirrhosis, respectively. Conventional culture was more sensitive compared to PCR in PD patients (71 versus 38 %; p = 0.04), which was less pronounced in cirrhosis (42 % versus 32 %; p = 0.74). While patterns of Gram-negative versus Gram-positive infection was comparable in PD and cirrhosis (35 % and 65 % in PD versus 29 % and 64 % with 7 % of Candida in cirrhosis), the main Gram-positive bacteria were coagulase-negative staphylococci in PD (35 %) while enterococci were frequent (21 %) in cirrhosis. Among the 11 pathogens not detected by PCR, 45 % were coagulase-negative staphylococci. Time to final positive result was 19 hours by PCR and 61 hours by conventional culture in real life ("p < 0.001").
Conclusion The automated multiplex PCR method yielded significantly faster, but less sensitive results, which was more relevant in peritonitis related to peritoneal dialysis than related to cirrhosis.

P2.03 Establishment and Validation of the new LIVERAID-ICU Score for Prognostic Assessment in Patients with Liver Cirrhosis and Infections in the Intensive Care Unit

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Introduction: Admission of patients with liver cirrhosis to the intensive care unit (ICU) due to infections is common and often leads to complications such as hepatic encephalopathy, renal failure, and circulatory insufficiency, significantly increasing mortality risk. Rapid diagnosis and treatment are essential for improving outcomes. In this context, scoring models are crucial in ICUs for accurately assessing disease severity and guiding therapeutic strategies. However, there are no specific scoring models to predict mortality in ICU patients with cirrhosis-related infections. This study aims to develop an improved prognostic scoring model that accurately predicts in-hospital mortality in liver cirrhosis patients with infections in the ICU.
Methods: A retrospective analysis was conducted on 620 patients with liver cirrhosis treated for infections between 2017 and 2019 in the gastroenterological ICU of the Department of Internal Medicine I at the University Hospital Regensburg. Based on this cohort, the LIVERAID (LIVER And Infectious Diseases)-ICU Score was developed and validated.
Results: The LIVERAID-ICU Score includes the Child-Pugh stage, serum urea level, and Horovitz quotient. It is designed for bedside calculation using simple clinical and laboratory data, without requiring additional tools. In the validation cohort, the LIVERAID-ICU Score demonstrated higher sensitivity and specificity (AUC = 0.83) in predicting in-hospital mortality compared to established scores like SOFA (p = 0.045), MELD (p = 0.097), Child (p < 0.001), and CLIF-C-ACLF (p < 0.001).
Conclusions: The newly developed LIVERAID-ICU Score is a robust, easy-to-use tool for predicting in-hospital mortality in liver cirrhosis patients with infections.

P2.04 Histopathologic Features of Biliary Atresia and Outcome Predictors of Kasai Portoenterostomy: A 10-Year Retrospective Study of a Philippine Cohort

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Objective: There is a dearth of information regarding the epidemiology of biliary atresia and outcomes of Kasai portoenterostomy (KPE) in the Philippines. We describe the histopathologic features of biliary atresia and identify outcome predictors of KPE in a local cohort.
Methodology This is a retrospective cohort study which reviewed all KPEs done in our institution from 2013 to 2023. Patients were categorized into having favorable or unfavorable outcomes based on a 3-month post-operative serum total bilirubin of more than 2 mg/dL or mortality at 3 months.
Results 71 patients underwent KPE, 41 of which had liver biopsies available for review. 28 had available outcomes. Fibrosis, ductular reaction, and portal tract cellular infiltrates were consistently present in all samples examined, with varying degrees of portal tract edema and giant cell transformation. High AST to Platelet Ratio Index pre-operatively was associated with a poorer prognosis. The presence of visible bile plugs in biopsy samples was the only histologic feature that had a significant correlation with the post-KPE outcome.
Conclusion: This study demonstrated the spectrum of histologic features in biliary atresia. Identifying significant laboratory and histologic features that can help predict native liver survival is essential in prognostication and in tailoring management goals post-KPE, especially in settings where liver transplant is not readily available.

P2.05 Interleukin-22 (IL-22) is associated with progression to Acute-on-Chronic Liver Failure (ACLF) and short-term mortality in cirrhosis

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Background and Aims IL-22 has the ability to promote hepatoprotective or adverse properties. Schwarzkopf et al. characterized the role of IL-22 in ACLF.

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We analyzed associations between IL-22 plasma levels and clinical endpoints of patients with liver cirrhosis with focus on ACLF dynamic.

Method Clinical data of patients (N = 204) with liver cirrhosis in respect to ACLF were analyzed retrospectively. IL-22 plasma concentrations were quantified at baseline and associated with clinical endpoints. Plasma levels of IL-22 were measured using ELISA.

Results Plasma levels of IL-22 were almost identical in patients with compensation compared with healthy controls. Patients with decompensation showed significantly higher IL-22 levels (healthy vs. decomp., P = 0,005) with further increase in patients with ACLF (healthy vs. ACLF, P = < 0,0001). Different courses of decompensation (chronic, acute stable, acute unstable) showed no significant changes in IL-22, whereas patients with pre-ACLF showed significantly higher IL-22 plasma concentrations in comparison to acute unstable decompensated patients (P = 0,0014). Further analysis revealed that IL-22 concentrations were low in patients without current ACLF and without progression to ACLF. Patients who recovered from ACLF during the observation period of 90 days showed intermediate IL-22 plasma levels. Highest IL-22 concentrations were observed in patients with stable ACLF and progression to ACLF within 90 days. Furthermore, IL-22 plasma levels were significantly higher in patients who died within 30 days independent of the presence of ACLF.

Conclusion IL-22 shows strong association with adverse outcomes of liver cirrhosis suggesting the use of IL-22 as a biomarker for prediction of ACLF dynamic.

P2.06 Liver Transplantation after Immune Checkpoint Inhibition in HCC Patients: Insights from an International Multicenter Registry

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Introduction: The use of immune checkpoint inhibitors (ICI) for hepatocellular carcinoma (HCC) has become standard in advanced stage and in selected cases also in intermediate stage (BCLC B) HCC. In suitable BCLC B patients with good tumor response upon ICI treatment, liver transplantation (LTx) without standard exception for HCC can be considered. However, the feasibility of LTx after ICI therapy remains debated due to the risk of potentially fatal allograft rejection. To analyze the outcome of LTx following ICI therapy, a multicenter registry was established.

Methods: Data from HCC patients transplanted after ICI treatment were collected from nine European transplant centers. Documentation included patient and tumor characteristics, ICI regimens, time between ICI and LTx, and adverse events. Overall and rejection-free survival rates were assessed using the log-rank test.

Results: Twelve patients underwent LTx for HCC after ICI therapy. Most patients (10/12) received Atezolizumab/Bevacizumab. 12-months survival rate was 78 % (7/9) with a median follow-up of 508 days. Three rejection episodes were documented: one fatal rejection 21 days after LTx and two non-fatal rejections at 8 days and five months, both successfully managed with an increase in immunosuppressive therapy. Importantly, the fatal rejection correlated with a brief ICI wash-out of only 13 days.

Conclusion: A 25 % overall rejection rate was observed in LTx patients after ICI. Importantly, the interval between ICI and LTx seems to be a predictor of rejection severity. This study shows that LTX following ICI therapy is safe for patients as long if sufficient ICI wash-out is considered.

P2.07 Therapeutic plasma exchange in patients with acute on chronic liver failure and severe coagulation disorder: a case series

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Background Bleeding complications with unsuccessful conventional stabilization are common in patients with acute on chronic liver failure (ACLF). A therapeutic plasma exchange (TPE), in which the recipient's plasma is replaced with healthy donor plasma, could be a beneficial procedure for these patients. In our single center case series, we examined the effect of TPE on coagulation parameters and the amount of transfusion products needed before and after TPE.

Study design and methods Inclusion of patients with ACLF and severe coagulation disorder. ROTEM analysis, coagulation parameters and the amount of transfusion products were compared before and after TPE.

Results 11 patients were included. While hemoglobin and platelet count were similar before and after TPE, both INR and aPTT were improved significantly (INR: 3.3 (2.5-7) vs. 1.8 (1.5-2.1), p-value < 0.001, aPTT: 172 (122-180) s vs. 81 (56-90) s, p-value 0.005). In ROTEM analysis, a significant improvement in clotting time was achieved in EXTEM, INTEM and FIBTEM. The need for transfusion of platelet concentrates, PCC and fibrinogen was significantly lower after TPE (platelet concentrates: 1.5 (1-2) vs. 0 (0-0), p-value 0.002, PCC: 3000 (1200-6200) I.U. vs. 0 (0-1500) I.U., p-value 0.0047, fibrinogen: 6 (2-9) g vs. 2 (0.75-3.25) g, p-value 0.01).

Discussion Blood plasma replacement by TPE could be an efficient option to stabilize coagulation in patients with ACLF and severe coagulation disorder. TPE can reduce the amount of required transfusion products, which could lead to stabilization of pro- and anti-coagulant factors in addition to a reduction in health care costs.

P2.08 Factor VIII/protein C ratio predicts post-TIPS transplantation-free survival

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Background and aims Factor VIII/protein C (FVIII/PC) ratio has been shown to be of prognostic relevance in patients with advanced chronic liver disease (ACLD) and it can predict decompensating events. However, its prognostic relevance after resolution of portal hypertension by implantation of a transjugular intrahepatic portosystemic shunt (TIPS) is unkown. Therefore, the aim of

this study was to analyze if FVIII/PC can predict further decompensation and mortality after TIPS.

Methods 142 patients with TIPS implantation and measurement of FVIII and PC were included in this study (NCT05782556). Differences between FVIII/PC and the indication for TIPS implantation and its correlation with established prognostic scores were evaluated. The predictive impact of FVIII/PC for predicting further decompensating events after TIPS was evaluated using uni- and multivariable competing-risk and Cox regression models.

Results Median FVIII/PC was 6.1 [4.2-8.6] before TIPS implantation. There were no difiierences between different indications for TIPS implantation (recurrent ascites, secondary prophylaxis of variceal bleeding or pre-emptive TIPS). FVIII/PC was not associated with further decompensation after TIPS implantation (sHR 1.03 [0.98-1.09], p = 0.191), development of acute on chronic liver failure (sHR 1.00 [0.93-1.08], p = 0.948, persistence of ascites (sHR 1.03 [0.95-1.13], p = 0.463 but with hepatic encephalopathy (HE, sHR 1.11 [1.03-1.20], p = 0.006) adjusted for the FIPS score. FVIII/PC was also associated with reduced transplantation-free survival (HR 1.10 [1.02-1.20], p = 0.013).

Conclusions FVIII/PC is associated with post-TIPS HE and predicts transplantation-free survival. Further, analyses are necessary to assess the pathophysiological links between HE and FVIII/PC.

P2.09 Excessive production and cleavage of fibroblast growth factor 23 in decompensated cirrhosis: pathophysiological and clinical implications

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Background The pleiotropic functions of fibroblast growth factor 23 (FGF23) beyond as phosphate hormone are increasingly recognized. Recently, the C-terminal proteolytic fragment of FGF23 (Cter-FGF23), previously considered inactive, has been shown to ameliorate inflammation-induced anemia by inhibiting hepcidin secretion. In the present study we assessed if FGF23 and Cter-FGF23 are also regulated in liver cirrhosis.

Methods Olink analysis was used to identify plasma proteins and mediators associated with decompensated cirrhosis and acute-on-chronic liver failure (ACLF). In two independent cohorts of hospitalized patients with cirrhosis, we quantified intact and Cter-FGF23 and assessed associations with clinical outcomes of cirrhosis, parameters of iron metabolism and inflammation.

Results FGF23 was one of the most strongly upregulated mediators in a panel of 76 plasma proteins (quantified by Olink analysis) in acute decompensation (AD) and acute-on-chronic liver failure (ACLF) compared to compensated cirrhosis. Cter-FGF23 concentrations exceeded intact FGF23 concentrations substantially in many patients, in particular in those with decompensated cirrhosis or ACLF, suggesting increased FGF23 cleavage and excessive production of the cleaved Cter-FGF23 in these patients. Notably, Cter-FGF23, but not intact FGF23, was a strong predictor of 30-day and 1-year mortality. Anemia was a frequent complication of AD and ACLF (92 % and 95 %, respectively). Cter-FGF23 (but not intact FGF23) was an independent predictor of anemia, and Cter-FGF23 correlated with hepcidin concentration and other determinants of iron metabolism.

Conclusion Cter-FGF23 might be a promising prognostic biomarker in patients with advanced liver cirrhosis and seems to play a role in iron metabolism in cirrhosis.

P2.10 Downregulation of interleukine-6 receptors on ascitic T cells may shape the immune compartment in the peritoneal cavity

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Background and Aims In patients with advanced liver cirrhosis, high cytokine levels in ascites indicate a dysregulated overshooting immune response in the peritoneal cavity. While it is already known that impaired intestinal permeability and bacterial translocation are triggers for this hyperinflammation, the resulting cellular mechanisms are not yet sufficiently understood. This study aims to analyze the effect of dysregulated interleukin-6 (IL-6) signaling on the T cell compartment in ascites.

Methods Ascites and peripheral blood samples from patients with liver cirrhosis were collected and immune cells were isolated. Cytokine and soluble receptor concentrations were determined by ELISA. T cell phenotype and surface receptor expression was assessed by flow cytometry.

Results In ascites, the natural IL-6 trans-signaling inhibitor soluble gp130 was found to be 14.4-fold higher than the soluble IL-6 receptor (IL-6R), suggesting that IL-6 trans-signaling is blocked. The surface expression of IL-6R and gp130 was significantly lower among T cells within ascites compared to those circulating in blood (P = 0.009 and P = 0.036, respectively). Overall, IL-6 classical-signaling reactive gp130 + IL-6R + T cells were significantly decreased in ascites compared to blood (P = 0.019). However, CD4 + Th17 cells, whose differentiation is dependent on IL-6, were significantly more enriched in ascites than in blood (P = 0.0025).

Conclusion We suggest that the blockade of trans-signaling and downregulation of IL-6 surface receptors on T cells may represent compensatory mechanisms to mitigate excessive IL-6 signaling induced by high IL-6 levels in ascites. Nevertheless, IL-6 signaling seems to shape the immune compartment in the peritoneal cavity and thus may contribute to systemic hyperinflammation.

P2.11 RNA profiling and respiratory measurements of liver tissue reveals profound hepatic mitochondrial dysfunction in patients with acute-on-chronic liver failure

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Background and Aims Acute-on-chronic liver failure (ACLF) is characterized by systemic inflammation, organ failures and high short-term mortality. Metabolome analysis have identified inflammation-induced mitochondrial dysfunction as a hallmark of ACLF. Here, we aimed to characterize mitochondrial function and associated pathways in liver specimens of patients throughout the clinical course of cirrhosis.

Method Liver tissue was collected from patients with liver cirrhosis with (N = 15) or without ACLF (N = 15) which underwent liver transplantation. Bulk RNA sequencing was performed, and data processed by bioinformatic analysis. Mitochondrial respiration was measured by respirometry (Oroboros).

Results Profound changes in the liver transcriptome were observed between patients with compensated cirrhosis, decompensated cirrhosis and ACLF. In particular, ACLF was associated with distinct changes of the hepatic transcriptome. Overall, 230 genes were significantly changed in patients with decompensated cirrhosis / ACLF compared to compensated cirrhosis. Deconvolution analysis revealed significant changes in the cellular composition of the liver in

ACLF regarding immune cell and hepatocyte subpopulations. Moreover, pathway analysis revealed functional enrichment in mitochondrial dysfunction, such as changes in mitochondrial translation (mitochondrial ribosomal protein family, $P \leq 0.001$). Additionally, structural changes such as mitochondrial swelling and decrease in cristae could be observed by electron microscopy. Analysis of mitochondrial respiration showed profound changes in the functionality of mitochondrial respiratory complexes in decompensated cirrhosis and in particular in ACLF.

Conclusion ACLF is associated with distinct signatures of the hepatic transcriptome. Among others, these transcriptional changes affect pathways regulating mitochondrial function, resulting in profound mitochondrial dysfunction in the liver of patients with ACLF.

P2.12 Clinically significant itch on the PBC-40 corresponds to moderate-severe itch on the worst itch numerical rating scale (NRS) in patients with pruritus and primary biliary cholangitis (PBC)

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Background: Cholestatic pruritus is a debilitating symptom of PBC; the impact of itch on health-related quality of life (HRQoL) is not routinely assessed. To evaluate pruritus burden, we assessed the relationships between pruritus severity measures and HRQoL assessed by PBC-40, EQ-5D, and Beck Depression Inventory-II (BDI-II).

Methods: Data were pooled from an observational 8-day PRO validation study (N = 141) and the Phase2b GLIMMER study (NCT02966834; N = 147). Patients recorded their worst itch twice daily using a 0–10 scale (WI-NRS). The worst daily itch (WDI) score was the higher of the two daily responses. Weekly itch score (WIS) was calculated as the average of the WDI scores over 7 days. EQ-5D and PBC-40 (7-day recall) were used to assess HRQoL; BDI-II assessed symptoms of depression.

Results: Patients with a WIS of 4 reported a mean(± SD) PBC-40 itch domain (PBC-40ID) score of 7.2(± 2.5). There was a strong correlation (r = 0.69) between PBC-40ID scores and WIS. At higher WDI scores, EQ-5D utility scores indicated worse HRQoL. There were moderate–strong correlations between EQ-5D utility scores and all PBC-40 domains (r = 0.41–0.56), and with BDI-II score (r = 0.61). Mean BDI-II scores were worse amongst those with the most severe pruritus.

Conclusions: The cutoff used to define moderate–severe pruritus on WIS (≥ 4) identifies the population with clinically significant itch (≥ 7) on PBC-40ID. More severe pruritus was linked to worse HRQoL and higher depression levels. Use of either WI-NRS or PBC-40ID can identify patients in need of pruritus management to improve their HRQoL.

P2.13 Insufficient control of cholestatic pruritus in primary biliary cholangitis (PBC) with current therapies: baseline data from the ongoing Phase 3 GLISTEN (Global Linerixibat Itch STudy of Efficacy and safety iN PBC) trial

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Background: Cholestatic pruritus is common in PBC, negatively impacts quality of life and efficacy of current therapies is limited. Linerixibat, an oral ileal bile acid transporter inhibitor, is currently in development for the treatment of pruritus in PBC. Here, we report baseline (BL) characteristics and pruritus treatment history in GLISTEN to characterize unmet patients' needs.

Methods: GLISTEN (NCT04950127) is an ongoing Phase 3, placebo-controlled study in adults with PBC and moderate–severe pruritus. Pruritus severity is assessed using a worst itch 0–10 numerical rating scale (NRS). Participants are either treatment-naïve, have received prior therapy or continue stable concomitant therapies for pruritus. A preliminary analysis of BL characteristics is presented.

Results: Data from 227 participants were included. At BL, 42 % had moderate pruritus (NRS 4-6), 58 % severe (NRS ≥ 7); 51 % had alkaline phosphatase levels < 1.67x upper limit of normal. The most common prior therapies for pruritus were antihistamines, bile acid binding resins, rifampin, and fibrates. Where specified, main reasons for stopping these treatments included lack of efficacy (83 %, 55 %, 69 %, and 13 %, respectively) and lack of tolerability (9 %, 45 %, 38 %, and 88 %, respectively). In total, 42 % of participants were receiving concomitant therapy that may reduce pruritus, including 22 % receiving fibrates.

Conclusion: Prior use of bile acid binding resins was low in the GLISTEN population despite its first-line position in treatment guidelines. Regardless of the use of multiple "off label" therapies, participants had evidence of ongoing moderate–severe pruritus, underscoring the unmet need for a targeted therapy for pruritus in PBC.

P2.14 Acute-on-Chronic Liver Failure Triggered by Streptococcus pyogenes Superinfection from a Mosquito Bite: A Case Report

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Introduction Global climate change has led to an increase in mosquito populations across Europe, a factor that is often overlooked in clinical practice. This case underscores the emerging health risks posed by indirect consequences of global warming, particularly for patients with pre-existing liver disease.

Case Report A 43-year-old male with known cirrhosis presented to a peripheral hospital following a fall at home, with complaints of chills, severe myalgia, and fever (39.2 °C). Physical examination was unremarkable, but laboratory results revealed infection, thrombocytopenia, and microcytic anemia. Ultrasound confirmed cirrhosis, while a CT scan failed to identify an infectious focus. The patient suffered a tonic-clonic seizure on the day of admission, followed by a marked increase in bilirubin and inflammatory markers, prompting transfer to a hepatology unit.

Clinical examination revealed a superinfected bite wound on the right shoulder, reported as a mosquito bite sustained four weeks earlier. The wound, characterized by intractable pruritus and intermittent purulent discharge, was identified as the likely entry point for infection. Blood cultures confirmed Streptococcus pyogenes infection. Despite antibiotic therapy, the patient developed acute-on-chronic liver failure (ACLF) with coagulopathy and acute kidney injury. PET-CT revealed enhanced FDG uptake at the bite site.

Conclusion This case highlights the potential for superinfected mosquito bites to cause severe infections, particularly in immunocompromised patients with liver cirrhosis. As global warming accelerates the spread of mosquitoes in tem-

perate climates, healthcare providers must remain vigilant for atypical infections contributing to ACLF.

P2.15 Alkaline phosphatase and bilirubin as predictors of long-term outcomes in primary biliary cholangitis: A systematic literature review

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Background: This systematic literature review (SLR) aimed to identify real-world studies investigating associations between biomarkers alkaline phosphatase (ALP) and total bilirubin, and long-term clinical and humanistic outcomes in primary biliary cholangitis (PBC).

Methods: Databases (MEDLINE, Embase, CDSR and DARE) were searched in April 2024, supplemented by searches of conference proceedings since 2022, current clinical guidelines and SLR bibliographies. Observational studies reporting univariate or multivariate analyses of associations between ALP and/or bilirubin and clinical or humanistic outcomes in adults with PBC were included. Studies with ≤ 25 patients and selected PBC cohorts were deprioritised. A narrative synthesis of the included studies is presented.

Results: Seventy-eight publications reporting on 73 unique studies were included; 68 studies quantified prognostic effects of serum levels of ALP and/or bilirubin on outcomes, and 11 studies assessed the accuracy of predictive models including ALP and/or bilirubin. Overall, 72.9 % (35/48), 91.7 % (55/60) and 91.7 % (11/12) of prognostic studies reported a significant association ($p < 0.05$) between ALP, bilirubin, or composite measures including ALP and/or bilirubin (e.g. GLOBE), respectively, and long-term outcomes, e.g. overall survival and transplant-free survival. Few studies evaluated the association between ALP and/or bilirubin and fatigue (n = 3), pruritus (n = 3) or PBC-40 score (n = 2).

Conclusion: These results suggest that measures of bilirubin, ALP and composites including ALP and/or bilirubin are effective surrogate markers of clinically- and patient-relevant long-term clinical outcomes in PBC in real-world contexts. More studies reported a significant association with bilirubin than ALP, suggesting bilirubin as a potentially better predictor of long-term clinical outcomes than ALP.

P2.16 Influence of low-dose acetylsalicylic acid on renal function in patients with liver cirrhosis and ascites

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Background/Aims Non-steroidal anti-inflammatory drugs are not recommended in cirrhosis with ascites due to acute kidney injury (AKI) risk. Nowadays, more patients require low-dose acetylsalicylic acid (ASA) for cardiovascular prophylaxis. This study aims to evaluate the impact of low-dose ASA on transplant-free survival, renal function, and further decompensation in patients with cirrhosis and ascites.

Methods This is a retrospective unicentric analysis of 1170 consecutive cases with cirrhosis and ascites from 2019 to 2022. Baseline data, including ASA intake, were collected. Follow-up was extended until 12/2023. Endpoints included transplant-free survival, changes in serum creatinine, incidence of AKI, and further decompensation. Variables were compared with T-student and Mann-Whitney U test. Propensity score matching (PSM) and Cox regression analysis was performed.

Results 303 patients (53, 17.5 % on ASA) were followed for a median of 350 days. Thirteen (31.0 %) ASA patients and 57 (28.5 %) controls died or received a transplant, with no difference in transplant-free survival (HR 1.13, 95 % CI 0.62-2.10). Seven (16.7 %) ASA patients developed AKI, of which three (42.9 %) were hepatorenal syndrome (HRS-AKI), compared to 23 (11.4 %) AKI cases [7 (30.4 %) HRS-AKI] in controls, with no significant differences (AKI: HR 1.46, 95 % CI 0.63-3.41; HRS-AKI: HR 1.94, 95 % CI 0.50-7.51). After PSM, no differences were observed in transplant-free survival (HR 1.18, 95 % CI 0.52-2.64) or AKI/AKI-HRS (AKI: HR 1.83, 95 % CI 0.53-6.29; AKI-HRS: HR 2.79, 95 % CI 0.29-26.84).

Conclusions Intake of low-dose ASA does not affect transplant-free survival, renal function during follow-up and the incidence of AKI in patients with cirrhosis and ascites.

P2.17 Novel predictors of major adverse liver outcomes employing the UK Biobank

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Background: Since liver disease is often clinically unapparent, plasma biomarkers predicting the future development of major adverse liver outcomes (MALO) are urgently needed. Therefore, we assessed the usefulness of a novel, proximity extension assay (PEA)-based high-throughput proteomic technique to predict MALOs.

Methods: PEA quantified > 2900 plasma proteins in 53003 participants (490 MALOs) from the UK Biobank (UKB) and in a validation cohort of 287 subjects with severe alpha1-antitrypsin deficiency (30 MALOs). In UKB, we also studied two high-risk sub-cohorts: obese and diabetic subjects. PEA-based values were compared to measurements with routine techniques. Differential abundance analysis and multivariable logistic regression were used to discover predictors.

Results: In UKB, PEA-based measurement of gamma-glutamyl transferase (GGT) and aspartate aminotransferase correlated well with routine values (r = 0.91/0.68). After adjustment for multiple testing, > 1700 plasma proteins significantly differed between subjects with vs. without future MALOs. The most altered proteins were predominantly of liver, intestine or lymphoid tissue origin and remained significant in the diabetic/obese sub-cohort. Five proteins, ADAMTS-like protein 2, polymeric immunoglobulin receptor, integrin beta-like protein 1, thrombospondin 2, and insulin-like growth factor binding protein 7 robustly predicted future MALOs at least as good GGT that constituted the best routinely available predictor. They were particularly useful in the high-risk sub-cohorts, yielding AUROCs 0.80-0.86. In the validation cohort, all novel biomarkers associated positively with degree of liver fibrosis and numerically outperformed GGT in predicting MALOs (AUROCs:0.86-0.95).

Conclusion: PEA-based proteomic assessment is a promising source of non-invasive predictors of MALO development.

P2.18 Inhibition of TGFb signalling attenuates surgical liver injury and improves liver regeneration after partial hepatectomy

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Liver regeneration is controlled by a complex interplay of different cytokines and cell types. In particular, intercellular communication between recruited macrophages and hepatocytes via activated TGFb appears to play an important regulatory role. Observations from recent studies suggest that blocking TGFbRII-mediated effects on liver macrophages, and in particular on monocyte-derived macrophages, may influence surgical injury and liver regeneration after partial hepatectomy (PHx). To further investigate the effects of inhibiting TGFb signaling on surgical injury and liver regeneration, a pilot study was conducted in animals undergoing PHx pre-treated with SB431542, an inhibitor designed to specifically inhibit the activation of ALK4 and ALK5, or with carrier solution as a control. The data showed that pre-treatment with SB431542 reduced the surgery-induced increase in AST, ALT and LDH, suggesting that inhibition of the TGFb pathway may alleviate PHx-induced liver injury. In addition, inhibition of the TGFb pathway results in increased proliferation during liver regeneration. This is accompanied by increased cytokine expression, particularly IL-6 and IL-10, under the influence of TGFb inhibition, which is consistent with the cytokine response of TGFbRII-deficient macrophages. In conclusion, these data support our hypothesis, based on the results of previous work, that inhibition of TGFb signaling may be an approach to improve the course of regeneration after partial hepatectomy. Cytokine measurements suggest that the influence of TGFb on the activation state of recruited liver macrophages plays a role in this context, in line with the results of previously published studies.

P2.19 Baseline Characteristics and Risk Profiles of 1111 Patients With Primary Biliary Cholangitis (PBC) in Need of Second-Line Therapy

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Up to 40 % of patients receiving first-line ursodeoxycholic acid (UDCA) for PBC have an ALP ≥ 1.67 × ULN and progress. We examined patients who screen failed due to ALP < 1.67 × ULN in 4 seladelpar clinical trials (2015–2022); 1111 patients with PBC were screened after UDCA treatment ≥ 12 months or UDCA intolerance. ALP ≥ 1.67 × ULN was required for enrollment. Baseline characteristics and risk profiles of enrolled patients (EN, ALP ≥ 1.67 × ULN) and screen failures (SF, ALP ≥ ULN, but < 1.67 × ULN) were compared. We stratified using proportions with Enhanced Liver Fibrosis (ELF) values ≥ 10.0 or bilirubin > 0.6 × ULN. The relationship of ELF and liver stiffness was confirmed when available. Screened patients were predominantly female (94 %) with mean (SD) age of 57 ± 9.5 years. Studies enrolled 54 % of screened patients (n = 603; EN cohort) with PBC duration 8 ± 6.5 years and UDCA dose 15 ± 3.9 mg/kg/day (92 % on UDCA). Overall, 26 % of patients (n = 284) screen failed due to ALP > ULN but < 1.67 × ULN (SF cohort). Differences in baseline ALP, GGT, and ALT were observed between cohorts. Higher-risk bilirubin levels were present in 51.1 % and 42.0 % of EN and SF cohorts, respectively. Elevated risk based on ELF was identified in 43.2 % of EN and 27.2 % of SF cohorts. Liver stiffness was assessed in 66 % of EN patients; mean liver stiffness of 9.7 kPa correlated with ELF (r = 0.50, P < 0.001). Thus, patients with ALP ≥ ULN, but < 1.67 × ULN, often have risk factors for disease progression and should be assessed for second-line therapies.

P2.20 Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Compensated Liver Cirrhosis in the Open-Label, Long-Term ASSURE Safety Study: Interim Results

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We report interim efficacy/safety in a subset of patients with compensated liver cirrhosis (CC) from the open-label, long-term, phase 3 ASSURE study (NCT03301506) of seladelpar in primary biliary cholangitis (PBC). Patients with an inadequate response or intolerance to ursodeoxycholic acid, participation in a prior seladelpar study (NCT02955602, NCT03301506, NCT03602560, NCT04950764), and no history of hepatic decompensation were eligible. All received seladelpar 10 mg orally daily. As of June 29, 2023 (data cutoff), 174 patients enrolled; 33 had CC at study entry. Efficacy endpoints included the composite biochemical response (ALP < 1.67 × ULN, ALP decrease ≥ 15 %, and total bilirubin (TB) ≤ ULN), ALP normalization, and change from baseline (CFB) in ALP, total bilirubin, GGT, ALT, and AST at Month (M) 12. Of 33 patients with CC, most were female (91 %), and mean age was 60.4 years. Eight patients (24.2 %) had portal hypertension, 93.9 % were Child-Pugh-A, and 6.1 % were Child-Pugh-B. At baseline, mean liver stiffness was 19.3 kPa, mean ALP was 241.9 U/L, and TB was 0.92 mg/dL (27.3 % > ULN). At data cutoff, 23 patients with CC completed 12M; 52.2 % met the composite endpoint, and ALP normalized in 39.1 %. Mean percent CFB at M12 in ALP, GGT, and ALT was − 38.1 %, − 35.1 %, and − 19.6 %, respectively; no changes occurred in AST or TB. No serious adverse events were liver or seladelpar related, and no discontinuations were due to adverse events. Seladelpar demonstrated clinically meaningful improvements in markers of cholestasis and liver injury and a tolerable safety profile in patients with PBC and CC.

P2.21 Organ Donation from Patients with Child-Pugh Class C Cirrhosis: A Clinical Feasibility or Ethical Dilemma?

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Introduction Germany faces a significant shortage of organ donations, ranking among the lowest in Europe. This shortfall leads to the deaths of thousands of patients each year. Brain-dead patients with advanced cirrhosis, particularly those with Child-Pugh Class C cirrhosis, are frequently deemed unsuitable for organ donation due to their critical clinical state.

Case Report We present the case of a 50-year-old patient with alcohol-induced Child-Pugh Class C liver cirrhosis, admitted for liver transplant evaluation. Following a thorough assessment, including psychiatric evaluation, our interdisciplinary team determined the patient to be eligible for transplantation. However, on the day she was scheduled to be placed on the transplant waiting list, she suffered a severe cerebral hemorrhage and was transferred to the intensive care unit. Despite maximal intensive care and neurosurgical intervention, brainstem areflexia was confirmed. After obtaining consent from the family, the patient was evaluated for organ donation and deemed a potential donor. In the subsequent hours, her condition deteriorated further, leading to hepatorenal syndrome with decreased urine output. Terlipressin and furosemide were administered to support renal function. After a prolonged waiting period,

one kidney was successfully transplanted into an adult recipient, with good post-transplant outcomes.

Conclusion Patients with Child-Pugh Class C cirrhosis are at an elevated risk of cerebral hemorrhage due to coagulopathy, which can result in brain death. Despite their compromised condition, organ donation should still be considered on a case-by-case basis, as demonstrated in this report.

P2.22 Kurzfristige Mortalität und Diagnose von ACLF wird durch TIPS bei hydropischer Dekompensation aufgehoben: Eine Fall-Kontroll-Studie

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Einführung: Die akute Dekompensation ist durch die portale Hypertension getrieben, welche auf das akut-auf-chronische Leberversagen (ACLF) übergehen kann. Letzteres weist eine hohe Sterblichkeitsrate auf. Der transjuguläre intrahepatische portosystemische Shunt (TIPS) ist die wirksamste Therapie für Komplikationen der portalen Hypertension, einschließlich hydropische Dekompensation (HD). Der therapeutische Nutzen von TIPS bei ACLF mit HD ist noch nicht untersucht.

Methoden: In dieser Fall-Kontroll-Studie wurden Patienten aus den prospektiven Kohorten CANONIC (n = 1324) und dem deutschen TIPS-Register (n = 724) auf HD untersucht und im Verhältnis 1:1 nach Geschlecht, Alter, MELD-Score sowie Vorhandensein und Grad von ACLF gepaart. Die passende Population umfasste 118 ACLF-Patienten, von denen 59 TIPS erhielten und 59 nicht. Die klinischen Parameter, der ACLF-Status und die Sterblichkeit wurden bewertet.

Ergebnisse: Es gab keine signifikanten Unterschiede zwischen den zwei Gruppe mit Hinblick auf die allgemeinen Charakteristika. Die Hauptindikation für TIPS war das hepatorenale Syndrom (61,0 %). ACLF-Patienten, die keinen TIPS erhielten, wiesen eine höhere 28-Tage-Mortalität (22,0 % vs. 5,1 %, p = 0,009). Die TIPS-Anlage bei ACLF wird mit verringerten Mortalitätsrate von 78 % nach 28 Tagen assoziiert (HR 0.22 [0,062 – 0,771]) und führte zu einer Verringerung von Aszites, hepatischer Enzephalopathie, MELD- und CLIF-OF-Scores. Ferner zeigten 61 % der TIPS-Fälle eine Auflösung der ACLF. Gerinnungs- und Kreislaufversagen, Bilirubin, INR, MELD und CLIF-OF waren mit der 28-Tage-Mortalität assoziiert. Der Überlebensvorteil von TIPS war nach 90 Tagen nicht mehr nachweisbar.

Zusammenfassung: TIPS verbessert die Kurzzeitprognose der hydropischen dekompensierten ACLF, aber eine sorgfältige Auswahl der Kandidaten ist notwendig. TIPS könnte in diesen Patienten eine Brückentherapie zur Lebertransplantation darstellen.

P2.23 Scherwellenelastografie übertrifft Fibroscan bei der Detektion von höhergradigen Ösophagusvarizen

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Einleitung: Ösophagusvarizen treten als Komplikation einer Leberzirrhose und portalen Hypertension auf. Ihre frühe Erkennung ist zur rechtzeitigen Therapieeinleitung mit Beta-Blockern wichtig. Der Baveno VII Konsensus empfiehlt Grenzwerte zur nicht-invasiven Detektion klinisch signifikanter portaler Hypertension (CSPH), wobei einige Patienten mit diesen Kriterien in eine Grauzone fallen. Diese Studie untersucht die Eignung elastographischer Leber- und Milzuntersuchungen für die Diagnose von Ösophagusvarizen.

Methoden: 69 Patienten wurden in diese monozentrischen Studie eingeschlossen, die in zwei Gruppen nach ihren zuletzt verfügbaren endoskopischen Befunden eingeteilt wurden: Ösophagusvarizengrade 0-1 und 2-4. Leber- und Milzsteifigkeit wurden durch ultraschallbasierte Untersuchungsmethoden gemessen: Hologic MACH 30 Ultraschallgerät (Scherwellenelastografie (SWE)) und FibrosScan 630 Expert (transiente Elastografie (TE)).

Ergebnisse: Die Kohorte bestand zu 37,4 % aus weiblichen Patienten mit einem medianen Alter von 54 Jahren und einer medianen Lebersteifigkeit von 26,64 kPa. Ätiologisch führen waren alkohol-assoziierte Lebererkrankungen mit 21,73 %. In univariablen Analysen zeigten sich SWE Messungen der Leber und der Milz als unabhängige Prädiktoren für höhergradige Varizen, mit Odds Ratios von 1,04 (p = 0,029) und 1,083 (p = 0,009), wobei in einer multivariablen Analyse nur die Milz-SWE signifikant blieb (OR = 1,072; p = 0,028). Die Milz-SWE hatte zudem den höchsten prädiktiven Wert für Ösophagusvarizen mit einem AUROC von 0,741. Milz- und Leber-TE und Leber-SWE schnitten schlechter ab mit AUROCs von 0,576; 0,633 und 0,692. Bei Anwendung des Baveno-VII Cut-Offs (Milzsteifigkeit unter 40kPa) zum Ausschluss einer CSPH, hatten bei der Milz-TE 4/14 und bei der Milz-SWE 1/17 Patienten Ösophagusvarizengrad 2-4.

Schlussfolgerungen: Milz-SWE Messungen zeigten gute Ergebnisse bei der Detektion höhergradiger Ösophagusvarizen und sollten deshalb weiter untersucht werden, um valide Cut-Offs festzulegen.

P2.24 Entwicklung eines klinischen Entscheidungsbaums für die nicht-invasive Diagnostik der Transplantat-Steatose bei Patienten nach Lebertransplantation

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Einleitung: Patienten nach Lebertransplantation (LT) haben ein hohes Risiko, eine Lebersteatose zu entwickeln, als Frühform pathologischer Transplantatveränderung. Die Leberbiopsie bleibt der Goldstandard zur Erkennung einer Transplantatsteatose, birgt jedoch durch periinterventionelle Komplikationen wie Blutungen und Schmerzen Risiken, sodass nicht-invasive Methoden benötigt werden. Diese Studie zielt darauf ab, einen Algorithmus zur nicht-invasiven Erkennung einer Transplantatsteatose zu entwickeln.

Methodik: In die Studie wurden LT-Patienten mit verfügbarer Leberhistologie eingeschlossen. Drei ultraschallbasierte Methoden wurden evaluiert: Attenuation PLUS (AttPLUS), Speed of Sound PLUS (SSpPLUS) am Hologic Mach 30 Ultraschallgerät und der Controlled Attenuation Parameter (CAP) am Fibroscan 630 Expert. Zusätzlich wurde der serum-basierte Hepatic Steatosis Index (HSI) berechnet. Die histopathologische Beurteilung der Steatose diente als Referenz.

Ergebnisse: Insgesamt wurden 113 Patienten in die Studie eingeschlossen (39 % weiblich, medianes Alter 59 Jahre (45-68), mediane Zeit seit LT 7 Jahre (2–21)). Alle Methoden zeigten signifikante Korrelationen mit dem histologischen Steatosegrad (p < 0,05). Für jede Form der Steatose (S1-3) wies SSpPLUS die höchste Genauigkeit auf (AUC: 0,758). Zur Erkennung einer signifikanten oder schweren Steatose (S2-3) und (S3) zeigte AttPLUS die besten Ergebnisse mit AUC-Werten von 0,801 bzw. 0,749, sodass der Entscheidungsbaum mit den Verfahren AttPLUS und SSpPLUS entwickelt wurde. Zuerst wurde mithilfe des maximalen Youden-Index der Cut-Off-Wert für eine S1-Steatose bestimmt (wenn SSpPlus < 1572 m/S, dann S1-Steatose, sonst keine Steatose). Anschlie-

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ßend wurde der Grenzwert für eine S2/S3-Steatose bestimmt (wenn Att-PLUS > 0,568 dB/cm/MHz, dann S3-Steatose, sonst S2-Steatose).
Schlussfolgerung: Neue ultraschallbasierte Methoden zur Messung der Transplantat-Steatose zeigten vielversprechende Ergebnisse bei LT-Patienten, bedürfen jedoch weiterer Validierung.

P2.25 Low rates of positive evaluation and early liver transplantation (LT) for acute-on-chronic liver failure (ACLF) in a European tertiary referral center

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Background: Identification of LT candidates and organ allocation in the management of ACLF remain controversial. Aim: To evaluate the LT evaluation process and outcomes in ACLF patients in a tertiary transplant center.
Methods: LT evaluations, listings and outcomes of all adult ACLF patients at the University Medical Center Hamburg-Eppendorf were prospectively assessed between 12/21 and 06/24.
Results: 132 ACLF patients were enrolled (41 ACLF I °, 31 ACLF II °, 60 ACLF III °). Of 17 patients previously listed for LT, 13 (76 %) underwent LT. In the 115 non-listed patients, LT evaluation revealed contraindications in 69 cases, mostly alcoholism and/or transplant-psychological factors (50/69). In 46 patients eligible for listing, mortality was 50 %: 23 patients were never listed, mostly due to infections, and 19/23 died. 23 patients were newly listed for LT with a median time from ACLF diagnosis to listing of 14 days, and 16 patients (69.6 %) underwent LT. Overall ACLF-LT 6-month survival was 89.1 %, contrasting 30.9 % in the ACLF non-LT group. Of 68 non-LT patients surviving to hospital discharge, 40 (58.8 %) developed recurrent ACLF, and 24 (35.3 %) of these patients died within 6 months of ACLF diagnosis.
Conclusion: In this single-center prospective study, only a minority (22 %) of ACLF patients underwent LT. Despite timely identification of ACLF-LT candidates, mortality among previously non-listed patients was 50 %, contrasting 17.6 % in patients listed prior to ACLF ($p < 0.05$). Recurrent ACLF constitutes a significant risk in ACLF non-LT patients, and identification of patients at ACLF risk and early listing of LT candidates may improve prognosis.

P2.26 Two cases of hepatic lues demonstrating the highly variable presentation of syphilis

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Lues is an important differential diagnosis in patients with aetiologically unclear hepatitis or liver lesions. Lues can present with a plethora of symptoms and organ-systems involved, leading to diagnostic obstacles. Syphilitic hepatitis can occur at any stage of lues. We present a case of severe syphilitic hepatitis and another case of hepatic gummas with hepatitis.
Patient 1: A 44-year-old man with HIV and previously treated Lues-infection was admitted with liver lesions (max. 2.8 cm) and cholestatic hepatitis (AP 276 U/l, ALT 88 U/l). The initial suspected diagnosis was lymphoma, whereupon a liver biopsy was performed. Histology revealed giant cell granuloma, serology showed no evidence of viral hepatitis/AIH. Cardiolipin-Microflocculation-Test (CMT) was positive (1:256). Ten days of intravenous ceftriaxone treatment led to normalization of transaminases/cholestatic parameters. Ultrasound examination showed a complete remission of the liver lesions and a decrease in CMT values (1:16, six months after treatment).
Patient 2: A 21-year-old man was admitted with jaundice (bilirubin 10.7mg/dl) and hepatitis (ALT 1300U/l). He reported sexual contact with men and the physical examination revealed perianal eczema. Viral hepatitis and HIV were negative, ANA 1:80, and CMT was positive (1:128). Treatment with ceftriaxone (penicillin allergy) followed, liver biopsy revealed severe hepatitis compatible with syphilitic hepatitis DD AIH. Due to progressively elevated bilirubin, short-term prednisolone treatment followed, which led to a rapid improvement. Follow-up examinations showed complete remission even after discontinuation of prednisolone three months after discharge.
Conclusion: Lues can present with hepatitis and hepatic gummas and should be included in differential diagnosis.

P2.27 Liver Cirrhosis as a Risk Factor for Gut Ischemia in the Intensive Care Unit

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DOI 10.1055/s-0044-1801051
Background: Ischemic gut is a life-threatening emergency with a high mortality in intensive care units (ICUs). It often occurs as a complication in critically ill patients, leading to septic shock and multiorgan failure. Timely diagnosis is challenging but critical, as delays can result in poor outcomes.
Methods: We conducted a retrospective, single-center study in the GI and liver intensive care ward of a German university hospital from January 2012 to August 2024. Clinical, laboratory, microbiological, endoscopic, radiological, and surgical data were collected from medical records for analysis.
Results: A total of 103 critically ill patients (median age: 62 years; 57 % male) with gut ischemia were treated. The median ICU stay was 14.7 days. Of these patients, 41 (40 %) had liver cirrhosis, 40 (39 %) developed pneumonia, and 12 (12 %) had pancreatitis. Thirty patients had cardiac comorbidities. The ischemia affected the right colon in 42 cases (41 %), the small bowel in 36 cases (35 %), and the stomach wall in four cases. Bowel perforation occurred as a complication in 15 patients (15 %). Arterial stenosis was identified in 25 patients (25 %), primarily in the superior mesenteric artery (13 cases). Importantly, 28 patients (27 %) had no radiological signs of ischemia, while 29 (28 %) showed only bowel wall thickening. The overall mortality rate was 75 %, with only 5 survivors (12 %) among patients with liver cirrhosis.
Conclusion: Gut ischemia poses a significant risk, particularly in patients with liver cirrhosis. Timely diagnosis and endoscopic evaluation are essential, as radiological findings may often be inconclusive. Regular monitoring of

P2.28 Digital single-operator cholangioscopy characterizes distinct phenotypes of primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC) carries a high risk for cholangiocarcinoma (CCA) development. Digital single-operator cholangioscopy (dSOC) is commonly recommended for evaluating indeterminate biliary strictures and suspected biliary malignancy. However, in the context of PSC, clinical guideline recommendations for the use of dSOC vary across countries and are based on limited scientific evidence.
Methods: This retrospective, single-center study aimed to characterize the cholangioscopic features of patients with PSC. dSOC findings and reports were evaluated based on visual assessment, categorizing the cholangioscopic appearance into a fibrotic-predominant, an inflammatory-predominant, or suspicious for malignancy phenotype.

Results: In a cohort of 77 PSC patients, 44 individuals (mean age 45 years [range 20–67]; 15 female, 29 male) underwent dSOC between 2014 and 2022, with a total of 132 dSOC procedures being analyzed. Six patients in the cohort were newly diagnosed with CCA. In 54 cases (40.9 %), a fibrotic-predominant phenotype was identified, while 62 cases (47 %) exhibited an inflammatory-predominant phenotype. Sixteen cases (12.1 %) were suspicious for malignancy, with 14 of these showing a predominance of inflammatory features (10.2 %). CCA diagnoses were predominantly confirmed in patients with the inflammatory-predominant phenotype (82.4 %).

Conclusion: We characterize distinct cholangioscopic phenotypes in primary sclerosing cholangitis. The findings suggest that cholangiocarcinoma in PSC is associated with a predominantly inflammatory cholangioscopic phenotype, indicating the need for early implementation of cholangioscopy in the diagnostic evaluation of PSC to identify patients at higher risk for developing CCA.

P2.29 Unveiling Cellular Heterogeneity and Liver Pathophysiology in Liver Transplant Recipients through Multiplex Image Analysis

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Liver transplantation represents the only curative treatment for patients with end-stage liver disease. Despite advances in immunosuppressive therapies and surgical techniques, post-transplant complications such as graft dysfunction, fibrosis, and rejection remain major clinical challenges. This study aimed to develop a multiplex immunofluorescence staining and analysis protocol for investigating liver graft biopsies, offering high-resolution insights into cellular and spatial tissue dynamics. Using a cohort of seven liver transplant recipients, biopsy samples were analyzed to profile histological changes of the common post-transplant complications fibrosis, drug-induced liver injury (DILI), and acute T-cell mediated rejection (TCMR). The developed protocol enabled detailed assessment of hepatocytes, cholangiocytes, macrophages, and immune cells across different disease phenotypes using key markers such as yH2Ax, Ki67, p62, TGF-beta, and cleaved caspase 3 to assess proliferation, apoptosis, and tissue damage. Spatial clustering analysis revealed distinct tissue regions associated with specific pathological conditions, particularly identifying areas enriched with proliferating and autophagy-impaired hepatocytes in TCMR. Additionally, spatial and neighboring analysis of CD3 + lymphocytes was successful in identifying their crucial role in inflammatory processes during acute rejection and identifying immune- and non-immune mediated origins for tissue damage in DILI. This workflow was validated by applying it to protocol biopsies from clinically healthy patients, revealing early signs of graft injury to be later identified as chronic rejection. The study demonstrates that multiplex staining combined with spatial analysis can provide a more granular understanding of post-transplant liver pathology, offering potential for more personalized immunosuppressive therapies and earlier intervention in graft dysfunction.

P2.30 Exploring the Role of Social Determinants of Health in autoimmune liver disease – a pilot study within the European Reference Network on hepatological diseases

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Background: Social Determinants of Health (SDOH) are conditions in which people grow, work, and age. Studies highlight the influence of SDOH on the development and progression of various chronic diseases.

Aim: To explore the relation between SDOH and quality of care, treatment and outcome parameters of autoimmune liver diseases (AILD)

Methods: An international multicentre cross-sectional patient-directed questionnaire is distributed among adults with AILD between October 2024 and January 2025. questionnaire comprises of established instruments covering sociodemographics, income, education, job and food insecurity, housing, early childhood development, social support, access to health services, and treatment and progression of AILD.

Results: After 14 days, 364 patients from 6 European countries answered the questionnaire. 13 % of the patients had primary sclerosing cholangitis, 43 % had autoimmune hepatitis, 36 % had primary biliary cholangitis, and 8 % had variant syndromes. 79 % were female, most participants were between 50-60 years old. Around 7 % of participants screened positive for food insecurity. Meanwhile, 57 % reported paying for liver medication despite health insurance, and 47 % for additional private health insurance. 13 % reported having liver cirrhosis, and 2 % had undergone liver transplantation. Hospitalizations during the past year were reported by 8 % of participants, while 68 % reported normalization of liver blood tests.

Discussion: Data collection will be completed by January 2025. Regression models will be employed to analyse the association between SDOH and AILD. Results may foster prospective studies.

P2.31 Duration and clinical relevance of viral shedding of HEV by the stool: results from an observational prospective study

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Background: Hepatitis E Virus (HEV) shedding in stool in India (endemic for HEV genotype 1) has been described to last up to 30 days. This has never been

investigated in genotype 3 regions, like Germany. This study covers the duration of HEV shedding and the resulting relevance of contamination of bathroom furniture.

Methods: Blood, stool, and urine from 12 immunocompetent patients with acute HEV infection were tested by PCR (Cobas TaqMan™). Additionally, surface contamination in the bathrooms of 13 patients with Hepatitis E following toilet use, was tested by PCR (Altona diagnostics).

Results: The observational cohort included 12 immunocompetent patients (8 men and 4 women, aged 39-83 years) with autochthonous HEV infection. Ten had acute Hepatitis E, and two were asymptomatic HEV-infected blood donors. HEV was detected in 83 %, (n = 10) in their stool. The maximum duration of viremia was 12 weeks (average 7 ± 2 weeks). Fecal virus shedding lasted up to 8 weeks (average 4 ± 2 weeks).

HEV-RNA was detected on toilet seats in six patients, flush buttons in three patients, faucet handles in five, and door handles in two patients, with very low contamination levels.

Conclusion: HEV infections in Germany (genotype 3) can persist longer than previously described in India (genotype 1). While blood viral load at diagnosis can predict the duration of viremia, initial stool viral load does not reliably predict the duration of HEV shedding. Surface contamination of bathroom furniture is low, suggesting a minimal risk of transmission through contaminated surfaces within a household.

P2.32 Genetic Variant Analysis in Low Phospholipid-Associated Cholelithiasis Patients through Whole Exome Sequencing

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Low phospholipid-associated cholelithiasis (LPAC) syndrome is a specific gallstone disease affecting around 1 % of hospitalized symptomatic gallstone patients in adults. Half of the LPAC patients carry a potentially relevant variant in the ABCB4 gene, encoding the MDR3 protein, responsible for phospholipid secretion into bile. This promotes cholesterol crystallization and recurrent gallstone formation, often persisting after cholecystectomy (CCE). Genetic variants in other genes may contribute to gallstone formation, including ABCB11/BSEP, involved in bile salt export, and ATP8B1/FIC1, which help maintain bile composition. ABCG8:p.D19H variant is also known to be associated with increased risk for gallstone formation.

The HiChol registry data on 20 LPAC patients reveals that 19 (95 %) of them underwent CCE at a median age of 32 years, which suits the LPAC criteria. The gender distribution showed a slight predominance of females (11 patients, 55 %) over males (9 patients, 45 %). The results from whole exome sequencing (WES) analysis revealed pathogenic variants in ABCB4/MDR3 in 6 patients (30 %), reinforcing the established genetic basis of the disorder. These findings emphasize the significant link between LPAC and CCE, underscoring the need for targeted diagnostic and therapeutic approaches. In around two-thirds of this cohort, no relevant ABCB4/MDR3 was detectable. In these cases, we identified variants affecting ATP8B1, ABCB11, MYO5B, NR1H4, ABCC12, and ABCC4 involved in bile metabolism and transport.

Ongoing analysis of WES data is being carried out to identify further potential genetic contributors to the LPAC phenotype. Moreover, clinical and quality of life data is documented for a genotype-phenotype correlation.

P2.33 Analysis of HEV infection rates in immunocompetent MPGN patients compared to controls

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Background Hepatitis B and C, are well-known causes of membranoproliferative glomerulonephritis (MPGN). Recently, hepatitis E virus (HEV) infections in immunosuppressed patients have been linked to the development of MPGN. This study aims, to investigate a possible association of HEV infections and MPGN in immunocompetent individuals.

Methods: A retrospective cohort of 73 MPGN patients was tested for anti-HEV IgG and IgM. A cohort of 1000 random blood donors and a cohort of 73 age- and sex-matched-pair blood donors served as control groups.

Results In the MPGN cohort, 21 patients (29 %) tested anti-HEV IgG positive (1.4 %), while in the random blood donor cohort, only 17 % of patients (n = 166) tested IgG positive (p = 0.01) and 25 % of patients in the matched-pair cohort of 73 blood donors were positive for anti-HEV IgG (p = 0.71). MPGN patients were significantly older and more often males compared to the unmatched blood donor cohort.

In the MPGN cohort, anti-HEV IgG positivity was found in 36 % of males (17/47) but only 15 % (4/26) of females (p = 0.05). Anti-HEV IgG positive MPGN patients were older when compared to anti-HEV IgG negative MPGN patients, albeit the difference did not reach statistical significance (median 63 years vs. 53 years, p = 0.06).

Conclusion: Although anti-HEV IgG positivity is more common in patients with MPGN compared to healthy blood donors, this difference does not hold up when a cohort of blood donors of similar age and gender is studied. Thus, previous HEV infections are not a relevant trigger for the development of MPGN in immunocompetent patients.

P2.34 Optimizing Piperacillin/Tazobactam Dosing in ACLF Patients through Interprofessional Therapeutic Drug Monitoring

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Background: Acute-on-chronic liver failure (ACLF) is a rapidly progressing condition in patients with pre-existing liver cirrhosis, often triggered by bacterial infections. Optimizing antibiotic therapy, particularly Piperacillin/Tazobactam, is crucial. Therapeutic drug monitoring (TDM) ensures effective dosing, improving patient outcomes. This study evaluates the impact of an interprofessional TDM strategy on Piperacillin/Tazobactam dosing in ACLF patients in an ICU setting.

Methods: This retrospective analysis was conducted in the ICU of the Department of Internal Medicine I at the University Hospital Regensburg, focusing on interprofessional collaboration between physicians, pharmacists, and nursing staff. The cohort included 27 ACLF patients who underwent initial TDM and 8 patients with follow-up TDM. Outcomes were compared to a control period without TDM. Piperacillin/Tazobactam dosing was adjusted based on weekly serum concentration measurements via high-performance liquid chromatography (HPLC). Patients were assessed using Child-Pugh, SOFA, MELD, and CLIF-C-ACLF scores.

Results: TDM results led to the recommendation of the interprofessional team to maintain the current dosage in 63 % of patients, reduce the dosage in 15 %, and increase the dosage in 7 %. Furthermore, antibiotic discontinuation was recommended for 11 % of patients, and in 4 %, a switch to an alternative antibiotic was advised due to resistance. Follow-up TDM indicated that 54 % of patients remained within the target range, 23 % exceeded it, and 8 % fell below it, with adjustments of the dosage recommended accordingly. All interprofessional recommendations were fully implemented.

Conclusions: The interprofessional TDM approach improved Piperacillin/Tazobactam dosing in ACLF patients, optimizing antibiotic management and supporting global antibiotic stewardship efforts in critically ill patients.

P2.35 Expression signatures of IL-18 and IL-18BP characterize stages of cirrhotic decompensation

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Background: Cirrhosis-associated immune dysfunction (CAID) favors infections and organ dysfunction to precipitate acute-on chronic liver failure (ACLF). Molecular CAID networks remain unresolved, but may include IL-18, a potent inflammatory cytokine and cell death modulator, and its antagonist IL-18BP as targetable agents.

Aim: To delineate patterns of IL-18 and IL-18BP expression in decompensated cirrhosis (DC) and ACLF, and to assess their relations to established inflammatory markers and disease severity in humans.

Methods: Hepatic mRNA expression was quantified via RNAseq. Plasma IL-18, IL-18BP, sCD14, LBP and iFABP levels were measured via ELISA in a prospective cohort of 111 cirrhosis patients (75 with ACLF), and correlated with CRP, IL-6, WBC and NLR, organ dysfunction, and outcomes.

Results: IL-18 and IL-18BP are increasingly upregulated in DC and ACLF livers. Circulating IL-18 increases with progressive hepatic decompensation independently of cirrhosis etiology, and a particularly high IL-18/IL-18BP ratio characterizes ACLF. IL-18 more robustly correlates with ACLF grade, MELD, MELD-Na and Child-Pugh scores than CRP, IL-6, WBC and NLR. IL-18, IL-6, WBC and NLR are significantly lower in ACLF survivors compared to non-survivors and patients requiring liver transplantation, whereas CRP and IL-18BP are not. Correlation between IL-18 and IL-18BP with IL-6 were only moderate (< 0,5), and remarkably low with markers of intestinal barrier dysfunction.

Conclusion: IL-18 induction characterizes hepatic decompensation, with expression patterns distinct from IL-6, WBC, CRP and NLR. In ACLF, an IL-18/IL-18BP imbalance inferred by relative IL-18BP underabundance may drive organ dysfunction and affect outcomes. The specific contributions of IL-18 to CAID mandate further.

P2.36 Identification of new potential genetic risk factors for cholestasis and gallstone disease: report of three-generation family with cholestatic phenotype

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Introduction: Gallstones are a frequent condition, typically asymptomatic but sometimes requiring invasive treatments. This study examines genetic testing in a family with a high incidence of symptomatic gallstones and cholestatic liver phenotypes.

Patients: We analyzed a three-generation family with a history of gallstones and elevated liver enzymes, including a 21-year-old male (patient 1), a 24-year-old female sibling (patient 2), their 70-year-old father (patient 3), 59-year-old mother (patient 4), and 64-year-old uncle (patient 5). The father showed mild liver fibrosis in a biopsy. The deceased paternal grandfather and his twin sister (not genotyped) also presented with gallstones. Genetic testing involved an in-house cholestasis panel for 15 cholestasis-related variants, followed by next-generation sequencing (NGS) of ABCB4, ABCB11, and ATP8B1 genes.

Results: Homozygosity was detected for the known ABCB4 variants c.504C > T and c.711A > T, and ABCB11 variants c.1331C > T and c.3084A > G. NGS revealed that all patients were homozygous for two intronic ABCB4 variants. Additionally, synonymous ATP8B1 base changes were found in patients 1-4, while patient 5 lacked the ATP8B1 variant rs319443. These variants may have functional implications despite being classified as synonymous. The major gallstone-predisposing variant ABCG8 p.D19H was homozygous in patients 1-3 and heterozygous in patients 4-5. Variants from recent GWAS (SPTLC3/LINC-01723, TMEM147, TNRC6B) were also identified in either heterozygous or homozygous state.

Discussion: The combined effect of these variants may explain the high prevalence of gallstone disease in this family, though functional studies are warranted. Expanding the use of NGS in clinical practice could help uncover new genetic risk factors for common diseases.

P2.37 Effects of sodium-linked glucose transporter 2 inhibitors in liver transplant recipients with impaired renal function

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Introduction Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have gained significant attention in clinical research due to its diverse therapeutic effects. The aim of the following retrospective study was to analyze the nephroprotective effects of SGLT2i in patients experiencing renal insufficiency following liver transplantation.

Methods Patients with renal insufficiency following liver transplantation with and without being treated with SLGT2i between 2022 and 2024 at the LMU University Hospital Munich were included in the study. We analyzed changes in eGFR, creatinine levels, liver parameters and the safety profile.

Results A total of 42 patients with SGLT2i treatment and 42 controls without treatment were included. Main characteristics such as age ($p = 0.08$), gender ($p = 0.34$), baseline kidney and liver parameters were observed to be similar in both study cohorts. Median observation period was 12 (range; 1-24) and 18 months (range, 2-32) in patients with and without treatment of SGLT2i. A significant improvement in creatinine ($p = 0.02$) and eGFR ($p = 0.04$) levels was observed during treatment with SGLT2i, while renal function (creatinine, $p = 0.01$; eGFR, $p = 0.009$) significantly deteriorated in the relating control cohort. Improvement in renal function under treatment with SGLT2i was also observed to be significant in a sub-cohort of patients with a baseline GFR < 30ml/min ($n = 10$; creatinine, $p = 0.02$). In contrast, no change in liver parameters could be detected in both cohorts during the observation period. Regarding the safety profile of SGLT2i in this specific population, no adverse events could be detected.

Conclusion SGLT2i seem to be safe and effective in patients with renal insufficiency following liver transplantation.

P2.38 Sarcoidosis of the Liver – An underdiagnosed entity

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Background Sarcoidosis is a multisystem disorder primarily affecting the lungs. Hepatic manifestations occur in 10-65 %, ranging from asymptomatic cases to severe complications like chronic cholestasis, portal hypertension, or cirrhosis. Due to its varied presentation, hepatic sarcoidosis is assumed to be underdiagnosed.

Methods Using ICD codes, 35 patients from a university hepatology center with clinically and/or histologically confirmed liver involvement in sarcoidosis were identified. Clinical characteristics were recorded at initial diagnosis, after three and twelve months.

Additionally, a second cohort of 356 sarcoidosis patients from a pulmonology center was examined for abnormal liver values or imaging findings.

Results In the first cohort, 20 % (n = 7) of patients with hepatic sarcoidosis showed isolated liver involvement, while 74.2 % (n = 26) had 2-5 organs affected. Common symptoms were fever (28.6 %) and weight loss (25.7 %), with 17.1 % (n = 6) being asymptomatic. In 62.9 % (n = 22), liver involvement was biopsy-proven, but only 40 % (n = 14) showed a morphological correlate in imaging. Laboratory results predominantly showed a cholestatic pattern with elevated ALP and gamma-GT. Glucocorticoids were used in 51.4 % (n = 18), 42.9 % (n = 15) received no therapy.

In the second cohort, 47.8 % (n = 170) of pulmonary sarcoidosis patients showed abnormal liver values or imaging.

Conclusion The first cohort data indicate that biopsy-confirmed liver manifestations can exist without imaging correlate. Self-limiting courses are possible, if necessary, glucocorticoids, immunosuppressants, or UDCA for cholestasis are used.

The high number of liver abnormalities in the second cohort suggests that hepatic sarcoidosis is underdiagnosed. Therefore, liver involvement should be ruled out in sarcoidosis patients. Screening using ALP levels is recommended.

P2.39 Increased Plasma Adiponectin Levels in Septic Patients with Liver Cirrhosis as an early biomarker

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Background Liver cirrhosis is a known risk factor for sepsis and sepsis-related mortality. However, clinical signs of sepsis are often mitigated in patients with liver cirrhosis, leading to delays in diagnosis and treatment. Furthermore, due to liver dysfunction, inflammatory markers may remain low even during infection, complicating the diagnostic process.

Methods The aim of this study was to evaluate plasma levels of adiponectin in patients with liver cirrhosis and patients with sepsis without liver cirrhosis as an early biomarker. Blood samples were collected from patients with various causes of sepsis, and Enzyme-Linked Immunosorbent Assays (ELISA) was used to measure adiponectin levels. A total of 156 blood samples were taken within 24 hours of admission to the intensive care unit.

Results Of the 156 patients, 32 (21 %) had liver cirrhosis. Plasma adiponectin levels in septic patients with liver cirrhosis were significantly higher than in septic patients without cirrhosis. A gender-specific analysis revealed that male septic patients with cirrhosis had significantly higher adiponectin levels compared to males without cirrhosis, with a similar trend observed in females. When cirrhotic septic patients were excluded from the analysis, septic patients without cirrhosis had significantly lower plasma adiponectin levels compared to healthy controls.

Conclusion Sepsis can be easily overlooked in patients with liver cirrhosis due to overlapping clinical features. Additionally, the diagnostic utility of traditional inflammatory markers is limited in these patients because of liver dysfunction. Plasma adiponectin may serve as a valuable biomarker for detecting infections in cirrhotic patients and could improve sepsis diagnosis in this high-risk group.

P2.40 Improved Mortality Risk Stratification in Decompensated Liver Cirrhosis and Acute-On-Chronic Liver Failure Using the Updated KDIGO AKI Criteria

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Introduction: Acute decompensation of cirrhosis is a landmark event with relevant implications for short- and medium-term mortality. For acute-on-chronic liver failure (ACLF), CLIF definition of renal organ failure (OF) requires a creatinine value ≥ 2,0mg/dl, regardless of etiology. However, creatinine is significantly impacted by a variety of patient-specific factors such as ethnicity or nutritional status and thus likely underestimates the degree of kidney function impairment in the cirrhotic patient.

Aims & Methods: We applied the KDIGO definition for AKI to patients with decompensated liver cirrhosis. From the LMU Klinikum hepatology biobank, all patients with decompensated liver cirrhosis were identified. Patients were assessed for evidence of AKI during baseline hospitalization according to the newest KDIGO definition and followed for adverse outcomes in the ensuing six months. 28-day, 3-month- and 6-month mortality were calculated using Kaplan-Meier analysis.

Results: We observed significant differences in mortality according to AKI stage regardless of interval. A subpopulation of patients with AKI stage 2/3 not fulfilliing CLIF-OF renal failure definition showed similar short-term mortality to ACLF-1, underlining the assumption that absolute creatinine values underestimate mortality risk in this patient population. In ROC analysis, AKI stage and relative as well as absolute change in creatinine had superior predictive capacity for short-term mortality compared to maximal creatinine and CLIF-OF renal failure.

Conclusions: Employment of the KDIGO AKI definition has superior capacity to discriminate at-risk individuals in decompensated cirrhosis. Definitions that use creatinine dynamics should replace stiff maximal creatinine values in assessment for organ failure in liver cirrhosis.

P2.41 Effekt der IL-17-Interleukin-Familie auf die Blutgerinnung bei Patienten mit akut dekompensierter Leberzirrhose, bewertet mittels Restricted Cubic Splines

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Einleitung PatientInnen mit akuter dekompensierter Zirrhose befinden sich in einem fragilen hämostatischen Gleichgewicht. Die IL-17-Gruppe, bestehend aus sechs Interleukinen, spielt eine Rolle bei der Thrombogenese, insbesondere bei der Organisation und Reifung des Thrombus. IL-17A und IL-17F sind proinflammatorische Interleukine, deren Rolle bei der Gerinnung bei PatientInnen mit Leberzirrhose bisher unzureichend erforscht ist. Diese Studie untersucht die Rolle der IL-17-Gruppe im Zusammenhang mit der Hämostase bei PatientInnen mit dekompensierter Leberzirrhose.

Methodik PatientInnen mit akuter dekompensierter Leberzirrhose wurden untersucht und die Interleukine IL-17A, IL-17F sowie IL-17E mittels ELISA gemessen. Klinische, laborchemische und ROTEM-Daten wurden erfasst. Die Verteilungen der Variablen wurden mit dem Shapiro-Wilk-Test überprüft. Normalverteilte Variablen werden als Mittelwert(SD) angegeben, sonst als

Median(IQR), und mit dem t-Test oder Mann-Whitney-U-Test miteinander verglichen. Mittels Restricted-Cubic-Spline-Regressionsmodell wurde die Korrelation zwischen IL-17A, IL-17F und IL-17E und verschiedenen ROTEM-Parametern und Fibrinogen untersucht.

Ergebnisse In die Studie wurden 75 PatientInnen mit dekompensierter Leberzirrhose eingeschlossen. 54 PatientInnen hatten eine akute Dekompensation, während 21 Patienten das Bild eines ACLF aufwiesen. IL-17A zeigte einen nichtlinearen, umgekehrt S-förmigen Effekt auf CTEXTEM mit positiver Korrelation bei IL-17A Werten < 167pg/ml und negativer Korrelation bei Werten zwischen 167 und 375 pg/ml. IL-17F hatte einen negativer Korrelation mit CTEXTEM bei IL-17F Werten < 49 pg/ml und positiver Korrelation zwischen 49 und 337 pg/ml.

Fazit Unsere Ergebnisse deuten darauf hin, dass IL-17F und IL-17A mit der Gerinnselbildungszeit der ROTEM-Analyse und somit mit der Blutungs-und Thromboseneigung korrelieren. Das Zusammenspiel zwischen den IL-17-Interleukinen und der Gerinnung sollte aus diesem Grund zukünftig weiter untersucht werden.

P2.42 Comparative analysis of surrogate markers of intestinal permeability, bacterial translocation, and gut vascular barrier damage in cirrhosis

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Background & aims: Portal hypertension, impaired gut barrier function, and pathological bacterial translocation are hallmarks of advanced liver disease, driving the complications of cirrhosis. As measuring gut barrier function is demanding, surrogate markers have been proposed; however, their intercorrelation and applicability across different stages of advanced liver disease, particularly in ACLF, is largely unknown.

Methods: proposed markers of gut barrier dysfunction and bacterial translocation were quantified in sera from 160 patients with cirrhosis across different disease stages of compensated and decompensated cirrhosis, as well as in hepatic and portal vein serum from 20 patients before and after the insertion of a transjugular intrahepatic portosystemic stent (TIPS) using ELISA.

Results: Across all stages of liver disease, the gut vascular barrier marker plasmalemma vesicle protein-1 (PV-1) correlated with the bacterial translocation markers endogenous endotoxin-core IgA antibodies (EndoCAb) and LPS-binding protein (LBP), but not with the intestinal damage markers intestinal fatty acid binding protein (I-FABP) and zonulin-family peptides (ZFP). PV-1 and EndoCAb levels were higher in decompensated cirrhosis patients without a further increase in ACLF. Among the investigated markers, only I-FABP was correlated with the portosystemic pressure gradient, and TIPS insertion significantly reduced portal concentrations within 24h hours. Higher PV-1 levels indicated poor transplant-free survival in univariate and multivariate analyses.

Conclusions: The investigated surrogate markers of bacterial gut barrier dysfunction and bacterial translocation appear to have limited use in advanced stages of cirrhosis and are confounded by hepatic synthesis capacity, portal congestion, and acute-phase responses.

P2.43 Hepatological Insights into Budd-Chiari Syndrome: A 13-Year Retrospective Study on Genetic Mutations and TIPS Efficacy

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Introduction Budd-Chiari Syndrome (BCS), caused by hepatic venous outflow obstruction, is a rare but life-threatening condition. Delayed diagnosis often results in severe complications. This study, conducted at the Department of Internal Medicine I, University Hospital Regensburg (UKR), provides a retrospective analysis of BCS patients, focusing on genetic predispositions and the role of transjugular intrahepatic portosystemic shunt (TIPS) in preventing cirrhosis.

Materials and Methods Seventeen patients diagnosed with BCS between 2010 and 2023 at the UKR were analyzed. Patients were categorized into acute (n = 10) and chronic (n = 7) BCS groups. Genetic testing for JAK2, Factor V Leiden, and MTHFR mutations was performed. Clinical outcomes, including the development of cirrhosis and the effectiveness of TIPS, were evaluated.

Results One patient died due to sepsis and acute liver failure, while another required liver transplantation. Genetic analysis identified JAK2 mutations in 10 patients, Factor V Leiden mutations in 2, and an MTHFR mutation in 1 patient. Hormonal contraception was the cause in one case, while two cases were idiopathic. TIPS was performed in 15 patients. Cirrhosis developed in 30 % of acute BCS patients and 71.4 % of chronic BCS patients.

Conclusion This study highlights the importance of early diagnosis and intervention, particularly with TIPS, in preventing cirrhosis in BCS patients. Genetic testing for JAK2 and Factor V Leiden mutations should be integrated into the diagnostic process. Early and effective management is crucial to improving outcomes in BCS.

P2.44 Identifying Risk Factors for Secondary Sclerosing Cholangitis in Critically Ill Patients: A Retrospective Analysis of ICU-Associated Variables

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Background: Secondary sclerosing cholangitis (SSC) is a serious complication that affects critically ill patients in intensive care units (ICU), often resulting in progressive biliary strictures and liver cirrhosis. Recently, SSC has been recognized as a distinct clinical entity, particularly in patients with prolonged ICU stays.

Materials and Methods: This retrospective study analyzed 2,910 patients treated in the surgical ICU at University Hospital Regensburg for at least five days between January 1, 2016, and December 31, 2021. Data were extracted from the hospital's SAP system and included demographic information (age, sex), laboratory results, medications, treatments, and complications encountered during hospitalization. Statistical analysis was conducted using SPSS to identify risk factors for SSC development.

Results: The analysis revealed a significant association between SSC and various clinical parameters, including patient age, sex, abnormal laboratory values, specific medications, and treatment interventions. Complications encountered during the hospital stay, such as infections or mechanical ventilation, were also linked to an increased risk of developing SSC.

Conclusion: These findings suggest that multiple ICU-related factors contribute to the development and progression of SSC in critically ill patients. Identifying specific risk factors, including demographic and clinical parameters, could improve early detection and intervention strategies, ultimately reducing the burden of SSC in critically ill populations.

P2.45 Patient safety, trans-sectoral quality of care, cost efficiency and interprofessional competence: An analysis of the interprofessional training wards

A-STAR in comparison to conventional wards with a hepatological focus at Regensburg University Hospital

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Introduction: Interprofessional collaboration is crucial. Since the introduction of interprofessional training wards in 1996, these have aimed to foster cooperation and communication among healthcare professionals. This study, conducted at the University Hospital Regensburg, evaluates patient outcomes, cost efficiency, transsectoral quality of care, and the satisfaction of patients, their families, and caregivers, comparing the interprofessional training ward A-STAR Regensburg to conventional wards.

Methods: The study was conducted from October 2019 to October 2024. Anonymized, standardized questionnaires were employed to assess patient outcomes, cost efficiency, and satisfaction, utilizing the Collaboration and Satisfaction About Care Decisions (CSACD) and Family Satisfaction in the Intensive Care Unit (FS-ICU) surveys. General practitioners and patients were also surveyed regarding transsectoral transfer quality.

Results: The analysis included 1,514 patients from the A-STAR and 5,847 from conventional wards. No significant differences were observed in clinical outcomes such as discharges against medical advice, complication-related readmissions, or mortality. The A-STAR ward demonstrated greater cost efficiency, with reduced material costs and higher DRG revenue per case. Patient, family, and caregiver satisfaction was significantly higher in the interprofessional ward. Additionally, improvements were noted in transsectoral care, including more accurate medication adjustments and fewer complications or new symptoms after discharge.

Conclusion: Interprofessional training wards like A-STAR provide patient care comparable to conventional wards while enhancing the quality of healthcare training. The results support the cost-effectiveness of IPTWs, increased satisfaction among patients and families, and improvements in transsectoral care quality. Their inclusion in medical curricula could positively influence patient safety and healthcare team dynamics.

P2.46 Incidence and risk factors of DILI in Ethiopian patients receiving tuberculosis treatment – do polymorphisms of hepatic transporter proteins play a role?

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Introduction: Tuberculosis (TBC) is a major global health threat with the highest prevalence in sub-Saharan Africa. Tuberculosis treatment (TBT) is often complicated by drug-induced liver injury (DILI), but the mechanisms are not fully understood. Hepatic transporter polymorphisms of bile salt export pump (BSEP) and multidrug resistance protein (MDR) 1 and 3 have been discussed as predisposing factors, but their impact on DILI has not been sufficiently investigated.

Methods: 410 TBC patients (56 % male, median 30 and range 1-85 years; 10 % < 18 years) were recruited before initiation of TBT in Ethiopia. Liver stiffness was evaluated by transient-elastography and blood samples were analyzed for serum liver injury markers, chronic hepatotrophic co-infections and BSEP/MDR1/MDR3-polymorphisms by PCR. Patients were evaluated for signs of DILI after 2, 4 and 8 weeks of TBT.

Results: Incidence of DILI was 4.9 % and 4.2 % after 2 and 4 weeks respectively and decreased to 1.2 % after 8 weeks. Severe DILI occurred in 1.2 % and 1 % after 2 and 4 weeks of treatment. Urban residency, non-compliance with questions about substance intake and signs of liver fibrosis at baseline were risk factors for DILI, but not hepatotrophic co-infections and gender. Analysis of hepatic transporter polymorphisms revealed an increased risk for development of severe DILI in patients with a heterozygous MDR3-polymorphism (rs2302386, RR 4.98; $p < 0.05$).

Conclusion: We demonstrated that, besides medical and sociodemographic parameters, polymorphisms of hepatic transporter proteins play a role as risk factors for DILI. The data supports the targeted monitoring of patients receiving TBT.

P2.47 Restricting datasets to classifiable samples allows prediction of immune checkpoint blockade-related hepatitis

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Immunological diseases are typically heterogeneous in clinical presentation, severity and response to therapy. Biomarkers of immune diseases often reflect this variability, especially compared to their regulated behaviour in health. This leads to a common problem that complicates biomarker discovery and interpretation – namely, unequal dispersion of immune disease biomarker expression between clinical subgroups necessarily limits a biomarker's informative range. To solve this problem, we introduce dataset restriction, a procedure that splits datasets into classifiable and unclassifiable samples. In advanced melanoma, restriction finds biomarkers of immune-related adverse event (irAE) risk after immunotherapy and enables us to build multivariate models that accurately predict immunotherapy-related hepatitis. The correct classification rate was significantly enhanced (73.3 %) after restriction in contrast to the baseline models (56.7 %). Hence, dataset restriction augments discovery of immune disease biomarkers, increases predictive certainty for classifiable samples and improves multivariate models incorporating biomarkers with a limited informative range.

P2.48 Low risk of variceal bleeding in chronic non-cirrhotic portal vein thrombosis

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Background: In patients with non-cirrhotic portal vein thrombosis portal cavernoma (PC) might occur within a few weeks. This leads to portal hypertension and variceal bleeding. There are few data available on the clinical course and prognosis in this rare disease.

Methods: 46 patients with chronic non-cirrhotic portal vein thrombosis were evaluated in a retrospective monocentric analysis over a ten-year period (January 1, 2014 – December 31, 2023).
Results: The study included 24 men (52 %) and 22 women (48 %). Concerning etiology, 24 patients (52 %) had a coagulation disorder, 5 patients (11 %) an abdominal inflammatory focus and 3 patients (6.5 %) a sleeve gastrectomy. 34 patients (74 %) received therapeutic anticoagulation. 11 patients (24 %) did not develop varices during the follow-up period. In 24 of the remaining 35 patients (68 %), varices were already present at the initial diagnosis of the PC. Variceal bleeding occurred in only 12 of the 46 patients (26 %), after a median period of 23 months after the initial diagnosis of the PC. Incidence of variceal bleeding was 10,9 %, 13 % and 19,6 % after 1,3 and 5 years after the diagnosis of PC, respectively. 27 patients (59 %) were treated with non-selective beta blockers. Only one patient died during the follow-up period.
Conclusions: In chronic non-cirrhotic portal vein thrombosis, varices are often present at the time of initial diagnosis of PC, but the risk of variceal bleeding appears to be lower than previously thought. The overall survival of these patients seems not to be limited with appropriate endoscopic and medical therapy.

P2.49 Value of plasma ammonia levels to predict hepatic encephalopathy after transjugular intrahepatic portosystemic shunt insertion

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Background: Placement of a transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for portal hypertension. Overt hepatic encephalopathy (oHE) is a complication after TIPS associated with increased morbidity. Elevated ratio of plasma ammonia (AMM) levels compared to local ULN has been associated with oHE, hepatic complications and increased mortality in patients with cirrhosis without TIPS. The role of AMM in risk stratification of post-TIPS oHE is unclear.
Methods: Patients with liver cirrhosis and TIPS placement were prospectively included. Follow-up (FU) was performed at 1, 3, 6 and 12 months after TIPS. Primary endpoint was oHE development, secondary endpoints were hepatic decompensation, infections or death/liver transplantation during one year after TIPS placement.
Results: Of 188 patients with TIPS, 148 patients with available baseline AMM levels were included. During FU, 37 % (55/148) of patients developed oHE. In multivariable competing risk analysis, baseline AMM/ULN (HR 2.03 [CI 1.42-2.89], p = 0.001) and FIPS score (HR 1.52 [CI 1.03-2.24], p = 0.037) were independently associated with oHE. AMM at FU1 was available in 100 patients, of whom 29 % (29/100) developed oHE after FU1. In multivariable competing risk analysis, AMM/ULN (HR 5.48 [CI 2.37-12.67], p < 0.001), PHES (HR 0.86 [0.78-0.96], p = 0.005) and FIPS (HR 3.57 [CI 1.79-7.14], p < 0.001) at FU1 were independently associated with oHE after FU1. No significant association between AMM/ULN and the secondary endpoints was detected.
Conclusion: AMM levels before TIPS are independently associated with oHE after TIPS. AMM levels may serve as an additional marker for risk stratification of patients.

P2.50 Identifizierung und Validierung eines idealen PSG-Reduktionskorridors zur optimalen Aszitekontrolle bei Minimierung des HE-Risikos nach TIPS-Anlage

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Einleitung und Ziele: Klinisch signifikante portale Hypertension (CSPH) ist eine Hauptkomplikation der Leberzirrhose und führt zu refraktärem Aszites und hepatischer Enzephalopathie (HE). Der transjuguläre-intrahepatische-portosystemische Shunt (TIPS) ist eine wirksame Behandlungsmethode der CSPH. Unklar ist, welcher Rückgang des porto-systemischen Druckgradienten (PSG) eine ausreichende Aszitekontrolle ohne signifikant erhöhtes HE-Risiko ermöglicht. Ziel dieser Studie ist die Identifikation dieses „idealen" Zielbereichs.
Methodik: In einer multizentrischen, retrospektiven Studie wurden Patient*innen aus Hannover, Wien und Hamburg (2000–2023) untersucht. Einschlusskriterien waren PTFE-beschichtete Stents, refraktärer Aszites, Leberzirrhose und kein HCC außerhalb Milan. Der PSG wurde vor/nach der TIPS-Anlage gemessen. Die Kohorte wurde in eine Trainings-(60 %) und Validierungskohorte (40 %) aufgeteilt. Die Auswertung erfolgte mittels Competing-Risk (CR) Random-Survival-Forest (RSF) Modellen und Partial-Dependence-Plots (PDP). Lebertransplantation/Tod waren konkurrierende Ereignisse.
Ergebnis: Insgesamt wurden 729 Patient*innen (medianer MELD: 13 (IQR 10–16), 66 % männlich, 23 % HE pre-TIPS) in die Analysen eingeschlossen. Zwischen Trainings (n = 438) und Validierungskohorte (n = 291) gab es keine signifikanten Unterschiede in den Baselinecharakteristika. In der Trainingskohorte wurde mittels maximaler Rangstatistik und PDP des RSF ein idealer PSG-Reduktionsbereich von 60-80 % ermittelt. In der CR-Analyse zeigten Patient*innen mit PSG-Senkung von 60-80 % signifikant weniger aszitischen Dekompensationen (AD) (p = 0.027, sHR:0.7[0.52–0.96]) bei gleicher HE Inzidenz (p = 0.62, sHR:0.92[0.67–1.27]) nach TIPS-Anlage. Der PSG-Reduktionsbereich konnte in der Validierungskohorte bestätigt werden (AD: p = 0.028, sHR:0.66[0.46–0.96]; HE: p = 0.59, sHR:0.89[0.61–1.32]).
Schlussfolgerung: Eine PSG-Reduktion um 60-80 % ist, im Vergleich mit einer Reduktion außerhalb dieses Bereichs, mit signifikant weniger AD und einem unveränderten HE Risiko assoziiert. Bei der TIPS-Anlage sollte daher eine Senkung des PSG in diesen Bereich angestrebt werden.

P2.51 Safety and efficacy of Upadacitinib in patients with primary sclerosing cholangitis: a multicentre, retrospective study

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Background and Aims: Primary Sclerosing Cholangitis (PSC) is closely associated with inflammatory bowel disease (IBD). Upadacitinib (Upa), a selective Janus-Kinase inhibitor (JAKi), was approved for IBD treatment in 2022/23. This study assesses the safety and efficacy of Upadacitinib on liver and bowel disease in PSC-IBD patients.
Method: Data from multiple centers were collected retrospectively at baseline and after 3, 6, 12 months follow-up (m-FU) and annually thereafter.

Results: Forty patients (70 % male, median age 21 years) from 9 centers were included, with 31 completing 3-month follow-up. Of these, 87.5 % had Ulcerative Colitis and 12.5 % had a Crohn's phenotype. Prior to Upa, 77.5 % received at least two biologicals, and 15 % another JAKi. Adverse events were reported in 10 cases, including 3x elevated transaminases, 3x anal fissures/abscesses, 1x low WBC and 3x respiratory infections. Upa was discontinued in 20 % of cases mostly due to lack of efficacy. In patients continuing Upa, ALP levels showed a non-significant decrease from 348 at baseline to 270 U/L at 3-m-FU (p = .068), while mucosal inflammation (Mayo Endoscopic subscore) significantly improved, with a median difference of -1 (p = .015) by 6 months. Transient elastography (p = .237; mean of 6.6 to 7.4 kPa at 6m-FU) and AST levels remained stable (144 vs 118 U/l at 3m-FU, p = .597).

Conclusion: Upadacitinib improved PSC-associated IBD, with a trend toward decreased ALP levels. However, the occurrence of hepatitis and infections highlights the need for further studies.

P2.52 ECP as a potential treatment for liver rejection after transplantation – influence of cell death on T cell activation

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Use of marginal livers in transplantation is increasing, leading to more complications resulting from pre-existing tissue damage and worse ischemia-reperfusion injury (IRI). Consequently, there is a major research focus on reducing early transplant injury and inflammation, which is partly driven by IL-17-secreting γδ T cells. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy applied in management of heart and lung transplant rejection. ECP leverages the potent suppressive effects of apoptotic cells, to control T cell-mediated diseases and to dampen acute and chronic inflammation.

In this study, we explored mechanisms of αβ and γδ T cell suppression by ECP using indirect coculture experiments. Apoptotic and pre-apoptotic PBMCs were obtained from clinical ECP products. These were indirectly cocultured with CD3/28/2-stimulated human T cells across a transwell membrane. The activation status of T cells was assessed by flow cytometry after 24h and 48h. Notably, we observed a reduction in CD69 expression in αβ (7.25 ± 11.99 %, p = 0.0244) and γδ (9.26 ± 19.62 %, p = 0.0302) T cells in ECP-treated cultures compared to control cultures (n = 14).

Our preliminary results support the hypothesis that apoptotic cell-derived, transwell-permeating factors influence T cell activation. These factors may include soluble mediators (such as cytokines, metabolites or miRNAs) and extracellular vesicles. In the clinical setting, we might expect suppressive factors, especially as particulates, to accumulate in liver after intravenous infusion of ECP products. Hence, we speculate that factors release by apoptotic PBMC may be therapeutically useful in controlling pathological immune responses after liver transplantation through suppression of IL-17-secreting γδ T cells, amongst other subsets.

P2.53 Circulating matricellular fibrosis markers TSP2, IGFBP7, TSP4 and the M2-macrophage marker CD163 in predicting disease stage and progression in primary sclerosing cholangitis

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Background: Primary sclerosing cholangitis (PSC) is a complex liver disease with a lack of biomarkers for the assessment of disease progression. We investigated five serum markers – Thrombospondin-2 and -4 (TSP2/-4), Insulin-like growth factor-binding protein 7 (IGFBP7), Cluster of Differentiation 163 (CD163) and PRO-C3 – as potential indicators of fibrosis and outcome in PSC.

Method: We analysed serum marker levels in 142 people with PSC from the University Medical Center Hamburg-Eppendorf using ELISA, alongside liver stiffness measurements, assessments of disease activity and patient outcome. Results were externally validated in 170 patients from Oslo University Hospital Rikshospitalet.

Results: In multivariable regression analyses, TSP2, IGFBP7, CD163, TSP4 and PRO-C3 were found to be independently and positively associated with liver stiffness (p < 0.001 – 0.014). ROC curve analyses indicated that especially TSP2, IGFBP7, CD163 and PRO-C3 were effective in distinguishing between patients with and without cirrhosis (AUCs 0.87 – 0.90). A newly developed fibrosis score, including a combination of the aforementioned markers, further enhanced the ability to discriminate for cirrhosis, resulting in an AUC of 0.95 (95 % CI: 0.92 – 0.98, p < 0.0001). In both, the derivation and validation cohorts, patients with baseline serum levels of TSP2 and CD163 indicating advanced fibrosis (stage ≥ F3), experienced significantly reduced transplant-free survival (Log Rank p < 0.001).

Conclusion: Circulating TSP2, IGFBP7, CD163, TSP4 and PRO-C3 levels were significantly associated with advanced fibrosis and cirrhosis in people with PSC. Furthermore, especially TSP2 and CD163 serum levels were associated with transplant-free survival, indicating their potential as prognostic biomarkers in PSC.

P2.54 Die Entstehung von ACLF ist mit einer geschlechtsunabhängigen Reduktion des Verbrauches von Leptin in der Leber assoziiert

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Einleitung: Bakterielle Infektionen (BI) sind ein häufiger Auslöser von akut-auf-chronischem Leberversagen (ACLF) bei leberzirrhotischen Patienten. Dysregulierte systemische Inflammation (SI) ist verantwortlich für die Entstehung eines ACLFs. Leptin, ein Stoffwechselhormon, das hauptsächlich von weißen Fettzellen sezerniert wird, ist wesentlich an der Regulierung von SI, aber auch an der Immunantwort gegen BI beteiligt. Bislang ist unklar, inwiefern Leptin die Entstehung von ACLF bei Leberzirrhose beeinflusst.

Methoden: Wir untersuchten den Zusammenhang zwischen Leptin und Lebererkrankungen retrospektiv in einer Kohorte mit Leberzirrhose-Patienten, die einen transjugulären intrahepatischen portosystemischen Shunt (TIPS) erhielten. Die Leptinkonzentration aus Vorhof, Lebervene, Pfortader und Kubitalvene wurde mittels Enzyme-Linked Immunosorbent Assay (ELISA) zum Zeitpunkt der TIPS-Implantation gemessen und die absoluten Konzentrationen in Pfortader und Lebervene wurden zur Kubitalvene normalisiert.

Ergebnisse: Insgesamt wurden 180 Patienten eingeschlossen (58 % männlich; medianes Alter: 58,87 Jahre; 59 % alkoholisch; ACLF: 25 %; CHILD-Pugh: 17 % A, 56 % B). Die Leptinkonzentrationen stiegen signifikant in Relation zum Body-Mass-Index (BMI) an (p < 0,0001) und korrelierten negativ mit der Anzahl der Leukozyten (p = 0,0181). Alter und Geschlecht waren keine signifikanten Einflussfaktoren. Patienten mit Leberzirrhose (CHILD A, B) wiesen signifikant hö-

here Leptin Konzentrationen in der Pfortader, verglichen mit der Lebervene auf (p = 0,0018). Interessanterweise ist dieser Effekt mit Fortschreiten der Leberzirrhose (CHILD C) und der Entstehung von ACLF nicht zu detektieren.
Schlussfolgerung: Unsere Ergebnisse legen einen hepatischen Verbrauch von Leptin, das mutmaßlich aus dem Splanchnikusgebiet stammt, nahe. Hierdurch sinkt vermutlich die SI (Leukozyten). Im Rahmen der Progression der Leberzirrhose kommt es zu einer Leptinresistenz, die SI und die Entstehung des ACLFs begünstigt.

P2.55 Evaluation of tacrolimus and mycophenolate mofetil as second-line therapy in autoimmune hepatitis – real-world data from the Charité Berlin cohort

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Introduction: Azathioprine with steroids is considered the standard first-line treatment for autoimmune hepatitis (AIH). The CAMARO study suggests mycophenolate mofetil (MMF) with steroids being equally effective in treatment-naive AIH. The optimal second line therapy for AIH, e.g. efficacy and tolerability of tacrolimus, is less well defined.
Methods: We performed a retrospective single-centre study on second-line therapies for AIH. Criteria for exclusion were additional autoimmune liver diseases or liver transplantation. Biochemical parameters were collected at change of therapy, after 12 months and at last follow-up. Biochemical remission was defined as normalization of transaminases and immunoglobulin G.
Results: At Charité Berlin, 59 out of 490 AIH patients received MMF or tacrolimus as second-line therapy. Of 59 patients, 12 received tacrolimus (50 % with cirrhosis) and 47 received MMF (19.1 % with cirrhosis) (cirrhosis: p = 0.036). Both groups showed significant ALT reductions after 12 months. Despite significantly higher levels of alanine aminotransferase (ALT) at change of therapy in the tacrolimus group (ALT/ULN 4.1 vs. 1.6 in the MMF group, p = 0.031), biochemical remission was achieved in more patients on tacrolimus compared to MMF (66.6 % vs. 50 %, p = 0.187). The median duration of second-line therapy was significantly longer with MMF (46 months) than with tacrolimus (25 months) (p = 0.007). Drug discontinuation due to side effects occurred in 2 tacrolimus patients and 5 MMF patients.
Conclusion: Our results indicate that both MMF and tacrolimus are effective second-line therapies for AIH, with tacrolimus showing numerically higher remission rates and being used more frequently in patients with advanced and more active liver disease.

P2.56 Unterschiedliche Cluster des intestinalen Mikrobioms bei fortgeschrittener Leberzirrhose korrelieren mit Antibiotikabehandlung, Störungen der Darmbarriere und systemischer Inflammation

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Hintergrund: Das Stadium der dekompensierten Leberzirrhose (dLZ) wird durch eine Dysbiose des intestinalen Mikrobioms gekennzeichnet. Unser Ziel war es, bakterielle und fungale Komponenten des Mikrobioms zu charakterisieren und ihren Zusammenhang mit der Darmpermeabilität, der systemischen Inflammation (SI) und dem Krankheitsverlauf von dLZ-Patient*innen zu untersuchen.
Methode: Prospektiv wurden von 2017–2022 Proben von 95 konsekutiven dLZ-Patient*innen gesammelt. Metagenomische Shot-Gun-Sequenzierung und durchflusszytometrische Mikrobiom-Analysen wurden durchgeführt und Plasma-Zonulin, sCD163 sowie 45 Zytokine gemessen, um die Darmpermeabilität und SI zu analysieren. Die 90-Tage-Inzidenz Zirrhose-assoziierter Komplikationen wurde in Competing-Risk-Analysen untersucht.
Ergebnisse: Die Patienten wurden in drei Gruppen (G1-G3) mit deutlich abweichenden bakteriellen Kompositionen eingeteilt. G1 wies die geringste Diversität auf und wurde von Enterococcus spp. dominiert (77,97 %), während die Mikrobiota von G2 hauptsächlich aus Bifidobakterien bestanden (52,31 %). G3 zeigte am meisten Ähnlichkeiten zu den gesunden Kontrollen (GK). Patient*innen wiesen im Vergleich zu GK reduzierte Bakterienkonzentrationen auf (Median 2,65x10^9 Zellen/Gramm Stuhl), insbesondere G1 (Median 2,65x10^9 Zellen/Gramm). Pilze fehlten bei GK weitgehend, während sie bei G1-Patient*innen in großer Anzahl detektiert wurden, insbesondere Candida spp. (51,63 %). Zudem erhielten G1-Patient*innen am häufigsten Antibiotika (86,8 %). Die G1-Plasmaspiegel von Zonulin (p = 0,044) und sCD163 (p = 0,019) überstiegen die der anderen Patient*innen deutlich. Außerdem wurden bei G1 signifikant erhöhte Konzentrationen von Interleukin (IL)-1alpha (p = 0,002), IL-17 (p = 0,038), IL-18 (p = 0,007) und weiteren proinflammatorischen Zytokinen festgestellt, die positiv mit der Enterokokkenhäufigkeit korrelierten. G1-Patient*innen wiesen eine numerisch höhere Infektionsinzidenz auf (p = 0,09).
Schlussfolgerung: Sogar im Endstadium der Zirrhose sind unterschiedliche bakterielle und fungale Muster nachzuweisen. Antibiotika verstärken diese Dysbiose, was zu einer erhöhten Darmpermeabilität, bakterieller Translokation und erhöhter SI beiträgt.

P2.57 Reduzierte Inzidenz von Peritonitis und verringerte Explantationsrate durch Beimengung von Silberpartikeln bei getunnelten Peritonealkathetern bei Patient*innen mit refraktärem Aszites

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Einleitung: Patient*innen mit therapierefraktärem Aszites könnnen Kontraindikationen gegen einen transjugulären intrahepatischen portosystemischen Shunt erfüllen. Hier bieten getunnelte Peritonealkatheter (PeKa) eine Alternativtherapie. Die Behandlung mit PeKa kann jedoch mit Device-Infektionen assoziiert sein. Um dieses Risiko zu verringern, wurden den Kathetern antimikrobiell-wirkende Silberpartikel (sPeKa) hinzugefügt. Ob dies jedoch die Infektions- und Explantationsrate dieser Katheter senkt, ist bisher unerforscht.
Methodik: Alle Leberzirrhose-Patient*innen ohne maligne Erkrankungen, außer HCC in Milan, denen zwischen 2012 und 2023 ein PeKa an der Medizinischen Hochschule Hannover implantiert wurde, wurden untersucht. Von 177 Patient*innen mit PeKa Implantation bekamen 27 einen sPeKa. Um eine Vergleichbarkeit der Gruppen zu gewähren, wurde ein 3:1-Propensity-Score-Matching nach den Faktoren MELD und Zustand nach spontaner bakterieller Peritonitis (SBP) durchgeführt. Final wurden 81 Patient*innen mit PeKa mit 27 mit sPeKa in einer Competing-Risk-Regressionsanalyse verglichen. Die Endpunkte waren Mortalität, Peritonitis, Deviceexplantation und Rehospitalisierung.
Ergebnis: Beide Gruppen waren in Baselinefaktoren wie Alter, MELD, Zustand nach SBP oder Norfloxacineinnahme vergleichbar (Alter: 64 ± 13 vs 61 ± 11,

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p = 0.29, MELD: 16 ± 5 vs 16 ± 5, p = 0.91; Zustand nach SBP: 33 % vs 33 %, p = 1.00; Norfloxacineinnahme: 70 % vs 59 %, p = 0.40). Die 1-Jahres-Mortalität war ähnlich (HR 1.66, 95 % CI 0.65-4.22, p = 0.29). Die Behandlung mit sPeKa war mit einer niedrigeren Peritonitis-Inzidenz (HR 0.38, 95 % CI 0.17-0.86, p = 0.02), sowie einer verringerten Explantationsrate (HR 0.39, 95 %CI 0.16-0.95, p = 0.04) assoziiert. sPeKa-Patient*innen hatten ein signifikant niedrigeres Rehospitalisierungsrisiko (HR 0.52, 95 % CI 0.27-0.99, p = 0.046). Infektionen stellten den häufigsten Explantationsgrund dar (sPeKa: n = 3 (43 %) vs PeKa: n = 19 (58 %)).

Schlussfolgerung: Gegenüber konventionellen PeKa sind sPeKa sind mit einer niedrigeren Peritonitis-Inzidenz und weniger Explantationen assoziiert.

P2.58 Unique histological liver phenotype in children and adults with severe alpha-1 antitrypsin deficiency (Pi * ZZ genotype)

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Aims/objectives: Liver disease in severe alpha-1 antitrypsin (AAT) deficiency (Pi * ZZ genotype) displays a biphasic pattern with the first peak in early childhood and the second, adult peak after the age of 40 years. Our aim was to histologically characterize the pediatric and adult liver disease.

Methods: We recruited 67 adults and 48 Pi * ZZ children aged four weeks to 17 years from six countries who underwent a liver biopsy/transplantation. A blind histological scoring was performed by two histopathologists.

Results: Pediatric Pi * ZZ samples originated more often from liver transplantation (64.6 vs. 21.2 %, p < .0001) and children displayed significantly higher liver enzymes than adults. Compared to adults, children presented a significantly higher fibrosis stage according to METAVIR (4.0 vs. 2.5, p < .0001). Pi * ZZ adults more frequently had higher liver steatosis, while bile plugs and duct paucity were significantly more common in Pi * ZZ children (bile plugs: 43.8 vs. 10.4 %, p < .0001; duct paucity 58.3 vs. 1.5 %, p < .0001). No difference in AAT accumulation (Clark) was found. When subdividing the pediatric cohort based on age (< 1 year, 1-5 years and 6-17 years), cirrhosis was more common in both older age groups than in younger children (64.7 vs. 75.0 vs. 30.8 %, p = .045). There were no differences in liver steatosis, inflammation, or cholestasis parameters, but youngest children displayed less AAT accumulation and less frequently had larger aggregates.

Conclusions: Our study reveals unique histological patterns in Pi * ZZ children and adults thereby providing basis for patient counseling and further mechanistic studies.

P2.59 Robust acute-phase response highlights necessity of time-matched sham-operated controls in early liver ischemia/reperfusion injury studies

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DOI 10.1055/s-0044-1801083

Most mechanistic studies on hepatic ischemia/reperfusion injury (IRI) are performed in rodent models with 30-60 min of 70 % warm ischemia (occlusion of left and median liver lobes), followed by 3-6 (early) or 24-48 hours (late) of reperfusion. These studies frequently demonstrate strong inflammatory responses. However, many investigations rely on a single sham-operated control group, often sacrificed after the longest reperfusion, leaving no controls for early reperfusion time points.

In this study, we compared hepatic IRI with sham-operated counterparts at early reperfusion times (30 min ischemia, 3 h and 5 h reperfusion). Both groups displayed similar robust inductions of pro-inflammatory cytokines (Il6, Osm, Il1b, Cxcl2), acute-phase genes (Saa2, Cd14, Lbp, Hamp1, Icam1), and modulation of cytokine receptor expression (Il6st, Osmr, Lifr). This suggests that much of the acute inflammatory response is triggered by the laparotomy needed for vascular occlusion rather than IRI itself. While most of the inflammatory response declined between 5 h and 7 h of reperfusion, the acute-phase gene Saa2 continued to increase, indicating it may be specifically linked to IRI.

In conclusion, our study underscores the importance of incorporating time-matched sham-operated controls to accurately assess and interpret hepatic IRI mechanisms, as laparotomy alone triggers a potent acute-phase response. Without these controls, it is challenging to distinguish IRI-specific and surgery-induced inflammatory responses during early reperfusion. Similarly, comparisons between wild-type and knock-out models require time-matched sham-operated controls to confirm that observed phenotypic differences are directly attributable to changes in response to hepatic IRI rather than to the general acute-phase reaction.

P2.60 Multi-Omics Gene Signatures Predict Disease Trajectory in a Cholestasis-Based ACLF Mouse Model

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Acute-on-chronic liver failure (ACLF) is a severe complication of chronic liver diseases, often fatal, with poorly understood pathomechanism and prognosis. We aiming to develop a novel in vivo model using aged Abcb4 knockout (KO) mice (cholestasis-based) treated with a sublethal dose of CCl_4, featuring the ACLF. Two distinct outcomes – good and poor prognosis – based on survivability and necrosis patterns were reported. Mice with good prognosis exhibited massive hepatic necrosis initially, followed by recovery, whereas poor prognosis mice showed minimal necrosis and die within 24h. To investigate the ACLF pathomechanism, we conducted a longitudinal multiomic analysis integrating transcriptomic and proteomic data. Using Multi-Omics Factor Analysis (MOFA), we identified two conserved dynamic trajectories. The "recovery trajectory" showed upregulation of candidates involved in metabolism, including Acot1, Hmgcs1, and G6pc, suggesting an adaptive metabolic response promoting recovery. The "injury trajectory" involved regulators of inflammation and injury pathways, i.e. Fgg, Itgam, and Cd63, indicating an immune response linked to poor outcome. Validation using public datasets demonstrated that the injury trajectory correlated with increasing chronic liver disease severity in ACLF patients. Then, we performed ROC analysis of transcriptomic and proteomic changes at 24h post-CCl_4, identifying nine prognostic biomarkers, including Abhd4, Cd14, and Slc38a2. Using Single-nuclei RNA-sequencing we identified clusters of hepatocytes, cholangiocytes, Kupffer cells, endothelial cells, and stellate cells, with genes involved in cell death, acute phase response, and ROS function enriched in the poor prognosis. Our multiomics approach identified novel ACLF-related biomarkers and underscore further exploration of secreted proteins, paving the way for prognosis, and personalized interventions.

P2.61 Ultrasound and Elastography for Detection of Portal Hypertension in Common Variable Immunodeficiency

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Background and Aims: Porto-sinusoidal vascular liver disease (PSVD) is a serious complication occurring in patients with CVID. Currently, there is a lack of well-defined non-invasive markers for early detection. This study aimed to assess the diagnostic accuracy of ultrasound and elastography for predicting clinically significant portal hypertension (CSPH) caused by PSVD in patients with CVID.

Methods: Patients from the outpatient clinic at the CCI, University of Freiburg, were included from 03/22 to 09/24. Exclusion criteria were liver cirrhosis, portal vein thrombosis and history of TIPS-implantation. All participants underwent a standardized abdominal ultrasound protocol, including duplex sonography of liver and spleen, and liver (LSM) and spleen stiffness measurement (SSM) using transient elastography.

Results: 17 patients with and 50 without PSVD were included. Varices were observed in 15 and ascites in 8 patients with PSVD. LSM and SSM were significantly elevated in patients with CSPH (LSM: 12.1kPa [9.4;15.7] vs. 4.9kPa [3.8;6.4], $p < 0.001$; SSM: 74.8kPa [62.1;75.0] vs. 26.5kPa [16.3;39.6], $p < 0.001$) compared to those without. The portal congestion index, measured as ratio between cross sectional area (cm2) and blood flow velocity (cm/sec) of the portal vein, was higher in patients with CSPH (0.17 [0.11;0.22] vs. 0.08 [0.06;0.11], $p < 0.001$). Optimal cut-offs determined by AUC analysis were 7.95kPa for LSM (AUC 0.948) and 42.9kPa for SSM (AUC 0.959).

Conclusion: LSM and SSM demonstrate high diagnostic accuracy for distinguishing patients with and without PSVD. Incorporating elastography into routine evaluation for CVID patients could facilitate timely diagnosis and management of complications.

P2.62 Intra and Extrahepatic Cholestasis Due to Hepatic Duct Compression Caused by Cavernous Transformation of the Portal Vein: A Case Report and Literature Review

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Introduction: Cavernous transformation of the portal vein (CTPV) is a rare but clinically significant vascular anomaly that often leads to portal hypertension and portal biliopathy. In CTPV, the development of a network of collateral veins occurs secondary to portal vein thrombosis, which can cause compression of the hepatic ducts. This report presents a case of intra- and extrahepatic cholestasis in a 37-year-old woman, highlighting the challenges in diagnosing and managing CTPV and its complications.

Methods: The patient presented with elevated liver enzymes and history of portal hypertension. Imaging studies, including abdominal ultrasound and MRCP, revealed common hepatic duct compression due to portal cavernoma. Endoscopic retrograde cholangiopancreatography (ERCP) was performed to manage biliary strictures. Literature review was conducted to explore current treatment options, ranging from anticoagulation therapy to endoscopic interventions.

Results: The patient exhibited significant intra- and extrahepatic bile duct dilation, with high-grade stenosis of the common hepatic duct. A stent was placed via ERCP, resulting in a marked reduction in liver enzyme levels and symptomatic relief. Follow-up ERCP three months later confirmed the persistence of biliary stenosis, requiring stent replacement. The patient remained stable without complications such as post-ERCP pancreatitis.

Discussion: This case underscores the complexity of diagnosing CTPV and managing its associated biliary strictures. ERCP proved to be an effective therapeutic tool in decompressing the bile ducts and improving liver function. Collaboration between hepatologists, radiologists, and endoscopists is crucial for successful CTPV's management. Further research is needed to optimize treatment strategies and long-term outcomes in this rare vascular condition.

P2.63 Symptom Self-Reporting in PBC: Consolidated results of a Mobile App Approach

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Background: Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease causing bile duct destruction and inflammation, impacting patient quality of life (QoL) due to variable symptoms. Digital symptom-tracker apps may improve patient care through enhanced monitoring. This study reassessed

symptom burden in PBC patients using a tailored symptom-tracker app, focusing on its usability, effectiveness, and impact on management and QoL.

Methods: Based on the Kautz5 gUG "Symptomtracker" questionnaire, our REDCap-based PBC-app allowed users to log symptoms over four weeks, alongside medication use. Ethics approval and data security complied with German regulations. User feedback was incorporated for better usability. Symptom data were standardized, and R software was used for descriptive statistics and Chi-square tests.

Results: From March 2023 to October 2024, 207 patients (184 female, 20 male) were enrolled, median age 51 years. Among 90 patients who completed the questionnaire, fatigue was most prevalent (87.8 %), followed by joint pain (80 %), concentration difficulties (74.4 %), abdominal discomfort (70 %), and sicca symptoms. Other common symptoms were leg cramps (50 %) and swollen feet (40 %); jaundice was rare (7.8 %). Older patients, especially those aged 50–60, reported higher symptom burden, but Chi-square tests showed no significant differences across age or gender.

Conclusion: This study highlights a significant symptom burden in PBC, particularly fatigue and joint pain. While older patients reported more symptoms, no significant differences were observed by age or gender. The symptom-tracker app enhanced monitoring and patient engagement, showing the potential of digital tools in PBC management. Further research is needed to evaluate long-term impacts.

P2.64 Feasibility and Mortality Prediction of Bedside Rectus Femoris Muscle Ultrasound for Sarcopenia Diagnosis in Liver Cirrhosis

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DOI 10.1055/s-0044-1801088

Background: Sarcopenia is highly prevalent in patients with advanced liver cirrhosis (LC), serving as an independent risk factor for increased morbidity and mortality. This study evaluated the feasibility and prognostic impact of bedside rectus femoris muscle (RFM) ultrasound in patients with LC to identify patients at risk for sarcopenia.

Method: 84 patients with LC hospitalized at a tertiary centre (05/22–02/24) were prospectively included. Sarcopenia assessment within 24–48h of admission included handgrip strength, chair rise test (CRT), RFM ultrasound, and bioelectrical impedance analysis (BIA). Physical performance was measured by timed up and go (TUG) test and short physical performance battery (SPPB).

Results: 77 % of patients had decompensated LC (CP B > CP C). The most common etiology was alcoholic LC. RFM thickness (MTRFM) and cross-sectional area (CSARFM) significantly decreased in CP C patients, also after normalizing for height (m^2). AUROC for predicting low PhA (≤ 4.9 °) by BIA was the highest for MTRFM/height^2 (0.723) and CSARFM/height^2 (0.758). Prolonged CRT and TUG test times were associated with lower MTRFM and CSARFM. Higher muscle echogenicity correlated with poorer TUG and SPPB performance. Patients with low RFM muscle mass had significantly shorter survival. Sarcopenia defined by prolonged CRT time and low CSARFM/height^2 effectively identified patients with highest HR (4.009; 95 %CI 1.792-8.967) for mortality.

Conclusion: In patients with LC, ultrasound of RFM is a feasible bedside method for detecting those at risk for sarcopenia. Combined with muscle strength assessment, it effectively identifies patients at high mortality risk, highlighting its value as a practical tool for diagnosing sarcopenia.

P2.65 Cytokine adsorption during normothermic machine perfusion of porcine livers

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DOI 10.1055/s-0044-1801089

Normothermic machine perfusion (NMP) enables the evaluation of donor liver viability and offers the potential for graft resuscitation prior to transplantation. However, the impact of NMP-induced inflammatory responses on liver allografts remains unclear, with possible consequences for graft function, rejection rates, and recipient survival. The use of Cytosorb for cytokine adsorption has shown promise in reducing inflammation during cardiopulmonary bypass and in critically ill patients with multi-organ failure. This study aimed to investigate the effect of the Cytosorb adsorber on liver grafts during NMP. Livers obtained from eleven pigs underwent NMP for 6 hours without cytokine adsorption (control group) or with cytokine adsorption (cytosorb group). NMP with cytosorb therapy showed a reduction of proinflammatory cytokines and danger-associated molecular patterns including IL6 (3308.44 vs. 1563.80; p = 0.030), IL1β (277.10 vs. 83.27; p = 0.126), IL18 (6838.79 vs. 383.96; p = 0.004) and HMGB1 (2442.20 vs. 74.17: p = 0.004) after 6 hours. In line with these results the liver injury was significantly reduced measured by AST values (2389.20 vs. 1319.00; p = 0.034). While bile production, as a marker of liver function, remained stable with CytoSorb use, there was a positive trend in lactate clearance. Our data suggest that removing pro-inflammatory mediators from the perfusate, potentially decreases inflammation and reduces liver injury. Thus, incorporating adsorptive therapies like CytoSorb during NMP could be a promising strategy to enhance graft viability and transplant outcomes.

P2.66 Abstract for section “Clinical Hepatology, Surgery, LTX”

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Introduction: Thrombospondin-1 (TSP-1) is involved in several biological pathways, including angiogenesis, tissue repair, and wound healing. Increased TSP-1 levels contribute to pathological processes like inflammation and ischemia, which can lead to excessive reactive oxygen species (ROS) production. In the liver, TSP-1 promotes hepatocyte proliferation and migration by interacting with integrin receptors on hepatocytes, indicating its potential as a target and prognostic marker for liver regeneration.

Methods: This prospective single-center study included 22 patients who underwent liver transplantation (15 deceased, 7 living donors) at Jena University Hospital from November 2021 to September 2022. TSP-1 concentrations were measured in the serum of transplant recipients via ELISA at several time points: preoperatively, during the anhepatic phase, after reperfusion, and on postoperative days 1, 2, 7, and 14. Clinical data, including cold ischemia time and lab values, were analyzed and collated in a SQL database.

Results: Recipients had a mean age of 57 years, and donors had a mean age of 61 years. TSP-1 concentrations changed significantly over time, peaking during the anhepatic phase. Younger recipients and donors exhibited higher TSP-1 levels, though without statistical significance. Patients with shorter cold ischemia times had significantly higher TSP-1 levels, as did those with longer operation durations and hospital stays.

Conclusion: The results suggest that TSP-1 may play a role in postoperative healing in liver transplant patients, offering insights into recovery and possible prognostic implications for surgical outcomes.

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Poster Visit Session III
METABOLISM (INCL. MASLD)
14/02/2025, 04.25pm – 05.00pm

P3.01 Stabilin1 mediates ingestion of oxidized erythrocytes by LSECs (efferocytosis)

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DOI 10.1055/s-0044-1801091

Backgrounds: Previous studies have identified hemolysis as an important predictor for survival in patients with alcohol-related liver disease (ALD). Here we aimed to study the role of liver sinusoidal endothelial cells (LSEC) on the clearance (efferocytosis) of oxidized red blood cells (RBC).
Methods: Real-time live videos of LSEC efferocytosis were taken using incuCyteS3. Protein and mRNA levels of HO-1, Nrf2, and stabilin-1 were measured by qPCR and immunoblotting. Stabilin-1 was knocked down using siRNA. LSEC efferocytosis was further studied in a mouse model of chronic ethanol exposure and in an in vivo hemolysis model using phenylhydrazine (PHZ) by immunofluorescence and immunohistochemistry.
Results: Live microscopy demonstrates that oxidized RBCs are rapidly ingested by LSECs, followed by induction of HO-1 and its upstream regulator Nrf2. In addition, LSEC efferocytosis was mediated by scavenging receptors such as Stabilin-1. Silencing of endothelial Stabilin-1 partially blocked efferocytosis by 50 %. Efferocytosis could also be induced by hemin and lysed RBC. In a PHZ-induced hemolysis and a chronic ethanol mouse model, uptake of RBCs by LSECs could be confirmed using immunofluorescence staining. RBCs could be primed for efferocytosis using ethanol starting from levels as high as 25 mM. Finally, we show in a cohort of heavy human drinkers (n = 34) that hepatic Stabilin-1 mRNA highly correlates with mRNA of HO-1 and Nrf2 (r = , P < 0.05).
Conclusion: We here show that oxidized and ethanol primed RBCs are rapidly taken up by LSECs, a process that is likely to contribute to hemolysis in ALD.

P3.02 Live(r) and Let Live: Combining AI and Citizen Science in Hepatology

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Background: The citizen science movement aims to better incorporate citizens in scientific processes. Technology makes it trivial to include citizens for classification, data acquisition, annotation or analysis tasks, thus raising awareness for unknown, yet prevalent diseases such as Metabolic dysfunction-associated steatotic liver disease (MASLD).
Methods: Hepatology inspiring citizen science literature was reviewed, including Galaxy Zoo (astronomy), eteRNA (biology), WOW (meteorology), and Telraam (traffic). Galaxy Zoo showcases the power of citizen based image annotation, leading to better understanding of galaxy formation, whereas eteRNA stimulates gamified problem solving, yielding new and relevant synthesised molecules for scientists. WOW demonstrates how local citizen measurements can produce increased precision for weather model estimates, whereas Telraam empowers citizens to measure traffic intensity, thus influencing policy making.
Results: A "liver zoo" where users annotate lesions, fibrosis and fat deposits on multiple images per patient over time, could enhance disease progression modelling with AI. Like eteRNA, gamification could incentivise nutritional and lifestyle changes, as part of liver patient treatment plans, yielding better health outcomes. A WOW analogy is the encouragement of patients to share nutrition and exercise information, with healthcare providers, allowing doctors to monitor patient progress, adjust treatments and provide feedback. An extension of Telraam is a federated learning approach, where locally trained AI models on data from wearables (thus maintaining privacy) are periodically uploaded to a central server, aggregating them to enhance AI models analysing liver diseases.
Conclusion: Previous findings across multiple disciplines suggest that citizen science can have a major impact on the hepatology community.

P3.03 30 % with hepatic steatosis – but who is at risk? Defining Risk Factors for major liver-related Outcomes in patients with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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Metabolic Dysfunction-Associated Liver Disease (MASLD) is characterized by fat accumulation in the liver and already affects nearly 30 % of the population. Understanding who is at risk of major adverse liver outcomes (MALO) is crucial for developing preventive strategies.
Methods: 9,692 participants with MRI diagnosed liver steatosis were analyzed regarding their biochemical, genetic and lifestyle risk factors for MALO (n = 26). Propensity Score Matching for sex, age and BMI was implemented in a 1:10 ratio.
Results: The strongest predictors for MALO were elevated alkaline phosphatase (m > 129U/L, f > 104U/L, OR = 5.54 [2.35, 12.2]), elevated aspartate aminotransferase (m > 50U/L, f > 35U/L, OR = 2.05 [0.87,4.49], all p < 0.02). Arterial hypertension and type 2 diabetes were more common in the MALO group (OR = 4.88 [2.19,11.9], OR = 4.29[1.81, 9,55], p = 0.003, p = 0.047). Previously risky alcohol consumption increased MALO chances (OR = 13.1 [3.8, 34.9], p < 0.001). In the unmatched cohort Transmembrane 6 superfamily member 2 (TM6SF2) polymorphism rs58542926 was associated with MALO (OR = 6.9 [1.07, 44.38], p = 0.042), while patatin-like phospholipase domain containing 3 (PNPLA3) I148M was not.
Discussion: Readily available tools, like biomarkers, are effective for identifying patients at risk of MALO, who might need more frequent screening. Lifestyle interventions are useful even in late disease stages, as common comorbidities heavily impact the disease course. Previous alcohol consumption affects MALO occurrence, even after years of abstinence. Genetic testing for common polymorphisms connected to liver disease should be evaluated in MASLD patients. These risk factors might identify a group of MASLD patients that need more frequent **attention.**

P3.04 In vitro characterization of the drug metabolizing capacity of hepatocytes from MASH livers and development of a PK model for MASH patients

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a leading cause of chronic liver damage worldwide. MASLD is characterized by excess

lipid accumulation in hepatocytes (>5 %) and can further progress to metabolic dysfunction-associated steatohepatitis (MASH), which is characterized by steatosis, inflammation and fibrosis. MASLD/MASH is often associated with the metabolic syndrome, hence, patients with metabolic dysregulations are more susceptible for MASLD/MASH formation. Currently, there are no FDA-approved pharmacological drugs available for the therapy of MASLD/MASH, as well as no accurate pharmacokinetic predictions for those patients.

Our aim is to establish a PK model supporting future clinical studies, drug research and dose adjustments in therapy or co-medication of MASH patients. The model will be based on in-depth characterization of hepatocytes and non-parenchymal cells in MASH and healthy state from human and rodents applying different in vitro and in vivo systems. Initially, we investigated drug metabolizing enzymes and liver-specific parameters of primary human hepatocytes (PHHs) in 2D suspension culture, 2.5D sandwich culture and the commercially 3D InSight™ Human Liver Co-Culture MASH Model (InSphero AG).

We observed changes in mRNA and protein expression as well as activity of drug metabolizing enzymes in healthy vs. MASH diseased cells. Liver-specific parameters also differentiate in healthy and MASH donors. Nonetheless, it has to be considered that there is a high donor variability in the 2D suspension culture system why more complex models (2.5D and 3D culture) should help to prevent such high donor variabilities by comparing a healthy and MASH diseased state from the same donor.

P3.05 Myeloid- and hepatocyte-specific deletion of group VIA calcium-independent phospholipase A2 leads to opposing phenotypes during HFD-induced NASH

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Background: Global deletion of PLA2G6 led to attenuation of hepatic steatosis but not inflammation after high-fat diet (HFD) feeding (BBA2019). We generated myeloid- (Pla2g6M-/-) and hepatocyte-specific (Pla2g6Hep-/-) KO mice, and they showed opposing phenotypes in non-obese NASH (BBA2023). Herein, we aimed to phenotype these KO in HFD-induced NASH.

Methods:Male Pla2g6flox (controls) and KO mice at 6 months old were fed with chow or HFD for 6 months. Livers were harvested for IHC and WB analyses. White-blood-cell counts, plasma lipids and cytokines were analyzed.

Results: Despite of reduction of body weights, HFD-fed Pla2g6M-/- and Pla2g6Hep-/- respectively exhibited worsen and improved levels of plasma lipids and NAFLD activity scores. Under chow or HFD, Pla2g6M-/- mice exhibited a significant increase in granulocyte and eosinophil populations associated with increased neutrophils-to-lymphocytes ratio, while lymphocytes, red blood cells, and hematocrits were decreased. Under HFD, Pla2g6M-/- showed a further increase in plasma IL-6 and IL-4, while Pla2g6Hep-/- showed attenuation of TNF-α, MCP-1, IL-13, and KC/CXCL1 as well as IHC positivity of liver F4/80 and eosinophil-cationic-protein. The latter was already observed in chow-fed Pla2g6M-/- mice. While Pla2g6M-/- mice under chow or HFD showed significant up-regulation of hepatic α-SMA, Pla2g6Hep-/- mice under HFD showed down-regulation of hepatic collagen IV.

Conclusions: Myeloid-Pla2g6 deficiency led to systemic and hepatic inflammation, anemia, and liver fibrosis, which was exacerbated by HFD. On the other hand, hepatocyte-Pla2g6 deficiency conferred NAFLD protection. Our study illustrates distinct contributions of cell-specific PLA2G6 inactivation to NAFLD/NASH, and provides therapeutic strategies for treatment of this disease.

P3.06 Comparison of histological and non-invasive assessment of significant fibrosis in a multicenter cohort of MASLD patients

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Background: Current guidelines recommend FIB-4 and transient elastography (TE) for non-invasive risk stratification in metabolic dysfunction-associated steatotic liver disease (MASLD). These tests have been established to predict the presence or absence of advanced fibrosis, but their accuracy in assessing histologically significant fibrosis (≥F2) is unclear.

Methods: In a multicenter cohort of 361 biopsy-proven MASLD patients, we evaluated the suitability of FIB-4 in identifying MASLD with significant fibrosis. Additionally, we compared the accuracy of FIB-4 with TE in a sub-cohort of 195 patients and assessed the diagnostic performance of their sequential use.

Results: We demonstrate that their accuracy in identifying MASLD patients with histologically significant fibrosis (≥F2) remains suboptimal resulting in a remarkable proportion of overdiagnoses and a non-negligible underestimation of MASLD with significant fibrosis.

Conclusion: Risk stratification using these tests leads to a misclassification of a considerable number of MASLD patients who would be inappropriately treated with novel MASLD drugs approved for F2/F3 fibrosis.

P3.07 The role of sex-specific mitochondrial changes in the pathogenesis of fatty liver disease

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Mitochondria are more than merely the primary source of cellular energy. Their physiological functionality exerts a pivotal influence on energy metabolism, which in turn affects the overall function of the cell. Mitochondrial dysfunction has been identified as a significant contributing factor in the progression of fatty liver disease. However, there is a lack of knowledge regarding the differences between males and females.

To investigate sex-specific changes in mitochondrial functions, an animal study was performed, whereby a western diet (WD) was administered for several time points (13, 26 and 32 weeks) to induce fatty liver disease. A control group of mice was given a standard diet (SD). Liver samples from the mice were processed for proteomic analysis and also underwent measurement of mitochondrial respiration via Seahorse analysis. Proteomics was utilized for a comprehensive core network analysis using Ingenuity Pathway Analysis (IPA) software. The data of the IPA analysis indicate an inverse effect between the sexes in the WD groups, characterized by up-regulation of essential mitochondrial pathways in females. Unexpectedly, no notable differences are observed between the WD and SD groups over time when considering only mice of the same sex. However, in this context, there is a greater degree of mitochondrial down-regulation in male WD mice.

The results suggest a notable discrepancy between males and females in the progression of fatty liver disease related to mitochondrial functionality, a subject that requires further investigation.

P3.08 Liver enzymes reductions from baseline over time in resmetirom treated patients in a Phase 3 study, MAESTRO-NASH

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Background: Resmetirom is indicated for treatment of MASH with stages F2 to F3 fibrosis. Liver enzyme data from the 52-week MAESTRO-NASH study was analyzed in patients on resmetirom co-administered with a statin, or who were not co-administered a statin.

Methods: Patients on 80 or 100 mg were monitored for changes from baseline in ALT, AST, and GGT for 52 weeks and changes in liver enzymes were assessed by statin treatment at baseline.

Results: A total of 473 (49.0 % of 966) patients including 23.1 % atorvastatin, 0.7 % lovastatin, 0.3 % pitavastatin, 6.5 % pravastatin, 11.8 % rosuvastatin, and 64 (6.6 %) simvastatin were assessed. 13 % were on high-intensity statin therapy (rosuvastatin 20 mg, atorvastatin 40 mg) and 36 % on moderate-to-low-intensity statins. 46.2 % patients received resmetirom 80 mg, 51.4 % resmetirom 100 mg, and 49.2 % received placebo. Patients on statins had ALT and AST at baseline than those not on statins. There was a mild and transient increase in AST and ALT at Week 4 in patients on statins vs. not on statins (did not exceed the level of ALT or AST at 4 weeks in patients not on statins). Elevations resolved by Week 8. At Week 48, in patients with ALT ≥ 30 at baseline ALT declined 20 % and 24 % on 80 and 100 mg; respectively, in patients on statins and declined by 37 % and 43 % at 80 and 100 mg; respectively, in patients not on statins.

Conclusions: Liver enzymes declined significantly in resmetirom treated patients relative to placebo beginning at Week 12.

P3.09 Dynamics of disease progression and regeneration in a multiscale liver model

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With a rising prevalence of lifestyle-associated diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD), the liver represents a focal point of medical research. As the central metabolic organ, the liver orchestrates carbohydrate, lipid and amino acid signaling and maintains energy homeostasis. Metabolic changes in response to obesity contribute to steatotic liver disease and liver cancer development. However, the complexity of the signaling networks involved and the plethora of factors affecting the liver, e.g. sex and diet, require a systems biology approach to investigate disease progression, regeneration, and possible therapeutic intervention points.

Murine and human liver samples with varying degrees of liver steatosis were analyzed using 2D and 3D immunofluorescent imaging and integrated into a multiscale 3D liver model. Additionally, transcriptomic and proteomic data of murine liver provides a basis for identification of candidate pathways and therapeutic targets in humans.

The study revealed the impact of sexual dimorphism dynamics of steatosis. In mice, proliferation, regeneration and cellular respiration are modulated in a sex-dependent manner. Additionally, a multiscale model showed morphological and architectural changes in the liver parenchyma.

The presented results demonstrate the interplay of sex difference, disease progression and regenerative capacity in the murine liver. Ongoing human parameterization and refinement of a dynamic multiscale model will aid with the prediction of liver disease progression, providing an important step in liver cancer prevention.

P3.10 Deep learning can predict PNPLA3 I148M homozygous carriers in SLD patients based on MRIs from UK Biobank

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Background: Steatotic liver disease (SLD) is the most common liver disease worldwide, affecting 30 % of the global population, which is strongly associated with genetic factors. However, identification of variant carriers is not part of routine clinical care and required infrastructure for genetic testing.

Methods: We analyzed MRI images and genetic variants PNPLA3 I148M, TM6SF2 rs58542926_T, MTARC1 rs2642438_A, HSD17B13 rs72613567_T and GCKR rs1260326_T with 45,603 individuals from the UK Biobank. Proton density fat fraction (PDFF) values were derived by using deep learning models and water fat separation toolbox. Individuals with (PDFF ≥ 5 %) and without SLD (PDFF < 5 %) were used to train and test a Vision Transformer classification model with five-fold cross validation, respectively.

Results: The predictive performance was generally higher in SLD group. Homozygosity for the PNPLA3 I148M variant demonstrated the best predictive performance among five variants with AUROC of 0.68 (95 % CI: 0.64-0.73) in SLD group. The AUROC for predicting PNPLA3 I148M was higher in females (0.61-0.71) and younger individuals (0.64-0.69). Additionally, attention maps for PNPLA3 I148M carriers showed that fat deposition in regions adjacent to the hepatic vessels, near the liver hilum, plays an important role in predicting the presence of the I148M variant.

Conclusion: Our study marks progress in the non-invasive detection of homozygosity for PNPLA3 I148M through the application of deep learning models on MRI images. Our findings suggest that PNPLA3 I148M might affect the liver fat distribution and could be used to predict the presence of PNPLA3 variants in patients with fatty liver.

P3.11 First successful pregnancies in patients with cerebrotendinous xanthomatosis treated with chenodeoxycholic acid in Germany

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Background and Aims: Cerebrotendinous xanthomatosis (CTX, OMIM #231700) is an autosomal-recessive bile acid disease due to defective mitochondrial sterol 27-hydroxylase CYP27A1, leading to tendon xanthomata, bilateral cataracts, diarrhea and ataxia. Standard therapy is chenodesoxycholic acid, 750 mg/d. During pregnancy untreated CTX patients are prone to develop

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miscarriages, peripartum infant death and subsequent mental deficits. There are little data on continuing treatment with chenodeoxycholic acid during pregnancy. We therefore present a patient with two successful pregnancies under CDCA for the first time in Germany.

Methods: In the event of pregnancy, the six-month presentation interval was reduced to quarterly. In addition to determining the cholesterol profile, vitamins and micronutrients were also monitored and an extended sonographic organ screening was carried out around the 20th week of pregnancy.

Results: Throughout first pregnancy 2020, cholestanol and 7α-hydroxycholesterol levels were within target range at 0.385 ± 0.072 mg/dl and 81 ± 15 ng/dl. The child was born on schedule, weight 3870g, length 54cm, head circumference 35cm, APGAR 9/9/10. So far, the child's development has been normal and there is no evidence of mental or physical impairment.

In 2022, the patient presented with the second pregnancy, treatment was continued. Cholesterol and 7α-hydroxycholesterol values were within target range and in 2023 a healthy child was born on schedule; weight 3470g, length 54cm, head circumference 34cm, APGAR 7/9/10

Conclusion: Treatment with CDCA in CTX patients during pregnancy is safe and, in contrast to untreated pregnancy, does probably not adversely affect the child´s development. All pregnant CTX patients should receive CDCA throughout.

P3.12 Machine learning can predict advanced but not early liver disease on brain MRI

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Background: Steatotic liver disease (SLD) is linked to cognitive decline and an increased risk of dementia. Metabolic and alcohol-related liver disease (MetALD) further impacts brain health due to alcohol's neurotoxicity. Advanced liver diseases like metabolic dysfunction–associated steatohepatitis (MASH) or cirrhosis can lead to increased inflammation. This study examines the effects of SLD on brain structure using UK Biobank MRI data.

Methods: Individuals with metabolic-associated steatotic liver disease (MASLD; n = 4584), MetALD (n = 411), at-risk MASH (n = 104), and hepatic failure/liver cirrhosis (ICD-10, K72 + K74; n = 26) were propensity-score matched to same-sized healthy control groups. Diagnoses were based on liver MRI and serological markers. Patients with diseases that affect the brain were excluded. We used random forest classifiers (RFCs) for class prediction, utilising imaging-derived phenotypes (IDPs) from brain MRIs. We also analysed residuals obtained from a normative model previously trained on separate healthy patients (n = 14810).

Results: The trained RFCs achieved average AUCs of 0.57 for MASLD, 0.61 for MetALD, 0.59 for at-risk MASH, but 0.79 for hepatic failure/liver cirrhosis on a 4-fold cross-validation . For hepatic failure/liver cirrhosis, the RFC consistently identified the left inferior parietal lobule as the most important feature in every fold on the residuals.

Conclusion: Our study reveals distinct brain features in advanced liver disease. Early SLD does not show significant single IDP differences from controls, but RFCs can still predict the disease, indicating that multiple IDPs may contribute, despite milder brain effects compared to severe SLD.

P3.13 Elevated uric acid levels are associated with an increased risk of fibrosis in MASLD

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The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing worldwide. Uric acid (UA) is a well-known component of metabolic dysfunction and also implicated as a risk factor for MASLD. Herein, elevated uric acid levels can increase insulin resistance, inflammatory response and oxidative stress in the liver, thereby promoting MASH progression. However, the role of uric acid in risk stratification of MASLD patients remains unclear. Uric acid levels were assessed in 96 MASLD patients and associated with established non-invasive surrogates of liver fibrosis (e.g. FIB-4, VTCE/CAP). Patients on uric acid-lowering therapy were excluded. Elevated UA was defined as ≥ 360 µmol/l.

UA levels showed a linear correlation with increased CAP (r = 0.27; p = 0.0094) and median values (r = 0.23; p = 0.032), suggesting greater hepatic steatosis and fibrosis. Among patients at increased risk of fibrosis (FIB-4 ≥ 1.3 or median ≥ 8 kPa), elevated UA was associated with an increase in non-invasive tests. Patients above the 75th percentile of UA (≥ 410 µmol/l) showed significantly higher FIB-4 and median in the at-risk population compared to the 25th percentile. Interestingly, patients with elevated UA had significantly higher triglycerides and lower HDL cholesterol. Of note, UA levels were independent of diabetes status and body weight, but patients with elevated UA levels had higher creatinine levels.

Conclusion: Uric acid levels significantly correlate with hepatological outcome in MASLD patients at high fibrosis risk, suggesting a potential relevance for risk stratification. Further longitudinal studies are needed to assess its prognostic value.

P3.14 Molecular Insights: Gene Expression in HCC and Testicular Cancer among ALD Patients

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Background: Alcohol-associated liver disease (ALD) leads to anomalies of hepatocellular carcinoma (HCC), and steatohepatitis. Though tremendous efforts have been made during the past 2 decades, ALD pathogenesis remains obscure. Currently, computational data analysis related to the residues of ALD patients is not widely emphasized, so most attention is needed on differentially expressed genes associated with HCC.

Methodology: A comparison between GSM4194985 (Healthy) and GSM4194987 (ALD) was conducted through the GEO database with the accession ID GSE141100 in the form of Raw RNA counts. IDEP analyzed data through bicluster heatmaps for upregulated and downregulated genes for potential effects of ALD on the patients followed by pathway analysis through Reactome.

Results: The study revealed the downregulated expression of KCNK15 alongside the upregulation of MLXIPL and ART4 owing to ALD discerning their progression in HCC. As KCNK15 and MLXIPL both are involved in metabolism, their pathway analysis alleged the dysregulation of ion and insulin homeostasis respectively could lead to the progression of HCC. ADH1B downregulation raises the possibility of poor alcohol metabolism, which exacerbates liver damage. Dysregulation of MLXIPL, KCNK15, and ART4 may accelerate the development of HCC. Furthermore, impaired spermatogenesis in ALD patients is associated with overexpression of C5orf58, KCNE1, and AKAP3.

Conclusion: This study reveals the inclination of developing HCC in ALD patients based on the differential expression of KCNK15, MLXIPL, and ART4 genes and liver toxicity by ADH1B with the development of testicular cancer owing to the upregulation of C5orf58, KCNE1, and AKAP3 in spermatogenesis.

P3.15 The ferroptosis mediator ACSL4 fails to prevent disease progression in mouse models of MASLD

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Metabolic-dysfunction associated steatotic liver disease (MASLD) is an increasingly prevalent condition with the potential to progress to liver cirrhosis and HCC. Elevated iron levels and disrupted lipid metabolism in MASLD patients point to a potential role for ferroptosis in disease progression. Previous work by Duan et al. (PMID: 34510514) demonstrated that inhibiting ferroptosis through hepatocyte-specific deletion of Acyl-CoA synthetase long-chain family member 4 (ACSL4LPC-KO), a key pro-ferroptotic gene, reduced MASLD progression in mice offering a potential therapeutic strategy.

Our study aimed to investigate whether dietary modifications similarly affect MASLD onset. ACSL4LPC-KO and wild-type (WT) mice were fed two distinct diets—choline-deficient high-fat diet (CD-HFD) or Western diet—over 20 or 40 weeks, representing different stages of metabolic liver damage and the development of metabolic syndrome. Mice were then subjected to metabolic analyses.

In contrast to the findings by Duan et al., our results show no significant differences between ACSL4LPC-KO and WT mice in terms of MASLD progression, weight gain, glucose tolerance, and hepatic steatosis. Moreover, fibrogenesis and MASLD-associated inflammation were unaffected under both the CD-HFD and Western diet. These findings suggest that ACSL4 does not influence MASLD progression and development under these dietary conditions.

The discrepancy between our results and previously published findings could be due to differences in diets or the influence of distinct microbiomes. Therefore, the results obtained with hepatocyte-specific ACSL4LPC-KO ought to be considered with caution, underscoring the importance of publishing negative or contradictory findings.

P3.16 Predicting Controlled Attenuation Parameter and Elastographic Modulus from Handheld Ultrasound Device Data using Machine Learning

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Background: The growing global health burden of steatotic liver disease (SLD) requires accessible and cost-effective diagnostic tools. Current non-invasive methods, such as controlled attenuation parameter (CAP) and elastography modulus (e-Mod) estimation, rely on expensive elastography equipment, limiting their accessibility in resource-constrained environments. This study builds on previous work by using a larger patient cohort and applying advanced machine learning techniques, including transformer-based models, to estimate CAP and e-Mod from raw radiofrequency signals (RFS) acquired by handheld ultrasound (HUS) devices.

Methods: From a cohort of n = 554 patients, raw ultrasound images were extracted using HUS(Clarius HD3, C3 & L15) and CAP and e-Mod were estimated using transient elastography.

Convolutional neural networks (CNNs) and transformer models will be applied for e-Mod and CAP prediction. Each model will be trained using a 5-fold cross-validation on a train set and evaluated on a previously separated test set, with a 1:1 train-test split.

Expected results: Previous experiments on a cohort of n = 77 with the same training setup show a mean(standard deviation) R2 = 0.5(0.07) for CAP-value prediction, and R2 = -0.6(0.3) for e-Mod prediction for CNN models.

We hypothesise that neural networks will be capable of predicting previously mentioned variables, once trained on the larger cohort. Especially for e-Mod, which has been a challenge in previous studies as models tend to overfit on smaller training sets. This approach could significantly improve the diagnosis of fibrosis and make liver disease screening more accessible in resource-constrained environments.

P3.17 Do genetic variants modulate liver injury in patients with diabetes mellitus? – results of a prospective, single center study

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Background: Type II diabetes (DMII) and metabolic dysfunction-associated steatotic liver disease (MASLD) are prevalent conditions. MTARC1 p.A165T variant has been identified as a protective factor against MASLD. We assess this polymorphism as a genetic modulator of MASLD in DMII patients, alongside six additional MASLD-linked variants.

Patients and methods: We prospectively enrolled 124 patients with DMII. Liver steatosis and fibrosis were evaluated using controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). The MTARC1 p.A165T, as well as, the HSD17B13, PSD3, MBOAT7, PNPLA3, TM6SF2 and SERPINA1 polymorphisms were genotyped with TaqMan assays. Serum oxidative stress was measured using ELISA and colorimetric tests in 40 patients with different MTARC1 genotypes.

Results: The median LSM was 6.6 kPa (range: 2–75 kPa) and median CAP 294 dB/m (range: 100–400 dB/m). MASLD was found in 52.4 % of patients, and cirrhosis (LSM > 15 kPa) in 14.5 %. CAP correlated significantly with BMI ($p < 0.01$), HbA1c ($p = 0.02$), triglycerides, LDL and total cholesterol ($p < 0.05$). LSM correlated with bilirubin ($p = 0.01$), alkaline phosphatase and GGT (both $p < 0.01$). MTARC1 p.A165T carriers showed 11 % lower maximal CAP and 71 % lower maximal LSM compared to non-carriers, with higher serum TrxR2 levels ($p = 0.01$). The TM6SF2, MBOAT7, and PSD3 variants significantly (all $p < 0.05$) modulated bilirubin, GOT, GGT, and GPT levels.

Conclusions: The MASLD prevalence in our cohort was consistent with further DMII cohorts. Studied genetic variants influenced liver function tests, and MTARC1 modulated steatosis and fibrosis. MTARC1's impact on oxidative stress suggests its protective role in liver disease.

P3.18 Machine learning identifies microbiome associations with MASLD biomarkers

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Background: Gut microbiome plays a crucial role in liver health through gut-liver axis. It may contribute to metabolic-dysfunction-associated steatotic liver disease (MASLD), a global concern in individuals without significant alcohol consumption. MASLD is driven by metabolic factors like obesity and dyslipidemia. Investigating the link between the microbiome and MASLD-biomarkers (BMI, triglycerides) could help in detecting and preventing MASLD via microbiome modulation.

Methods: Lifelines biobank's data, including over 16,700 participants, is utilized to extract 422 individuals with 16S rRNA gene amplicon sequencing and phenotypic data (age, gender, BMI, triglycerides, dietary intake). Due to the lack of data on the presence of MASLD ICD codes, BMI ≥ 25 kg/m^2 and triglycerides ≥ 1.7 mmol/L are used to identify patients at risk of MASLD. We then used machine learning models like Random Forest and XGBoost, with microbiome features (Shannon index, relative phyla abundance) and phenotypic data to define predictors of obesity and hypertriglyceridemia.

Results: Firmicutes are found to be more abundant in obese patients, while Bacteroidetes are less abundant. For obesity, Random forest performed better with an AUC of 0.72 on test set (83 samples). For hypertriglyceridemia, XGBoost outperformed Random Forest with an AUC of 0.74 on test set (83 samples). Shannon index and microbiome phyla, including Bacteroidetes, Actinobacteria, and Desulfobacterota, are identified to be among top 7 features in classifying BMI and triglycerides and might also be important for MASLD.

Conclusion: The study highlights the potential of identifying microbiome-based MASLD-biomarkers, and the role of machine-learning. Still, biopsy validation in MASLD is needed.

P3.19 Impact of Diabetes and its management on MASLD risk

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease, affecting up to 30 % of the adult population. Diabetes Mellitus (DM) is an important risk factor for MASLD. However, it is rarely differentiated whether DM is known and well controlled. The primary objective of our study is to evaluate the impact of DM and its management on the risk of MASLD development.

Methods: This study included 419,325 participants from the UK Biobank database. We conducted a univariate Cox regression analysis across six groups based on presence and management of DM by including ICD codes, medication history as well as current glucose and HBA1c levels, focusing on the risk of developing MASLD (diagnosed by ICD-10 codes).

Results: Compared to the Definitely-No-DM group, the risk of MASLD significantly increased in all five other diabetic groups. Among these, the Well-Managed-DM group (DM patients whose HbA1c < 53 mmol/mol after taking antidiabetic medication) had still a 380 % increase in MASLD risk, while the Poorly-Managed-DM group had an even higher increase of 433 % (HR = 4.80, HR = 5.33, p < 0.001). Patients in the Undiagnosed-DM had a 64.9 % elevated MASLD risk compared to controls.

Conclusion: The study findings indicate that effective blood glucose management is associated with a reduced risk of MASLD. When looking at DM in MASLD patients, DM should be recognized, and DM management should be started especially in patients at risk of MASLD.

P3.20 Soluble CD46 as a diagnostic biomarker for steatotic liver disease

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Background and Aims: Steatotic liver disease (SLD) is a major driver of chronic liver damage and early detection is crucial to improve the patients' prognosis. Currently, there is a lack of accurate diagnostic options for screening the general population and monitoring treatment responses. Here, we have identified soluble CD46 (sCD46) as an accurate marker to non-invasively detect SLD.

Methods: sCD46 was measured in plasma and serum samples of patients from two independent patient cohorts (n = 156 and n = 91) using two newly developed assays, a flow cytometry-based immuno-competition assay and an ELISA. Studies to identify the underlying mechanism were performed using HepaRG cells and primary hepatocytes in combination with intrahepatic lymphocytes.

Results: Patients with SLD showed an overrepresentation of IL-4 + iNKT cells within intrahepatic lymphocytes. The preferred development of IL-4 + iNKT cells was also evident in an in-vitro fat-loading model. Here, the induction of matrix metalloproteases was revealed, which led to an indiscriminate cleavage of immune receptors. The loss of CD46 on the cell surface led to a disinhibited IL-4 + iNKT cell differentiation. Analyses of patient samples showed an increase of sCD46 in the blood of SLD patients. By determining discriminatory cut-off values, patients could be correctly classified according to histological steatosis grades with a correct classification rate of 97.8 % for high-grade steatosis.

Conclusion: sCD46 is a promising clinical marker that can non-invasively and reliably detect SLD which can complement and improve existing diagnostic options.

P3.21 Dynamic changes in macrophage populations in MASLD and its influence on prostaglandin E2-mediated signaling

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The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is rising rapidly. In the severe form of steatohepatitis (MASH) steatosis is accompanied by an infiltration of immune cells, inflammatory processes and beginning fibrosis, which increases the risk of developing hepatocellular carcinoma. Kupffer cells, resident liver macrophages, represent the largest pool of macrophages in the organism and, in parallel with other inflammatory mediators, primarily produce the prostanoid prostaglandin E2 (PGE2), which acts mainly in a paracrine and autocrine manner. During MASLD progression to MASH the hepatic macrophage pool changes and this could influence PGE2-mediated signaling processes. The aim of the study was to characterize the macrophage pool in MASH and its sensitivity to PGE2.

Flow cytometry analysis of mice liver identified three macrophage pools in animals fed with a MASH-inducing diet compared to one pool in animals fed a standard diet. The number of Kupffer cells decreases over time and were replaced by monocyte-derived cells with a Kupffer cell similar phenotype. The largest increase was quantified from monocyte-derived macrophages with a clear pro-inflammatory phenotype, which infiltrate the liver. Parallel in-vitro studies with primary isolated Kupffer cells and potential infiltration macrophages sources from wildtype and cyclooxygenase 2-deficient mice were performed to inves-

tigate the role of PGE2. Compared to Kupffer cells, monocyte-derived macrophages produce less PGE2 but react much more sensitive to this prostanoid, which could inhibit the basal and lipopolysaccharide-mediated expression of TNFalpha and other pro-inflammatory signaling mediators. In conclusion, differences in PGE2-sensitivity in macrophages may influence inflammatory processes in MASH progression.

P3.22 Unraveling MASH: Kupffer Cell-Driven Inflammation and Fibrosis within Hepatic Spheroids as a 3D Disease Model

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Background: Chronic inflammation and fibrosis are central to the progression of metabolic associated steatohepatitis (MASH). Hepatic spheroids, composed of hepatocytes, stellate cells, Kupffer cells, and endothelial cells, offer a more accurate model of liver disease, capturing cell interactions and fibrosis better than traditional 2D cultures.

Materials and Methods: 3D liver spheroids were generated using HepaRG cells, stellate cells, and endothelial cells, with and without Kupffer cells, to simulate different liver conditions. Steatotic conditions were induced with palmitic and oleic acids, while MASH-like conditions were created by adding lipopolysaccharide (LPS). Cytotoxicity was measured using an LDH assay, and fibrosis and steatosis were evaluated through collagen III, fibronectin, Sirius red, and Nile red staining. Inflammatory cytokine levels (IL-6, IL-1β, TNF-α) were measured using ELISA and PCR.

Results: MASH spheroids containing Kupffer cells exhibited significantly higher levels of IL-6, IL-1β, and TNF-α, as well as increased LDH release, compared to spheroids without Kupffer cells and those in steatotic conditions. These findings suggest enhanced inflammation and cytotoxicity in MASH spheroids, highlighting the crucial role of Kupffer cells in driving inflammatory responses.

Conclusion: The 3D liver spheroid model is a valuable tool for studying MASH pathogenesis, especially for investigating liver inflammation and fibrosis. Kupffer cells are crucial for accurately modeling the disease, as they significantly amplify inflammatory and cytotoxic responses. Their inclusion is essential for understanding liver injury mechanisms, making this model effective for testing therapeutic interventions.

P3.23 Targeting ICAM and VCAM in MASH: The Role of Nintedanib and Dasatinib in Reducing Inflammation, Fibrosis, and Growth Factor Expression in Liver Spheroids

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Background: ICAM and VCAM, key adhesion molecules, play crucial roles in MASH by mediating immune cell infiltration and inflammation through Kupffer and endothelial cell interactions. These molecules, along with growth factors like VEGF and PDGF, drive fibrosis and liver damage, making them essential therapeutic targets.

Materials and Methods: Liver spheroids were generated under control and MASH conditions. ELISA measured ICAM, VCAM, VEGF, PDGF, IL-1β, IL-6, and TNF-α on Days 8 and 12. Immunohistological staining, including Nile red for steatosis, Collagen III for fibrosis, and Sirius Red for fibrotic tissue, was also performed. Spheroids were treated with Dasatinib (0.01 µM, 0.1 µM, 1 µM) and Nintedanib (0.1 µM, 0.5 µM, 1 µM) to assess their effects on adhesion molecules, growth factors, cytokines, and fibrotic markers.

Results: MASH spheroids showed significantly elevated ICAM, VCAM, VEGF, and PDGF levels. Nintedanib reduced ICAM at 0.5 µM and VCAM at 1 µM, while Dasatinib reduced both molecules at 0.1 µM and 1 µM, with the strongest VCAM effect at 1 µM. VEGF and PDGF were downregulated by both drugs, particularly at higher concentrations. IL-1β, IL-6, and TNF-α were significantly reduced after treatment with both drugs, with Dasatinib showing the greatest effect on pro-inflammatory cytokines.

Conclusion: Nintedanib and Dasatinib effectively downregulate ICAM, VCAM, pro-inflammatory cytokines, and growth factors in MASH spheroids. Nintedanib is more effective for ICAM reduction, while Dasatinib shows stronger effects on VCAM, VEGF, PDGF, and cytokines. Targeting these pathways could provide therapeutic benefits in MASH treatment.

P3.24 Vitamin A metabolism in MASLD development during mouse aging

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Declines in hepatic lipid metabolism are linked to the development of steatotic liver disease and sarcopenia during aging, though the origins and directionality of these associations remain unexplained. Impairments in Vitamin A (VitA) metabolism are evident in steatotic liver disease, yet their functional roles have not been investigated. This study elucidates that a Vitamin A-free diet (VAFD) influences lipid metabolism in the aging liver. We will present specific mechanisms that contribute to this rescue during specific time-windows of organism aging. In addition, we present data indicating that aging-associated impairments in liver fat metabolism influences sarcopenia development in geriatric mice by induction of specific catabolic pathways. The results support the model that aging does not progress uniformly across all organs, highlighting hepatic lipid metabolism as a critical vulnerability causing comorbidities , which can be mitigated by liver-specific reactivation of lipid metabolism.

P3.25 ASMD (acid sphingomyelinase deficiency), formerly Morbus Niemann-Pick type A/B: four adult cases with idiopathic hepatosplenomegaly and first results from enzyme replacement therapy (ERT) with olipudase alfa

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Indroduction: Acid sphingomyelinase deficiency (ASMD) is an ultrarare lysosomal storage disorder with hepatosplenomegaly (HSM), interstitial lung disease (ILD) and dyslipidemia, caused by an autosomal-recessively inherited deficiency of acid sphingomyelinase (ASM) activity. Enzyme replacement therapy (ERT) with recombinant olipudase alfa is available since 2022.

Methods: Three-center retrospective study of NP-B patients between 2014-2024.

Results: Four patients were diagnosed enzymatically/genetically with ASMD. Patient#1, female, year of birth(YOB) 1962, posttraumatic splenectomy, had ILD in HR-CT and a HDL-Cholesterol concentration of 15mg/dl. Chitotriosidase activity(CTA) and lysosphingomyelin(Lyso-SPM) were massively elevated. CO diffusion lung capacity(DLCO) was 26 % of normal. Pat.#2, male, YOB 1999, had hepatosplenomegaly, elevated CTA and lyso-SPM, low HDL-C and DLCO of 49 %. Cognitive deficits, mild ataxia and microcephalus were found. Pat.#3, YOB1992, had hepatosplenomegaly and exertional dyspnea. CTA and lyso-SPM were elevated, HDL-C 21 was mg/dl. DLCO was 49 %. Pat.#4, female, DOB2011, showed growth retardation, cognitive deficits, severe hepatosplenomegaly with liver

cirrhosis, interstitial lung disease and dyslipidemia. Patients #1 and #3 were classified as type B ASMD, patients #2 and #4 as type A/B because of significant neurological findings. ERT was initiated. In Pat.#1 one year of ERT Tx led to an increase of DLCO from 26 to 53 %, Lyso-SM normalized. In Pat.#2 and #3 spleen sizes decreased significantly, in both pts. CTA and lyso-SM improved, and DLCO increased. Pat. #4 is currently LTFU.

Conclusion: Olipudase alfa Tx seems to be safe and efficient with decreased biomarkers and improvement of visceral and lung manifestations in patients with ASMD type B and A/B.

P3.26 Abrogation of Hepatic TRβ Action Protects the Liver from Acute Liver Injury

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Overdose of acetaminophen (APAP) is a well-known trigger for acute liver failure. Even if the underlying mechanisms of ALF are not yet fully understood, it is well known that triiodothyronine (T3) positively favors hepatocyte proliferation via thyroid hormone receptor β (TRβ) signaling. We observed that abrogation of hepatic TRβ action attenuates APAP-induced acute liver injury and that a crucial time-specific modulation of ALF through TH exists whereas T3 improved hepatocyte proliferation during liver regeneration.

ALF was induced via i.p. injection of 300 mg/kg body weight of APAP (or solvent control) in male C57BL/6J mice w/o hepatocyte specific TRβ knockout. 1- 24h post APAP intoxication, liver function test, liver histology, proliferation and hepatic T3- and APAP-responsive markers were evaluated.

APAP intoxication in hepatocyte-specific TRβ deletion mice (hepTRβKO) resulted in absence of pericentral hepatocellular necrosis and absence of elevated serum transaminases 24 hours post APAP intoxication as compared to WT mice. Interestingly, 12 hours after APAP application injured hepatocytes surrounding central veins could be observed in hepTRβKO mice.

We hypothesize a hepatocyte-intrinsic detrimental TH effect in disease development, whereas TH action during liver regeneration is beneficial. These findings harbor great translational potential for novel therapeutic strategies, e.g. to antagonize or agonize local TH action, depending on the disease status of patients suffering from ALF. It is of high clinical relevance if one could support the so far only therapeutic option NAC in the treatment of APAP-induced ALF, preferably with a prolonged therapeutic window.

P3.27 Absence of cholesterol gallstone formation in male C57BL/6 mice by abrogation of hepatic thyroid hormone action

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Thyroid hormone (TH) impacts the hepatobiliary system. Epidemiological studies suggest a link between thyroid dysfunction and cholestatic liver disease. In previous studies we could confirm that a severe systemic TH deficiency promotes cholesterol gallstones. Using the lithogenic mouse model, we investigate whether changes in the systemic TH status or abrogation of hepatic TH action impact cholestatic liver disease.

Male C57BL/6 wildtype (WT) mice received a six weeks lithogenic diet either under iodine sufficient or deficient condition. Male hepatocyte specific TRβ knockout (hepTRβKO) mice received a six weeks lithogenic diet to investigate the role of abrogated hepatic TH action. Biliary cholesterol gallstone and crystal prevalence, liver histology, liver and thyroid functions test, TH- and cholestasis-responsive markers were evaluated.

Cholesterol gallstones were observed in lithogenic diet supplemented WT mice under iodine sufficient condition. In the iodine deficient group, a higher prevalence of cholesterol gallstone formation was observed, and the low iodine regiment reduced both systemic TH concentration and hepatic deiodinase 1 (Dio1) mRNA expression. In hepTRβKO a six-week lithogenic diet treatment could not induce macroscopic visible cholesterol gallstones, whereas a reduced lipid content and elevated gene expression of the cytochrome P450 enzyme Cyp2c39 were observed.

Systemic TH deficiency increases the pro-lithogenic response of male mice. Abrogation of hepatic TH action in male hepTRβKO mice shows an anti-lithogenic effect with an elevated expression of hepatic Cyp2c39 encoding for an n-3 fatty acid producing enzyme. The results provide new insights into the regulatory principle of local TH action in the hepatobiliary system.

P3.28 TLR4 and CD14 as potential therapeutic targets for LPS-induced acute-on-chronic liver failure

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Acute-on-chronic liver failure (ACLF) is characterized by rapid decompensation of liver functions as a result of acute insult in patients with pre-existing chronic liver disease. The lack of mouse models successfully recapitulating the human ACLF hinders the efforts to understand the underlying mechanism and to identify therapeutic options. In order to bridge this gap and to better understand the event cascade leading to the hepatic decompensation, a mouse model for ACLF was established. First, metabolic dysfunction–associated steatotic liver disease (MASLD) was induced by feeding mice on Western-style diet for 48 weeks. MASLD was characterized by extensive hepatic alterations, including bridging fibrosis, immune cell infiltration, and elevated liver enzymes. Next, MASLD mice were challenged with lipopolysaccharide (LPS) as an acute insult. Similarly to the human ACLF, the MASLD mice were more susceptible to LPS than age-matched standard diet fed mice, leading to aggravated cytokine storm and multi-organ failure. Interestingly, some components of the LPS internalization machinery, such as CD14 and Tlr4, were found to be upregulated in the MASLD mice. To understand their relevance in the increased susceptibility to LPS, MASLD mice were pre-treated with Tlr4 and CD14 inhibitors 30 minutes before LPS administration. Inhibiting these targets strongly attenuated the inflammatory cytokine response to LPS and increased the mouse survival rate. In conclusion, blocking Tlr4 and CD14 strongly ameliorated the effect of LPS in mice with advanced MASLD, and could be a promising therapeutic target for human ACLF.

P3.29 Antibiotic-mediated microbiota depletion limits IgA-related fibrogenesis in metabolic dysfunction-associated steatohepatitis

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Metabolic dysfunction-associated steatohepatitis (MASH) is the fastest-growing cause of hepatocellular carcinoma (HCC). Due to the direct connection between the gut and the liver, the intestinal microbiota is suspected to be involved in inflammatory and metabolic processes during MASH development. Therefore, in this study we aimed to investigate the role of the gut microbiota in a mouse model of MASH-to-HCC transition.

C57Bl/6 mice were fed a choline-deficient high fat diet (CD-HFD) for 6 or 12 months to induce MASH and MASH-to-HCC progression, and the microbiota was depleted using broad-spectrum antibiotics (ABx). Microbiota composition and liver pathogenesis were analyzed by shotgun metagenomic sequencing, serology, immunohistochemistry, RNA sequencing and metabolomics.

We showed that IgA from gastrointestinal B cells was sufficient to induce fibrosis through IgA-dependent activation of hepatic FCGR1 + cells. Furthermore, we found that the role of B cells in MASH was independent of the gut microbiota since germ-free mice were not protected from MASH development. However, therapeutic ABx-mediated microbiota depletion significantly reduced fibrosis development during MASH progression without affecting obesity, steatosis and T-cell infiltration. ABx treatment also significantly decreased hepatic myeloid cell activation and intestinal and systemic IgA, leading to reduced activation of hepatic FCGR1 + cells. Moreover, ABx treatment was associated with significant metabolic changes compared to non-treated CD-HFD mice.

Our results demonstrate that the intestinal microbiota promotes MASH progression through IgA-mediated fibrogenesis. Furthermore, our data suggest that certain immunological features of MASH occur independent of the microbiota while metabolic processes regulated by the microbiota might be involved in the pathogenesis.

P3.30 Clinical Utility of Metallothionein Immunohistochemistry (MT-IHC) for Early Tissue-based Diagnosis of Wilson Disease (WD)

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Wilson Disease (WD) is an inherited disorder resulting from ATP7B gene mutations, causing toxic copper accumulation in the liver and central nervous system. Traditionally, WD diagnosis in symptomatic patients relies on blood, urine, and genetic testing; however, patients with isolated liver enzyme elevations may remain undiagnosed, risking progression to cirrhosis. Recently, Metallothionein immunohistochemistry (MT-IHC) has shown robust diagnostic performance for tissue-based WD diagnosis (Stokes et al., 2024; Wiethoff et al., 2023). To explore its clinical utility, we analyzed the test results of MT-IHC one year after integration into the routine workup of liver biopsies at the Institute of Pathology, University Hospital Heidelberg. Over 20 months, 154 liver specimens (147 biopsies, 7 explants) were stained for MT, where WD was a differential diagnosis based on clinical or histological findings (median age: 44 years, IQR: 30–61.25; 62 % male). 16 biopsies stained positive for MT; 11 of these exhibited advanced fibrosis or cirrhosis (Stage 3-4). WD was confirmed clinically and genetically in 5 cases and remained a relevant differential in 9 cases, with available follow-up data for 1 case harboring a relevant ATP7B gene mutation. Notably, MT-IHC established WD diagnosis in 2 asymptomatic cases, including 1 case, where the diagnosis was determined only after liver transplantation, highlighting the clinical value of MT-IHC as a screening tool in any liver biopsy, where WD is a potential differential. Our findings support the clinical utility of MT-IHC for early WD diagnosis in liver biopsy specimens, emphasizing its role in improving outcomes through timely intervention.

P3.31 Angiopoietin-1 Receptor (CD202b) Identifies IL-4-secreting Human Invariant Natural Killer Cells

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The relationship between lipid-induced stress in human hepatocytes and inflammation in metabolic dysfunction-associated steatotic liver disease (MASLD) remains unclear; however, innate immunity is an important factor in disease progression. The discovery that IL-4 + iNKT cells were overrepresented amongst intrahepatic lymphocytes from patients with steatotic liver disease suggests a pathogenic role, but their immunological function is uncertain. To study this rare population, we needed a reliable marker set that allows us to isolate living cells. Here, we report a combination of cell surface markers that can accurately predict IL-4 production by in vitro-expanded iNKT cells. Our multivariate models identify several combinations of up to 5 markers that reliably distinguish IL-4 + iNKT cells. CD202b (angiopoietin-1 receptor, Tie2) emerges as a predominant factor in these predictions. We conclude that the CD202bhigh CD25low phenotype predicts IL-4 + iNKT cells in vitro with an accuracy of 93.02 ± 2.61 %, a sensitivity of 75.22 ± 17.23 % and a specificity of 95.01 ± 4.75 %. Hence, we are now able to detect and sort living, in vitro-expanded IL-4 + iNKT cells without directly measuring IL-4 production.

P3.32 Association of the PNPLA3 p.I148M common variant with increased resting energy expenditure in the context of cold adaptation in humans

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Genome-wide association studies linked the common PNPLA3 variant p.I148M (rs738409) to increased hepatic steatosis. This variant is conserved in modern humans and was fixed in archaic humans, putatively due to advantages in cold-adaptation.

To investigate the role of this variant in the context of thermogenesis, we utilized data of the FREECE cohort that studied the effect of cold-exposure (CE) on resting energy expenditure (REE), metabolites and hormones across 140 individuals in the context of genetic variation. Additionally, brown adipocyte marker gene expression was assessed in 17 individuals.

Our results show a risk allele frequency for rs738409 of 0.18 across the study population (89 CC, 44 CG, 7 GG). We observed a numerically increased fat-free mass-adjusted REE after CE in normal-weight individuals with the largest delta increase in GG-carriers (median deltaREE ± SD (kcal/d): 148 ± 98(GG), 42 ± 153(CG), 79 ± 150(CC), p = 0.1359). Simultaneously, median supraclavicular temperature was increased by + 0,17 °C in GG compared to CG and CC. We did not detect relevant differences in blood lipid concentrations. Analysis of

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mRNA levels points towards a small decrease of brown adipocyte marker genes in heterozygous but not homozygous risk allele carriers, suggesting a UCP1-independent mechanism. For validation, we analyzed RNAseq-data of subcutaneous adipocytes and found no difference in UCP1 expression but a genotype-dependent effect on the expression of lipid cycling genes.
In conclusion, our data suggests a potential thermogenic adaptation mechanism via increased REE in homozygous p.I148M carriers independent of changes in blood lipids and brown adipocyte marker gene expression, however further validation in a larger cohort is needed.

P3.33 Towards Establishing L-Ornithine-L-Aspartate as a Potential Basic Medication for Metabolic Dysfunction-associated Steatotic Liver Disease

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DOI 10.1055/s-0044-1801123
L-Ornithine and L-aspartate play key roles in detoxifying ammonium (NH3) and synthesizing proline and polyamines. Sufficiently synthesized de novo in healthy individuals, these amino acids have to be supplemented in, e.g., the metabolic dysfunction-associated steatotic liver disease (MASLD). Since the stable salt L-ornithine-L-aspartate (LOLA) enables the detoxification and excretion of NH3 by the urea cycle via activating carbamoyl phosphate synthetase 1, we investigated further potential therapeutic targets of LOLA. In primary hepatocytes from MASLD patients, the catabolism of branched-chain amino acids (BCAAs) decreased with disease severity. This could be partly reverted by LOLA via increasing the expression rates of the BCAA enzyme transcripts bcat2, bckdha and bckdk. Also, in both untreated HepG2 hepatoblastoma cells and HepG2-based models of steatosis, insulin resistance and metabolic syndrome, LOLA (i) reduced the release of NH3; (ii) beneficially modulated the expression of genes related to fatty acid import/transport (cd36, cpt1), synthesis (fasn, scd1, ACC1), and regulation (srbf1); (iii) reduced cellular ATP and acetyl-CoA; and (iv) favorably modulated the expression of master regulators/genes of energy balance/mitochondrial biogenesis (AMPK-α, pgc1α). Moreover, LOLA reconstituted the depolarized mitochondrial membrane potential ΔΨm without impairing mitochondrial integrity and/or inducing superoxide production. Most aforementioned effects were concentration-dependent at ≤ 40 mM LOLA. Our results thus evidence for LOLA an impressive range of reconstituting effects on metabolic carriers and targets of catabolism and energy metabolism that are impaired in MASLD. These results warrant further investigation to establish LOLA as a safe, broadly efficacious and cost-effective basic medication for the ever-increasing MASLD pandemic.

P3.34 Mobile Ultrasound Screening Program for MASLD in High Cardiovascular Risk Communities in Rural Colombia: Initial Results

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DOI 10.1055/s-0044-1801124
Introduction The global prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) is rising. In rural Colombia, limited healthcare access hinders MASLD assessment and management. This study piloted a mobile ultrasound screening program in resource-limited regions to identify MASLD prevalence, characteristics, and risk factors in high cardiovascular risk communities, providing timely interventions to vulnerable populations.
Methods Under the UMM-UdeA GIZ-Klinikpartnerschaften program, patients from the Colombian cardiovascular screening initiative were evaluated in Leticia, Gómez-Plata, and Frontino. Risk factors such as hypertension, type-2 diabetes, obesity, dyslipidemia, and prior cardiovascular events were assessed. Hepatic imaging specialists performed liver ultrasounds, categorizing patients as high or low MASLD risk based on clinical history and ultrasound findings. High-risk individuals were referred to hepatologists for diagnostic confirmation and treatment planning.
Results A total of 278 high cardiovascular risk patients were evaluated. In Gómez-Plata (n = 59; 39 men, 20 women), MASLD incidence was 55.9 %, with 44 % grade I, 44 % grade II, and 12 % grade III steatosis. In Leticia (n = 100; 47 men, 53 women), the incidence was approximately 59 %, mostly grade I, indicating early-stage disease. Frontino (n = 119; 97 men, 22 women) had a higher disease burden, with 68 % (n = 81) diagnosed with moderate to severe MASLD (grade II or III).
Discussion Our study suggests significant regional variations in MASLD prevalence across Colombia, likely due to cultural, medical, or dietary factors. Understanding these disparities is crucial for developing targeted interventions. Future studies focusing on nutritional, genetic, or sociocultural determinants could provide valuable insights and guide personalized strategies tailored to each community's specific needs.

P3.35 Health related quality of life (HRQoL) in patients Metabolic dysfunction-associated steatotic liver disease (MASLD)

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Background Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease globally, with an estimated prevalence of approximately 30 %. Although MASLD is often considered asymptomatic in its early stages, emerging research suggests the presence of subtle symptoms that may affect health-related quality of life (HRQoL).
Patients and Methods This prospective study included 213 patients, of whom 68 had confirmed MASLD, and 145 were obese individuals exhibiting pathologically elevated liver enzymes. All participants completed three HRQoL questionnaires: the Short Form Health Survey (SF-36), the Chronic Liver Disease Questionnaire (CLDQ), and the Nottingham Health Profile (NHP).
Results Analysis of the HRQoL questionnaires revealed deviations from general population reference values. For the CLDQ, MASLD patients scored an overall average of 4.8 ± 1.0, compared to a reference value of 5.9 ± 1.1, with a pronounced discrepancy in the fatigue domain (3.6 ± 1.4 vs. 5.4 ± 1.3 in the reference group). Similar trends were noted in the NHP energy level, where MASLD patients scored 58.6 ± 38.0, against a general population reference of 17.3 ± 30.2.
Age-stratified analysis suggested a trend of declining CLDQ scores with advancing age. Gender-specific analysis within age-matched groups also indicated lower HRQoL scores for women over 40 in several questionnaire domains.
Conclusion These findings indicate that MASLD negatively impacts HRQoL, with physical symptoms more pronounced than psychological ones. Among

the most prominent changes in HRQoL were fatigue symptoms measured by the CLDQ.

P3.36 Long-term outcomes of Metabolic dysfunction associated steatotic liver disease (MASLD) patients in a prospective, German real-world cohort

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DOI 10.1055/s-0044-1801126

Background: MASLD is the most frequent liver disease but longitudinal data of clinical outcomes in Germany are lacking. Aim of this study is to analyse long-term outcomes in a prospective, German real-world cohort.

Methods: 310 MASLD patients diagnosed by histology or liver stiffness/CAP were prospectively followed (2012–2023). Statistical analyses of liver-related outcomes and mortality were conducted using SPSS.

Results: 310 MASLD patients were followed for a median of 36 ± 16 months (56.8 % male, mean age 52.3 years, mean BMI 32.5 ± 6.4kg/m^2), 40 % had T2DM, 58 % arterial hypertension and 36 % hypercholesterinemia. 36 % were diagnosed histologically (of those 36.9 % F2-F4) and 59 % staged by elastography (12 % LS 8-12kPa, 21 % > 12kPa). Longterm-FU showed that patients with cirrhosis had significantly more liver-related outcomes compared to those without (HR 3.501 (95 %-CI 1.835-6.682)) and a higher mortality (HR 11.572 (95 %-CI 3.030-44.194)). Patients with F2-F3 in histology had a higher rate of liver-related outcomes compared to F0-F1 (HR 3.638 (95 %-CI 1.345-9.840)). Stratified by LS, the highest rate of liver-related outcomes was detected for > 12kPa (HR 11.738 (95 %-CI 4.421-31.167)) followed by 8-12kPa (HR 4.630 (95 %-CI 1.514-14.160)), both compared to < 8kPa. Mortality was similarly increased for > 12kPa (HR 13.489 (95 %-CI 1.622-112.152)) and 8-12kPa (HR 6.044 (95 %-CI 0.546-66.876)). In the longitudinal study 3.5 % (n = 11) of patients died, 3 due to liver-related complications.

Conclusion: In this first German longitudinal MASLD cohort, patients with significant fibrosis or cirrhosis have the highest risk for liver-related outcomes and overall mortality. This underscores the need for regular monitoring of at-risk-patients.

P3.37 Overweight, but not alcohol is associated with increased risk for advanced liver disease in patients with chronic hepatitis C infection- results from the German Hepatitis C-Registry (DHC-R)

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DOI 10.1055/s-0044-1801127

Background: Obesity and alcohol are important risk factors for liver cirrhosis, but their impact in patients after chronic HCV infection (cHCV) remains unknown. Data are lacking weather the co-existence of both risk factors has a supra-additive effect on disease progression. We aimed to analyze the impact of obesity and alcohol in cHCV patients.

Methods: Patients from the German Hepatitis C-Registry were classified into six groups by overweight (BMI ≥ 25/ < 25) and alcohol consumption (none, moderate < 30g/40g, severe > 30g/40g per week for female/male). Primary endpoint was progression to liver cirrhosis. Secondary endpoint was mortality in combination with disease progression.

Results: In total, n = 5967 were included after antiviral treatment. Patient with BMI ≥ 25/no alcohol (O/nA) had an increased risk for disease progression compared to BMI < 25/moderate alcohol (L/mA). In a multivariate analysis, obesity and diabetes were independent risk factors for disease progression (OR for BMI > 35 3.021 (1.811-5.039), OR for diabetes 1.532 (1.036-2.267)). O/nA and O/mA patients also had an increased risk for overall mortality and disease progression compared to L/mA. Multivariate analysis of the secondary endpoint identified again diabetes and obesity as the only independent cardiometabolic risk factors for disease progression and mortality. Interestingly, neither alcohol consumption alone nor in combination with obesity influences disease progression.

Conclusion: In conclusion, obesity increased the risk for disease progression after cHCV infection, while neither alcohol alone nor in addition to obesity impacts disease progression. Therefore, weight management in patients after cHCV is important to prevent disease progression.

Poster Visit Session lV
TUMORS
15/02/2025, 08.30am – 09.10am

P4.01 Therapeutische Sequenzen der systemischen Therapie nach Atezolizumab plus Bevacizumab zur Behandlung des HCC: Eine Real-World-Analyse der IMMUreal-Kohorte

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DOI 10.1055/s-0044-1801128

Hintergrund: Die Zulassung neuer systemischer Therapien hat die Behandlung des fortgeschrittenen Leberzellkarzinoms (HCC) verändert. Die Einführung von Atezolizumab/Bevacizumab (atezo/bev) als bevorzugte Erstlinientherapie hat Unsicherheiten bezüglich der Therapiefolge geschaffen.

Ziel: Diese Studie untersucht die sequentielle Therapie nach atezo/bev und liefert Daten aus einer prospektiven Real-World-Kohorte.
Methoden: In der IMMUreal-Kohorte wurden 124 Patienten aus zwei Zentren in Bayern analysiert, die zwischen Juni 2020 und Dezember 2023 mit atezo/bev behandelt wurden. Die Machbarkeit der sequentiellen Therapie wurde in prognostischen Untergruppen untersucht.
Ergebnisse: Die mediane Gesamtüberlebenszeit betrug 21,5 Monate. Weniger als die Hälfte der Patienten (41,2 %) erhielten eine Therapie der 2. Linie, und nur 19,2 % eine Therapie der 3. Linie. Der Rückgang an Patienten für weitere Behandlungen ging mit einer Verschlechterung der Leberfunktion einher, gemessen durch ALBI- und Child-Pugh-Scores. Eine verkürzte Therapiedauer zwischen den Linien wurde beobachtet. Es gab keine Korrelation zwischen der Anzahl der Therapie-Linien und negativen prognostischen Faktoren wie Leberzirrhose, extrahepatischer Ausbreitung oder makrovaskulärer Invasion.
Schlussfolgerungen: Wir schließen daraus, dass eine sequentielle Therapie nach der Erstlinientherapie nur für ausgewählte Patienten mit fortgeschrittenem HCC machbar ist. Die Anwendbarkeit nachfolgender Behandlungen könnte durch die Verschlechterung der Leberfunktion eingeschränkt sein. Die Optimierung der Wirksamkeit der Multi-Linien-Therapie bei gleichzeitiger Erhaltung der Leberfunktion scheint entscheidend für die Verbesserung der Ergebnisse bei Patienten mit fortgeschrittenem HCC zu sein.

P4.02 Proteome comparison of pre-neoplastic lesions in different non-cirrhotic models of liver carcinogenesis in mice

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Introduction: The early processes underlying human hepatocarcinogenesis are insufficiently understood, especially in absence of liver cirrhosis. Over several years, different experimental mice models of liver carcinogenesis were conducted at our institute with the common goal to identify new pathways for the onset of liver carcinoma in non-alcoholic fatty liver disease. In those models, constitutive pre-neoplastic lesions, especially early clear cell foci, were observed. To gain new knowledge of the molecular background behind these histological observations the aim was to analyze the proteome of those lesions and compare the different models and liver tissue.
Methods: Already archived FFPE tissue from mentioned models with pre-neoplastic foci was serially cut and stained for HE. Using the LEICA Laser Capture Microdissection System, pre-neoplastic lesions where marked, cut and collected. From each model, four mice were processed both for pre-neoplastic lesions and unaltered liver tissue. After protein extraction, the proteome of these samples was analyzed by data independent tandem mass spectrometry.
Results and Outlook: The first proof of principle on histologically unaltered liver tissue of mice provided identification of 6000 different proteins on average with good representation of liver specific proteins.
Next steps for the proteome comparison of pre-neoplastic lesion in different mice models of liver carcinogenesis are in progress and detailed methods as well as the first results will be presented. This method can bring new knowledge of the molecular pathways of non-alcoholic fatty liver disease and liver carcinogenesis as well as facilitate work up of different FFPE tissue concerning other research questions.

P4.03 MR guided catheter-based radiotherapy/ brachytherapy of liver tumours – first experience and feasibility

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Aim: To show feasibility and safety of MR guided catheter-based radiotherapy/ brachytherapy of primary or secondary liver tumours.
Methods: Between June 2023 and April 2024, 27 patients with 54 liver lesions were treated within a prospecitve single-center trial (MR BRIGHT trial). Treatments were performed under conscious sedation and LA using a 1.5T MRI system. Gadoxetic acid was administered for contrast enhancement, followed by insertion of an coaxial needle and navigation to the lesion via real-time gradient-echo fluoroscopy sequences. The needle was exchanged for a 6F angiography sheath with a brachytherapy catheter. 3D T1-weighted sequences were sent to the radiation department for brachytherapy with an IR192 high-dose-rate (HDR) afterloading unit. Target doses ranged from 15 to 25 Gy, depending on tumor type (HCC, CRC, GIST, NET, and other metastases). Catheters were removed after BT, and the tract sealed with gelatin sponge.
Results: The average lesion diameter was 13 ± 6 mm, whereas the average clinical target volume (CTV) was 3.0 ± 2.9 cm3. The average room time was 74 ± 35 minutes, the average time for catheter placement was 19 ± 11 minutes. The mean dose administered per lesion (D100) was 18.9 ± 3.6 Gy. Complications during and after BT were rare with only 2 patients having a minor bleeding without need for blood transfusion or intervention.
Conclusions: Overall, MR-guided catheter-based radiotherapy for liver tumours is feasible and safe, particularly for small lesions. With low complication rates and precise dosimetry achieved through advanced imaging, this approach holds promise for effective tumour management.

P4.04 Five-year overall survival (OS) and OS by tumour response measures from the Phase 3 HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma (uHCC)

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DOI 10.1055/s-0044-1801131

Background: In the Phase 3 HIMALAYA study (NCT03298451) in uHCC, STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved OS vs sorafenib in the primary analysis (Abou-Alfa et al. NEJM Evid 2022). Here, we report the first 5-year OS analysis in uHCC.

Methods: Participants (pts) with uHCC were randomised to STRIDE, durvalumab monotherapy or sorafenib. OS, 5-year OS rates, OS by disease control (DC), changes in tumour size and depth of response (DpR) and serious adverse events (SAEs) were assessed. Extended long-term survivors were described.

Results: The OS hazard ratio for STRIDE vs sorafenib was 0.76 (95 % confidence interval, 0.65–0.89). The 5-year OS rate was 19.6 % with STRIDE vs 9.4 % with sorafenib and was further improved in pts who achieved DC (28.7 % vs 12.7 %). OS rates for pts who achieved ≥ G2 (> 25 %) tumour shrinkage were 58.0 % (57 pts at risk) vs 36.0 % (8 pts at risk) at 48 months and 50.7 % (34 pts at risk) vs 26.3 % (4 pts at risk) at 60 months for STRIDE vs sorafenib, respectively. The rate of treatment-related SAEs with STRIDE did not change from the primary analysis.

Conclusions: STRIDE demonstrated an unprecedented 5-year survival rate, with no additional serious safety events in the extended follow-up. The improved OS outcomes observed across multiple tumour response evaluations, including DC and DpR, provide novel insights on the clinical benefit of dual immune checkpoint inhibition beyond conventional measures of response.

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P4.05 Single Shot Liver: MR-guided stereotactic body radiotherapy (SBRT) for hepatic malignancies and metastasis

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DOI 10.1055/s-0044-1801132

Background: In the treatment of inoperable hepatic malignancies and metastases, the importance of SBRT has increased significantly in recent years. Up to now, multi-day concepts (often 3-5 fractions) have been the standard therapy. In the prospective Single Shot Liver study, MR-guided single-shot radiotherapy is being investigated with regard to feasibility, toxicity and local control.

Methods: Patients with 1-3 hepatic metastases or malignancies < 5 cm receive MR-guided irradiation with 1 x 28 Gy dosed to the PTV (80 % isodose). The primary objective is to record 1-year local control, toxicity, laboratory chemical changes and extrahepatic tumour control. From 09/2021 to 07/2024, 36 patients have been included: this analysis includes the data of the first 26 patients who have reached the 1-year follow-up (31 irradiated fractions, 34 lesions).

Results: Acute side effects associated with radiotherapy occurred up to a maximum of CTC °1-2 (most common fatigue, nausea, diarrhea). 6 patients died before the end of the 1-year follow-up (not RT-associated). One patient showed a recurrence after one year (primary colon carcinoma), one metastasis was resected after 6 months due to rest vitality (primary NET pancreas). All other lesions (94 %) are controlled up to the available follow-up.

Conclusion: MR-guided single-dose irradiation is a safe and effective therapy for hepatic metastases and primary tumours (1-year local control rate 94 %). There have been no major side effects to date. In the future, multi-day concepts can be shortened in favour of single-dose irradiation if feasible in terms of dosimetry of organs at risk.

P4.06 Hepatic stellate cells show protumorigenic effects on melanoma cells

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The liver represents a very attractive niche for metastasis of different tumours including melanoma, however the underlying molecular mechanisms are largely unknown. In primary liver cancer, activated hepatic stellate cells (HSC) are known to promote tumour progression. The aim of this study was to analyse the effects of HSC on melanoma cells.

Immunohistochemical (IH) analysis of alpha-smooth muscle actin (alpha-sma), a marker of activated HSC, showed that HSC surround and infiltrate the stroma of hepatic metastases from melanoma patients. In melanoma mouse models, HSC activation occurs early during hepatic colonization of melanoma cells as shown by IH of alpha-sma. In vitro, conditioned medium (CM) from HSC induced proliferation and colony formation of melanoma cells. Furthermore, CM from HSCs acted as a potent chemoattractant in Boyden chamber assays and also increased migratory activity of melanoma cells. Moreover, CM from HSC induced the activity of protumourigenic pathways and protumourigenic gene expression of melanoma cells. Boiling the CM abolished the protumourigenic effects. The growth-promoting effect of HSCs on melanoma cells was also demonstrated in spheroid formation assays, where mixed spheroids of melanoma cells and HSC formed significantly larger spheroids than the sum of either cell type alone.

The here provided data indicate protumourigenic effects of HSC on melanoma cells and suggest that at least part of these effects are mediated by secreted proteins. We propose that our in vitro model system can be used to identify HSC secreted candidate factors as potential diagnostic markers and therapeutic targets for hepatic metastasis in melanoma patients.

P4.07 Expression and function of G protein-coupled receptor 37 in hepatocellular carcinoma

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DOI 10.1055/s-0044-1801134

G protein-coupled receptors (GPRs) play a critical role in different types of cancer, including hepatocellular carcinoma (HCC). GPR37 is an orphan receptor associated with the development and progression of some types of cancer, but its role in liver disease and liver cancer is unknown. The aim of this project was to analyze the expression and function of GPR37 in HCC.

GPR37 expression was significantly higher in human HCC tissues than in corresponding non-tumorous liver tissues. In addition, in silico analyses showed that increased GPR37 expression in HCC correlated with poor progression-free and overall survival. Expression of GPR37 was also significantly higher in different human HCC cells compared to primary human hepatocytes at the RNA and protein level as analyzed by RT-qPCR and Western blotting. To get insight into the functional role of GPR37 in HCC, GPR37 was suppressed in HCC cells using RNAi technology. GPR37-suppressed HCC cells exhibited reduced proliferation and spheroid formation. Moreover, GPR37 suppression led to reduced activation of protumorigenic signaling pathways and reduced proinflammatory gene expression in HCC cells.

Our data indicate that GPR37 acts as a protumorigenic factor in HCC. Further studies are required to identify the ligand(s) that act via this G protein-coupled receptor on HCC cells and to assess the potential of GPR37 as a prognostic marker and therapeutic target in HCC.

P4.08 Immune Modulation in Untreated, Contralateral Hepatic Metastases after Yttrium-90 Radioembolization of Microsatellite Stable Colorectal Cancer

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Purpose: The study aimed to evaluate the immune response in untreated distant tumors following Y90-radioembolization for colorectal liver metastases (CRLM).

Material and Methods: Ten patients (nine male) with microsatellite-stable (MSS) CRLM with over five lesions were included. A baseline biopsy was performed before the Y90-radioembolization treatment of one liver lobe, followed by a second biopsy of yet untreated tumors in the other lobe directly before the second treatment (median interval between biopsies 13(4-49) days. Tumor biopsies and peripheral blood mononuclear cells (PBMCs) were analyzed for immune activity, including PD1, CD4, CD8, FoxP3, and CD68 in the tumor samples by multiplex immunophenotyping, while PBMCs were analyzed for quantification of lymphoid cell populations and expression of checkpoint molecules, including PD-1, TIGIT, CTLA-4, and TIM-3. Patients with an objective response or stable disease six months post-therapy were classified as "responders."

Results: At baseline, biopsies of responders displayed lower FoxP3 + cell and co-location of CD4 + FoxP3 + cell density compared to nonresponders (both $p = 0.02$). At the second biopsy, nonresponders demonstrated higher CD68 + macrophage density ($p = 0.0014$). Responders exhibited fewer CD4 + FoxP3 + regulatory T cells than CD8 + T cells at both time points ($p = 0.02$ and $p = 0.0428$). At the second biopsy, nonresponders tended to have an increased CD8 + PD1 + /CD8 + ratio ($p = 0.062$). Flow cytometry of nonresponders showed lower CD8 + PD1 + T cell density and CD8 + PD1 + /CD8 + ratio at both timepoints.

Conclusion: Y90-radioembolization induces local immunogenic effects in untreated MSS CRLM lesions and systemic exhaustion of immune cells in nonresponders. The role of synergism of Y90-radioembolization and checkpoint inhibition warrants further investigation.

P4.09 Uptake of fatty acids and lipid accumulation promote prometastatic characteristics of colorectal cancer cells

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The liver is the most common site of colorectal cancer (CRC) metastasis, and hepatic metastasis is the primary driver of disease-specific mortality for patients with CRC. Obesity is frequently associated with hyperlipidemia and is a risk factor for development of hepatic metastases, however the underlying mechanisms are incompletely understood.

The aim of this study was to assess the impact of hyperlipidemic conditions on prometastatic behaviour of CRC cells and to analyze the effects of obesity and lipid accumulation in human CRC tissues and liver metastases. CRC cell lines were incubated with free fatty acids (FFA) complexed to albumin to mimic hyperlipidemia. This led to an uptake of FFA, enhanced triglyceride (TAG) accumulation as well as CPT1 expression and beta-oxidation, known to promote (hepatic) CRC metastasis. These metabolic changes significantly induced proliferation, migratory activity as well as expression of proinflammatory genes. Expression of the lipid droplet associated protein perilipin 2 (PLIN2) was identified as a surrogate marker for TAG accumulation in CRC cells. Analysis of human CRC tissues showed higher PLIN2 expression in obese compared to lean patients, and high PLIN2 expression correlated with poor overall survival. Moreover, we detected high PLIN2 and CPT1 expression in hepatic metastases of CRC patients.

Our data indicate that hyperlipidemic conditions promote prometastatic behaviour of CRC cells and that PLIN2 expression might serve as a prognostic marker for hepatic CRC metastasis. Furthermore, interference with exogenic high-fat supply could be a promising strategy to prevent and treat liver metastasis of CRC patients.

P4.10 The role of 6-phosphofructo-2-kinase/ fructose-2,6-biphosphatase 3 (PFKFB3) in hepatocellular carcinoma

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Metabolic reprogramming such as glycolysis even in aerobic environments (Warburg effect) is a hallmark of different types of cancer including hepatocellular carcinoma (HCC). The bifunctional enzyme 6-phosphofructo-2-kinase/ furctose-2,6-biphosphatase 3 (PFKFB3) is an important regulator of glycolysis. PFKFB3 has been implicated in the progression of several types of cancer. However, its role in HCC is largely unknown.

The aim of this study was to analyze the expression and function of PFKFB3 in HCC.

Methods and results: PFKFB3 mRNA and protein expression is significant higher in different human HCC cell lines (Hep3B, PLC, SNU449 and Huh7) compared to primary human hepatocytes as analyzed by RT-qPCR and Western-blotting. PFKFB3 was further increased in HCC cells under hypoxic conditions, and also in human HCC tissues. PFKFB3 showed a significant correlation with the glucose transporter GLUT1, a known marker for hypoxia. RNAi-mediated PFKFB3 suppression in HCC cells resulted in reduced glucose consumption and lactate production. Furthermore, PFKFB3 suppressed HCC cells showed significantly reduced colony formation and growth, proliferation and migratory activity. Similar results were found in HCC cells treated with a specific PFKFB3 inhibitor. In HCC patients, high PFKFB3 expression correlated with poor progression free and overall survival.

Conclusion: Our data indicate that enhanced PFKFB3 expression induces glycolysis and acts as a protumorigenic factor in HCC. Therefore, PFKFB3 appears as a potential prognostic marker and therapeutic target in HCC.

P4.11 CLEAN-DUCT / TRITICC-3 (IKF070) – A Phase IIa, Prospective, Single-Arm, Open-Label, Non-Randomized, Multi-Center Pilot Study of Durvalumab + Intraductal Radiofrequency Ablation (ID-RFA) in Extrahepatic Cholangiocarcinoma

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Background: The prognosis of patients with non-resectable or metastatic biliary tract cancer (BTC) is dismal. Combining gemcitabine/ cisplatin (GC) and durvalumab has proven efficacy in the TOPAZ-1 trial. Intraductal radiofrequency ablation (ID-RFA) was suggested to improve stent patency, rates of cholangitis, and long-term survival in patients receiving systemic treatment for non-resectable or metastatic extrahepatic biliary tract cancer. Combining

immunochemotherapy with ID-RFA might further improve the therapeutic outcome in these patients when given as first-line treatment.

Methods: CLEAN-DUCT/ TRITICC-3 (IKF070) is an interventional, prospective, open-label, non-randomized, exploratory, multicenter, single-arm phase IIa clinical trial performed at 15 sites with expertise in managing BTCs across Germany. A total of 42 adult patients with histologically verified non-resectable or metastatic extrahepatic biliary tract cancer will be included to receive a combination of GC / durvalumab plus ID-RFA. Study treatment will be continued until disease progression or occurrence of unacceptable toxicity. The effect of GC/ durvalumab plus ID-RFA on 12 months survival, defined as the proportion of patients alive 12 months after enrollment, will be analyzed as the primary endpoint. Safety (according to NCI-CTCAE), overall survival, and the time to occurrence of cholangitis are secondary endpoints. A comprehensive translational research program is part of the study and might provide findings about predictive markers concerning response, outcome, and resistance to treatment.

Discussion: CLEAN-DUCT/ TRITICC-3 aims to evaluate the safety and efficacy of GC/ durvalumab in combination with ID-RFA as the first-line treatment of patients with non-resectable or metastatic extrahepatic biliary tract cancer.

P4.12 Investigation of CD4 T cell help and MHC II in therapeutic vaccinations against liver cancer

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The role of CD4 T cells in tumor immunity is not completely understood, as CD4 T cells recognize MHC class II epitopes expressed on antigen-presenting cells but not on tumor cells. Nevertheless, they send critical signals to dendritic cells, which then upregulate the expression of MHC class I molecules, costimulatory molecules, and secretion of cytokines. The overall goal of our study is to determine the importance of CD4 T cells in adaptive immune responses and immunotherapy against HCC.

Mice underwent implantation with HCC cells with different expression of MHC class II epitopes, the resulting tumor growth kinetics, overall survival and specific CD8 and CD4 T cell immune responses in peripheral blood were analyzed by flow cytometry. Using heterologous T cell vaccination (DC-CoAT) that allows for rapid and strong T cell responses, we generated CD8 T cell responses specific for the MHC class I neoantigen Adpgkmut, as well as CD4 T cell responses specific for the MHC class II neoantigen Itgb1mut. Boosters were performed with or without concurrent administration of the MHC class II epitope Itgb1mut. Treated mice showed a high tumor specific immune response for both CD8 and CD4 T cells. Furthermore, their survival was prolonged with partially tumor regress. In treated mice that were inoculated with an HCC cell line containing the MHC class II transactivator CIITA, the tumors even regressed completely. To better understand the mechanisms of CD4 T cell help, future experiments will characterize the composition of tumor-infiltrating cells by histology and spectral flow cytometry.

P4.13 Deciphering genomic dependencies: A systematic exploration of synthetic lethal interactions induced by chromosomal deletions

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In this project, we aim to identify synthetic lethal genes associated with chromosomal deletions. To illustrate this, we focused on chromosome 1p, a region frequently deleted in the early stages of liver cancer. After in silico data mining, genes of interest were validated by reverse genetic screens. We created sets of genetic instructions (sgRNAs) to target these genes, introducing them into HCC cells with and without chromosome 1p deletion. After modifying the cells, we performed tests to see how knocking out these genes affected them. Interestingly, we discovered that some HCC cell lines were less affected when we turned off a gene called GPX4, which normally prevents a type of cell death called ferroptosis. This led us to hypothesize that certain liver cancer cell lines might have a reduced vulnerability to ferroptosis, and this could be linked to the specific chromosomal deletions they carry. Our findings suggest a complex relationship between chromosomal deletions and how cells respond to ferroptosis.

P4.14 Circulating tumor cells predict recurrence risk in early HCC treated with local ablative therapy

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Background: Early hepatocellular carcinoma (HCC) has a recurrence rate exceeding 50 % following local ablation. Current imaging criteria are insufficient to detect micrometastases within the first two years post-therapy. The aim of this study was to assess the utility of serial EpCAM-positive circulating tumor cell (CTC) testing in identifying patients at higher risk of recurrence after local ablation.

Methods: A total of 43 patients (mean age 68 ± 8 years) undergoing local ablation between 2021 and 2023 were prospectively enrolled. Blood samples were collected pre-treatment and at follow-up visits (3, 6, 12, and 24 months) and processed using the CellSearch™ system. Baseline samples were obtained from both proximal and distal sites. The primary endpoint was recurrence-free survival (RFS).

Results: Recurrence was observed in 18 patients (42 %) within 24 months. Patients with CTC positivity at 6 months exhibited a significantly higher risk of recurrence (HR: 6.55, p = 0.007) and reduced RFS (p = 0.0018). When CTC were combined with alpha-fetoprotein (AFP) levels, CTC-positive status at baseline (proximal blood only), 3 months, and 6 months was associated with an elevated risk of recurrence, with HR of 2.60 (p = 0.057; 95 % CI, 0.95-7.10), 3.49 (p = 0.014; 95 % CI, 1.23-9.49), and 3.26 (p = 0.023; 95 % CI, 1.10-8.84), respectively.

Conclusion: CTC detection at 6 months post-ablation is a strong indicator of increased recurrence risk. The combination of CTC and AFP improves risk stratification, demonstrating prognostic value at CTC when collected at baseline, 3 months, and 6 months post-therapy.

P4.15 TGF-β critically determines the activation state of both, the macrophage subpopulation that is particularly recruited in the context of MASH progression, as well as of TAMs

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. Metabolic dysfunction-associated steatotic liver disease (MASLD) will become the predominant cause for the development of HCC worldwide by 2030, currently accounting for 20 % of HCC cases in Western countries. There are two main subtypes of MASLD-related HCC, with and more rarely without cirrhosis. Microenvironmental factors are thought to be the driving force for HCC development in both, with steatohepatitis being the major cause of HCC in non-cirrhotic patients. Using spatial transcriptomics of MASH-HCC patient samples, we identified tumor-associated CD68-positive macrophages (TAM) that exhibit an activation state distinct from non-tumor regions, with for example reduced expression of the TGF-β activator Dermatopontin (DPT). This suggests an altered response of macrophages to TGF-β signaling with disease progression. Interestingly, CITE-seq analysis of liver tissue from a Western-type diet-(WD) fed mouse model suggests a selective increase in a macrophage subpopulation characterized by high CD11b/CD14 expression, whose activation state is particularly determined by TGF-β early during the progression from MASLD to MASH. Blunting TGF-β signaling in these macrophages changes their acitvation state towards increased production of IL-10 and upregulated expression of CD163 and CD206, representing known features of TAM. In conclusion, these results suggest that TAMs are characterized by an altered sensitivity to TGF-β. TGF-β signaling influences the activation state of distinct macrophage subpopulations, which are also important in the progression of MASH and may be a prerequisite for the development of TAM.

P4.16 Serum IL-6 is a prognostic biomarker for advanced hepatocellular carcinoma treated with atezolizumab and bevacizumab

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Background: Immunotherapy with atezolizumab/bevacizumab (atezo/bev) is an established first-line treatment for patients with non-resectable hepatocellular carcinoma (HCC). Despite notable successes, only a subset of patients shows treatment response, highlighting the need for biomarkers to identify those likely to benefit from this therapy.

Methods: In this biomarker study, 143 patients with atezo/bev-treated HCC were enrolled across three European centers. Baseline cytokine levels were measured using a flow cytometric multiplex bead assay. Overall survival (OS) analysis, reported as hazard ratios (HR), was conducted in an unbiased manner, with patients divided into a discovery cohort (one center, 63 patients) and a validation cohort (two centers, 80 patients).

Results: Our cohorts show typical baseline characteristics of Western HCC patients, with alcohol-related liver disease (35.0 %) and hepatitis C (21.7 %) as the main HCC etiologies. Elevated serum IL-6 (cut-off 18.22 pg/ml) was associated with poor OS in both the discovery (HR 2.6, 95 % CI 1.2-5.6, p = 0.013) and validation cohorts (HR 2.4, 95 % CI 1.3-4.4, p = 0.005). Multivariate analysis confirmed elevated IL-6 to be a significant predictor of poor OS (HR 2.1, 95 % CI 1.1-3.9, p = 0.021) after adjusting for established risk factors such as Child-Pugh class, BCLC stage, ECOG, macrovascular invasion, extrahepatic spread, viral HCC etiology, and AFP.

Conclusion: We identify elevated serum IL-6 levels as independent prognostic biomarker in patients with advanced HCC in Western countries. Importantly, this association was independent of infection with viral hepatitis, thus extending the previously reported associations between IL-6 and treatment response in East Asian cohorts.

P4.17 Repurposing passenger amplifications for specific therapeutic targeting of liver and other solid cancers

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Current cancer therapies focus on targeting driver alterations responsible for tumorigenesis. However, these alterations are often not actionable or are only present in small a subset of patients. We hypothesized that passenger events in amplified regions could be therapeutically exploited by providing actionable molecules on the cell surface. Using publicly available multi-omics data, we identified the cell surface protein-coding gene MPZL1 (Myelin protein zero-like 1, in chromosome 1q), which is amplified in 75 % of hepatocellular carcinomas (HCCs), accompanied high mRNA expression in tumors compared to normal livers. We further validated MPZL1 protein expression in a wide range of human cancer entities (n = 2244) and normal tissues (n = 90) by immunohistochemistry, and found that a high percentage of tumors present scores 2 or 3 (e.g. 48 % of HCCs), whereas healthy tissues are mostly negative or faintly positive (scores 0 or 1). Next, we developed a monoclonal antibody directed to the extracellular domain of MPZL1, whose scFv was then used to generate a CAR (chimeric antigen receptor) construct targeting MPZL1. Corresponding CAR-T cells showed specific killing of several human cancer cell lines in vitro, along with enhanced cytotoxic cytokine production (TNFα, IFNγ, GZMB, IL-2) when encountering the specific antigen. Importantly, MPZL1-28ζ CAR-T cells induced complete eradication of murine autochthonous liver tumors with overexpression of human MPZL1 protein. In summary, our findings reveal MPZL1 as a new target for treatment of 1q-amplified cancers, opening an avenue for innovative drug development approaches by targeting passenger events within large chromosomal amplifications.

P4.18 High expression of SLIT2 in intrahepatic cholangiocarcinoma stroma

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Introduction Intrahepatic cholangiocarcinoma is the second most common primary liver cancer with very poor prognosis. SLIT2 is the ligand of ROBO-receptors, which were shown to be deleted exclusively in invasive CCA (Goeppert et al., 2022). Project aim is to investigate SLIT2-ligand in iCCA tumor-microenvironment. [1]

Methods To detect expression of SLIT2 in iCCA microenvironment spatially, RNA-Scope was applied with vimentin co-detection in healthy liver, fibrotic liver and iCCA tissue samples. For in-vitro functional assays SLIT2 was knocked-down

in LX-2, a hepatic stellate cell line, using siPOOL. The effects were investigated in colony-formation assay and cell-adhesion assay. Knockdown confirmation and changes in target genes were checked by qPCR.

Results We have optimized and validated RNA-scope assay. The results revealed the localization in the tumor stroma, which was then confirmed with vimentin co-detection. Low SLIT2 was observed in healthy liver; fibrotic liver showed an increase in SLIT2 signal and the strongest signal was detected in the tumor stroma in iCCA. In LX-2, clonogenicity and adhesion of the cells were increased with knockdown of SLIT2. alpha-SMA and Fibronectin were significantly downregulated, whereas ICAM was upregulated.

Conclusion RNAScope showed iCCA tumor stroma has enriched SLIT2 levels. SLIT2-knockdown in LX-2 cells showed downregulation at fibrosis genes. Further investigation of SLIT2 related effects on CCA cell lines will be done.

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P4.19 Analysis of mitotic stress-induced activation of the cGAS/STING signaling pathway in human hepatocytes

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Hepatocellular carcinoma (HCC) has been classified as a "genomically unstable" cancer due to the typical presentation of chromosome breakage and aneuploidy. Recent investigations demonstrate that micronuclei, which are formed as a consequence of genotoxic stress, have the capacity to activate innate immune signaling pathways via the cGAS-STING pathway.

The objective of this study was to investigate mitotic stress-induced activation of the cGAS-STING signaling pathway in THLE-5B cells, a SV40 LT immortalized human hepatocyte cell line. In contrast to cancer-derived cell lines these cells are near diploid and express all proteins of the cGAS-STING cascade, rendering them an optimal model for examining this pathway in the context of mitotic stress.

Inactivation of the spindle assembly checkpoint by CFI402257, an inhibitor of the MPS1 kinase, was employed to induce mitotic errors in THLE-5B cells, resulting in the accumulation of aneuploid cells and formation of micronuclei and chromosomal bridges. Confocal microscopy demonstrated the colocalization of cGAS with mitotic abnormalities, and Western blot analysis revealed the activation of the cGAS-STING signaling pathway.

Furthermore, CFI402257-treated THLE-5B cells exhibited the characteristics of a senescence-associated secretory phenotype (SASP) as indicated by SA-β-Gal activity and expression of pro-inflammatory cytokines, including IFN-β, CCL2, and IL-1β.

While SASP enhances immune surveillance to target damaged cells, it may also promote chronic inflammation, which can have adverse effects, including fostering a tumor-promoting environment or accelerating cellular aging and chronic inflammation. The study emphasizes the potential of THLE-5B cells for investigating the cGAS-STING signaling pathway in the context of chromosomal dysregulation in hepatocytes.

P4.20 BMP-9 – a tumour-suppressive factor in the liver?

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Bone morphogenetic protein (BMP)-9, a member of the TGFβ-family, is mainly produced in hepatic stellate cells in the liver and constitutively circulates in the blood of healthy individuals. According to current knowledge, it mainly exerts homeostatic actions, thereby stabilizing the functional, differentiated phenotype of cells but also antagonizing cell proliferation. Due to these functions, BMP-9 could act tumour suppressive.

Our present data show that injection of a low dose of LPS to mice leads to a significant drop of hepatic BMP-9 expression. Furthermore, pre-stages of human liver disease, like steatosis and especially diabetes present with reduced BMP-9 serum levels. HCC cells seem to respond differentially to BMP-9, depending on their expression level of the main BMP-9 receptor, ALK1. In non-ALK1 expressing cells (like healthy hepatocytes), or HCC cells with low ALK1 expression (Hep3B), BMP-9 antagonizes cancer stem cell formation (via ALK2) and stabilizes the differentiated phenotype. In tissue samples from HCC patients, BMP-9 expression negatively correlates with that of stem cell markers like LGR5.

In summary, BMP-9's tumour-suppressive function on liver cells is executed mainly via acting through other receptors than ALK1, e.g. ALK2. Some HCC cells may rebranch the BMP-9 signal by upregulating ALK1, capturing BMP-9, but without transducing the signal. Thereby ALK1 expressing cancer cells support the tumor's own growth, even in the presence of high BMP-9 levels.

High serum-levels of BMP-9 are related to a generally better health status in humans and a drop in BMP-9 serum levels could serve as an early marker for disease development.

P4.21 Epitope-flanking amino acid substitutions facilitate enhanced antigen processing and improve anti-tumoral T cell immunity

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Hepatocellular carcinoma (HCC) is a major leading cause of cancer-related death and the fifth most common kind of cancer worldwide.

Anti-tumoral immune responses are often hampered by reduced antigen presentation of cancer epitopes. Antigen processing is largely governed by amino acids that flank the putative epitopes, thereby controlling presentation of T cell targets on the surface of cancer cells.

Here, we applied systematic testing of amino acid substitutions that flank a defined CD8 T cell epitope to enhance surface antigen presentation on mouse MHC class I molecules.

Liver cancer cell line Hep55.1C was transduced with retrovirus containing different gene cassettes encoding for tumor neoepitopes that were flanked by either wild-type or processing-optimized sequences. Mice bearing subcutaneous tumors that contained processing-optimized sequences showed higher endogenous specific CD8 T cell responses and had longer survival than mice with wild-type sequences expressed in the tumor.

Utilizing a rapid heterologous T cell vaccination regimen, consisting of long polypeptides-pulsed dendritic cells for priming and costimulatory CD40 antibody, TRL3 agonist polyI:C and peptide for boosting, resulted in higher frequencies of specific CD8 T cells when processing-optimized sequences were used, compared to the wild-type polypeptides.

These findings allowed us to define patterns that could improve antigen processing and recognition by anti-tumoral CD8 T cells, thus contributing to tumor growth control. In the upcoming experiments, we will validate the processing-optimized peptide sequence using defined human antigens, which might have implications for human T cell vaccination strategies.

P4.22 Linker Phosphorylation of Smad3 as a Driver of Cholangiocarcinoma Progression and Chemotherapy Resistance

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Cholangiocarcinoma (CCA) is the second most prevalent primary liver cancer, with an increasing incidence in the western world. Despite significant differences in their molecular pathogenesis, CCA patients are traditionally classified based on the anatomic location of the tumor and receive similar chemotherapies. Aberrant phospho-Smad (pSmad) signaling has been suggested as one mechanism underpinning the malignant switch of TGFβ in multiple tumor entities. However, how alternative Smad phosphorylation and variant downstream signaling contributes to CCA progression and therapy response remains elusive. To address this, we assessed Smad3 phosphorylation patterns in liver tissue of CCA patients and patient-derived CCA cell lines and functionally correlated the findings with tumorigenesis and disease prognosis. We observed increased cell numbers with linker phosphorylated Smad3 (pSmad3L) in CCA areas and an inverse correlation with Smad3 C-terminal phosphorylation (pSmad3C), as compared to adjacent tissue. Given the involvement of several kinases in pSmad signaling, we performed a kinase screen using known inhibitors as well as a newly-synthesized small molecule. The results show that Erk/p38 MAPKs as well as GSK3b are involved in Smad3L phosphorylation in CCA. Consistent with this, modulation of signaling and rebranching the pathway from pSmad3L to pSmad3C reduces CCA cell proliferation and migration, and resensitizes CCA cells to more efficient chemotherapy. Our findings suggest pSmad3L signaling as a new targetable molecular mechanism underlying CCA progression and chemotherapy resistance

P4.23 Trends und Entwicklung des hepatozellulären Karzinoms durch ätiologische Verschiebung von 2005 bis 2020 in Deutschland: Bundesweite bevölkerungsbasierte Studie

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Einführung: Das hepatozelluläre Karzinom (HCC) ist mit einer hohen Sterblichkeit und häufige stationäre Aufnahmen verbunden. Das Hauptrisiko für HCC ist die Leberzirrhose. Die Rolle der anderen Risikofaktoren, insbesondere metabolischen Komorbiditäten, ist jedoch noch unklar. Daher analysierten wir die Trends der Krankenhaussterblichkeit bei HCC, unter besonderer Berücksichtigung der zugrundeliegenden Ätiologie.
Methodik: 393.230 Aufnahmen mit HCC wurden von 2005 bis 2020 auf der Grundlage des Diagnosis-related-Groups-Systems über ICD-10-GM-2023- und OPS-2023-Kodes betrachtet. Alle Trends wurden mithilfe linearer Regressionen oder Mann-Whitney-U-Tests verglichen.
Ergebnisse: Die stationären Aufnahmen von HCC-Patienten haben während des Beobachtungszeitraums deutlich zugenommen (+21,78 %; p < 0,001), ebenso wie die Zahl der durchgeführten bildgebenden Untersuchungen (1,6-fachen Anstieg). Die häufigste Ätiologie war die alkoholbedingte Lebererkrankung (55,48 %), die im Laufe der Jahren zunahm (+22,78 %; p = 0,002), jedoch mit einem signifikanten Rückgang der Krankenhausletalität (p = 0,010). Ferner wiesen Patienten mit metabolischer Dysfunktion-assoziierter Steatohepatitis/Lebererkrankung (MASH/MASLD) einen 3,7-fachen Anstieg auf, den stärksten unter den Ätiologien.
Indikatoren des metabolischen Syndroms traten bei HCC-Patienten im Beobachtungszeitraum signifikant häufiger als weiteren Komorbiditäten auf (+88,89 %; p < 0,001). Insbesondere arterielle Hypertonie (18.54 % Unterschied), Herzinsuffizienz (21.98 % Unterschied) und Dyslipidämie (9.43 % Unterschied) schienen unabhängig von Leberzirrhose mit einem erhöhten Risiko mit der HCC-Diagnose assoziiert zu sein. Der Anteil von Adipositas, Diabetes mellitus, arterieller Hypertonie und Herzinsuffizienz war bei HCC-Patienten im Vergleich zu anderen gastrointestinalen Krebserkrankungen, wie Pankreaskarzinom, signifikant häufiger (p < 0,001).
Zusammenfassung: Diese Studie zeigt die zunehmende Belastung des stationären Sektors durch HCC. Interessanterweise sind stoffwechselbedingte Risikofaktoren die häufigsten Komorbiditäten bei HCC, selbst wenn keine Zirrhose vorliegt, und sollten in künftigen Studien berücksichtigt werden.

P4.24 Targeting p53 Isoforms: A Novel Approach for Anticancer Therapy

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Introduction: The tumor suppressor p53 is expressed as at least 12 distinct isoforms, each with unique functions. To identify compounds that differentially regulate these isoforms, we employed the exon-specific isoform expression reporter system (EXSISERS). By integrating three split-intein-flanked luciferases into exons 2, 4, and 7 of TP53, we quantified the de novo synthesis of the tumor-suppressive full-length (FL) p53 and Δ40p53 isoforms, relative to the pro-survival Δ133p53 and Δ160p53 isoforms.
Methods: We stably integrated EXSISERS into wild-type p53-expressing cells using CRISPR/Cas9. The effects of 4,863 anticancer compounds (MCE, HY-L025) on the differential expression profiles of p53 isoforms were assessed in a high-throughput manner. Simultaneously, the total quantity of p53 isoforms was determined using tandem mass spectrometry (MS).
Results: Through EXSISERS, we identified substances that enhanced p53-mediated tumor suppression and cell death while inhibiting pro-survival p53 isoforms. We identified 121 significant (p < 0.025) p53 Tumor Suppressor Isoform Enhancers (TIEs) and 121 Pro-Survival Isoform Enhancers (PIEs). MS of isoform-specific p53 peptides, using 15N-labelled recombinant p53 as an internal standard, confirmed these findings.
Conclusion: EXSISERS enables luminescence-based analysis of protein isoforms, allowing: 1) quantification of target proteins, 2) differentiation of isoforms, 3) time-series data collection, 4) measurements in living cells, and 5) high scalability for screening. This system facilitates the identification of anti-tumor therapeutics that efficiently induce pro-apoptotic p53 isoforms.

P4.25 Artificial Intelligence for differentiation of focal liver lesions using contrast-enhanced ultrasound (CEUS)

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Background and Aims: Characterization of focal liver lesions (FLL) remains an important yet challenging task in routine patient care. Contrast-enhanced ul-

trasound (CEUS) is a reliable tool but depends on the examiner's expertise. Lately we showed that weakly supervised attention-based multiple instance learning (aMIL) algorithms can distinguish benign from malignant FLL. This study aims to further develop and evaluate such an algorithm.

Method: In this retrospective study, we used CEUS data from patients with four types of FLL: focal nodular hyperplasia (FNH), hemangioma, hepatocellular carcinoma (HCC), and metastasis. Features were extracted from examination video frames using a pretrained convolutional neural network. A 20 % class-balanced test set was randomly removed, and the remaining data were used for training with a hyperparameter grid search and five-fold cross-validation. To choose the final set of hyperparameters we averaged the receiver operating curve (AUROC) of each five-fold crossvalidation run. The five models within this run were ensembled yielding our final classifier.

Results: Data from 370 patients (FNH n = 52, Hemangioma n = 149, HCC n = 67, Metastasis n = 102) were included. The average AUROC was 0.82 during cross-validation. The final model achieved AUROCs of 0.85 for FNH, 0.87 for hemangioma, 0.92 for HCC, and 0.93 for metastasis. Post-hoc explainability analysis suggested that the model focused on frames being judged diagnostic by human experts.

Conclusion: Our model can classify FLL according to their appearance in CEUS with very good performance without requiring resource-intensive pre-processing. After validation in prospective trials such weakly supervised algorithms could help clinicians to assess FLL.

P4.26 ROBO receptors function as tumor suppressors in cholangiocarcinoma

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Introduction Cholangiocarcinoma (CCA) is a rare but highly aggressive malignancy of the bile duct with inadequate therapy options and poor prognosis. Genetic alterations in ROBO receptors were identified exclusively in the invasive form of CCA (Goeppert et.al, 2022). ROBO receptors act as axon-guidance-cues during neuronal development, but are deregulated in many cancers in a context-dependent manner. The aim of this project is to functionally characterize the ROBO receptors in CCA.

Methods ROBO1 and ROBO2 were introduced into intrahepatic-CCA cells with a doxycycline-inducible expression system by using lentiviral transduction. Functional assays were performed such as viability, migration, and colony formation. RNA-seq analysis was performed to detect ROBO downstream signaling. BioID, a proximity-based labelling method was used to identify interacting partners of ROBOs. Hydrodynamic-tail-vein injections (HDTV) served to assess the function of ROBO1 and ROBO2 in vivo.

Results ROBO1 and ROBO2 restricted cell viability, migration, and clonogenicity of cells in vitro. RNA-seq revealed a decrease in cell cycle and DNA-replication whereas an increase in interferon response. BioID identified candidate interaction partners of which the majority is involved in MAPK signaling. In-vivo experiments with HDTV showed striking tumor suppressor features of ROBO1 and ROBO2.

Conclusion ROBO receptors restrict tumorgenicity in vitro and in vivo. Additionally, they may play a role in anti-tumor immunity or anti-inflammatory responses. Further experiments may reveal interaction partners, downstream signaling pathways and their involvement in anti-tumor/anti-inflammatory response. Therefore, our research on ROBO1/2 might be useful to develop better therapy options.

P4.27 In-depth histological evaluation and comparison of mouse models for cholangiocarcinoma studies

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Cholangiocarcinoma (CCA) is one of the aggressive cancers, which arises in the bile ducts, representing approximately 10-15 % of liver cancers. It is known for its challenging late-stage diagnosis and limited treatment options. In the recent studies, new insights into CCA were revealed, accentuating the complex nature of the disease and exploring more effective treatment options, primarily focusing on mice studies.

The aim of this study is to characterize the existing mouse models used in the CCA research, evaluating their ability to mimic human CCA by comparing their characteristics, along with their respective advantages and challenges.

In this study, we used tissue-based techniques, including H&E staining and immunohistochemistry, targeting 14 markers. We extensively evaluated their histomorphological characteristics and the tumor microenvironment (TME), across seven mouse models that are used in the CCA studies.

In our results, we have observed those mouse models presented with different CCA subtypes, with various tumor growth patterns, diverse morphological and TME changes. In addition, we detected preneoplastic liver lesions and other neoplastic lesions, such as hepatocellular carcinoma and non-neoplastic alterations of the liver parenchyma (e.g., steatosis).

To conclude, six of the mouse models proved to be suitable for the CCA research. Nevertheless, before conducting the study we recommend that for the selection of the appropriate mouse model, the objectives and targets of the CCA research be defined in advance. Thus, ensuring the optimal model suitability for the future studies.

P4.28 Predictive Value of Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte ratio in Advanced Hepatocellular Carcinoma Treated with Sorafenib Monotherapy or Combined with Radioembolization

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Background To explore the predictive value of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with advanced HCC treated with sorafenib monotherapy or radioembolisation/sorafenib combination.

Methods Patients randomized to sorafenib monotherapy or radioembolisation/sorafenib within the per-protocol population of SORAMIC trial were evaluated in this exploratory post-hoc analysis. The median baseline value of NLR and PLR were used as cut-off values to describe subgroups. Kaplan-Meier curves with log-rank tests were used to evaluate the median survival of sorafenib and radioembolisation/sorafenib arms in each subgroup. Multivariable Cox regression analysis was applied to eliminate the effect of confounding factors.

Results A total of 274 patients with a median overall survival of 12.4 months were included in this analysis. The median NLR value of the cohort was 2.77, and PLR was 26.5. There was no significant difference in the overall survival of sorafenib and radioembolisation/sorafenib arms in patients with low NLR (p = 0.72) and PLR (p = 0.35) values. In patients with high NLR values, there was no statistically significant difference in the median overall survival between radioembolisation/sorafenib and sorafenib cohorts (12.1 vs. 9.2 months,

p = 0.21). In patients with high PLR values, the overall survival in SIRT/sorafenib arm was significantly longer than in the sorafenib arm (15.9 vs. 11.0 months, p = 0.029). This significant difference was preserved in the multivariable analysis (radioembolisation /sorafenib arm HR 0.65 [0.44-0.96], p = 0.03) incorporating age, Child-Pugh grade, and alpha-fetoprotein levels.

Conclusions PLR is a potential predictive factor of benefit from additional SIRT in HCC patients receiving sorafenib therapy.

P4.29 Characterization of T cell subsets and dynamic remodeling following immune checkpoint inhibition in hepatocellular carcinoma

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Immune-checkpoint inhibitors (ICIs) have recently shown promising results in advanced hepatocellular carcinoma (HCC) by targeting molecules like PD-1 and CTLA-4 to enhance anti-tumor immunity. In the prospective phase 1b HCC-PRIME study, safety and efficacy of ipilimumab and nivolumab combination prior to liver resection were analyzed. Here we investigate whether neoadjuvant ICI induces changes in the peripheral immune compartment and if these changes are associated with therapeutic efficacy.

30 patients with radiologically or histologically confirmed HCC were included. Ipilimumab was given once on Day1, and nivolumab on Day1 and Day22, over two 21-day cycles. Blood samples were collected at Cycle1 and 3 weeks post-treatment. Response to therapy was based on radiological criteria (RECISTv1.1 criteria). Peripheral blood mononuclear cells (PBMCs) were analyzed using cytometry by time of flight (CyTOF).

Our study demonstrated remodeling of the peripheral immune landscape during the initial weeks of checkpoint-inhibition therapy, affecting both CD4 and CD8 T-cell compartments. High-dimensional data analysis identified a CD8Tex cluster ($PD1^+TOX^+CD38^+TIGIT^+GzmK^+$), which was elevated in responders at baseline and further increased in all patients following therapy. Furthermore, a $CD8^+PD1^+CD103^+$population that co-expressed CXCR6 and showing a large percentage of nivolumab binding($IgG4^+$) was enriched post-therapy, suggesting a relationship to tumor resident T-cells responsive to ICI. In the CD4 compartment, regulatory T-cells($CD127^+FoxP3^+$) were expanded, while T follicular helper cells ($PD1^+CD127^+CXCR5^+$) decreased after treatment.

Our findings provide insight into the dynamic immune remodeling of T-cell subsets following immune checkpoint inhibition in HCC patients, suggesting that monitoring T cell dynamics may serve as a biomarker for therapy efficacy.

P4.30 The Impact of Perioperative Infections on Long-Term Survival After Liver Resection for Hepatocellular Carcinoma and Cholangiocellular Carcinoma: A Retrospective Analysis

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Background: Hepatocellular carcinoma (HCC) and cholangiocellular carcinoma (CCA) are the most common primary liver tumors. Only in early stages of the disease, tumor resection may offer long-term survival in selected patients. However, morbidity and mortality remain high following extended liver surgery, with perioperative bacterial infections being major complications. This study evaluates the impact of perioperative infections on overall survival (OS) after resection of HCC or CCA.

Materials and Methods: A total of 202 patients who underwent liver surgery for HCC (n = 139) or CCA (n = 63) at university hospital Duesseldorf between 2008 and 2020 were included in this analysis. Infections before or after surgery were assessed through patient records and correlated with survival rates and other clinical characteristics.

Results: Patients with perioperative infections had significantly worse OS compared to those without documented infections (419 days (95 % CI: 262–576) vs. 959 days (95 % CI: 637–1281); log-rank $X^2(1) = 10.28$; $p < 0.001$). In subgroup analysis, this effect was only observed in HCC patients, while outcomes in CCA patients were independent of pre- or postoperative infections. Non-anatomical resection was associated with better survival in HCC patients (1541 days (95 % CI: 1110–1972) vs. 749 days (95 % CI: 0–1528); log-rank $X^2(1) = 5.387$; $p = 0.02$) but had no impact on OS in CCA patients.

Conclusion: Perioperative infection is an important prognostic factor after liver resection for HCC but not for CCA. Non-anatomical liver resection improves long-term survival in HCC but not in CCA.

P4.31 Chimeric VSV-NDV mediates a multimechanistic therapeutic response supported by immune activation in orthotopic hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) represents a challenging malignancy due to its advanced stage at diagnosis and the underlying tolerogenic environment in the liver. Oncolytic virotherapy can provide a promising therapeutic approach through direct tumor cell lysis and induction of local inflammation, thereby reprogramming the tumor microenvironment. We have developed a novel chimeric oncolytic virus platform, VSV-NDV, based on the vesicular stomatitis virus (VSV) backbone and expressing the fusogenic envelope proteins of Newcastle disease virus (NDV), which offers an excellent safety profile and potent therapeutic effects in several tumor models. We have now performed a comprehensive preclinical evaluation of oncolytic VSV-NDV therapy in HCC and investigated the resulting immune-cell signatures in the liver and tumors. In vitro, we demonstrate a potent oncolytic effect of VSV-NDV in human HCC cell lines and patient-derived organoids, which leads to dendritic cell (DC) activation in co-culture. Using inducible and implantable models of HCC in mice and rats, VSV-NDV demonstrates delayed tumor growth and significant prolongation of survival. We have characterized an early increase in innate immune cells

and myeloid cells in the liver and a significant increase in total and effector CD8 + T cells on day 7 post-treatment in the liver and tumor of VSV-NDV-treated mice. Furthermore, rVSV-NDV-mediated expression of a high-affinity soluble PD-1 mediates further enhanced therapeutic effects, coinciding with systemic increases in CD8 + T cells, and prolongs survival in an aggressive multifocal orthotopic model of HCC. These results support the further development of oncolytic rVSV-NDV vectors as a potentially valuable immunotherapy modality for HCC.

P4.32 Genomic Alterations and Tumor Immune Microenvironment as Predictors of Immunotherapy Outcomes in Advanced Biliary Tract Cancer

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Background: The response to immunotherapy is limited in advanced biliary tract cancer (BTC). Response prediction is a serious challenge clinically.
Methods: This study included 55 patients with advanced BTC, who received anti-PD-1 treatment. 520 gene panel sequencing was performed in 30 patients, while multiplex circulating cytokine testing was done in 50 patients. Entropy and mutation features were analyzed using the previously optimized pipeline. The repeated LASSO algorithm was used to identify the optimal features. The associations between sequence features and cell communication were explored by analyzing publicly available single-cell transcriptome data of BTC (GSE125449). Cox regression was used to develop an integrated model. Prediction performance was assessed by time-dependent C-index, Kaplan-Meier, and receiver operating characteristic curve determination.
Results: TP53, NRAS, FBXW7 and APC were identified as prognosis related genes. The average C-index of sequence entropy and mutation for overall survival were 0.819 and 0.817, respectively. They were significantly higher than 0.392 and 0.638 in tumor mutation burden and mutation score. Single-cell transcriptome data inferred that TP53, KRAS, and NRAS are enriched in plasmacytoid dendritic cells (pDCs), and that the communication between pDCs and macrophages is mediated through the CXCL signaling pathway. An EM-CXCL10 integrated model shows powerful predictive performance, including on survival status (AUC: 0.863) and objective response rate (AUC: 0.990), in patients receiving immunotherapy.
Conclusion: Through a multi-dimensional strategy, this study presents a promising predictive model for selecting BTC patients prone to immunotherapy. A further clinical study with a large patients cohort is required to validate its predictive performance.

P4.33 Role of CD44 in early hepatic carcinogenesis in Mdr2 knock-out mice

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DOI 10.1055/s-0044-1801160

Background and aims: The membrane protein CD44 is upregulated in subpopulations of cancer cells and has been linked to cell proliferation and migration. In liver cancer mouse models, such as in diethylnitrosamin (DEN)-induced hepatocellular carcinoma (HCC) and in Mdr2-/- mice, CD44 is overexpressed in liver tumors. Importantly, DEN-treated Cd44-/- mice showed a significantly reduced tumor burden in comparison to controls. To further determine the role of CD44 in hepatic carcinogenesis, we induced HCC by in chronic cholestatic inflammation-induced in Mdr2-/-;Cd44-/- mice.
Methods: Mdr2-/-;Cd44-/- and Mdr2-/- mice were aged for 15 months and livers were analyzed for tumor development by histomorphology and immunohistochemistry for proliferation markers.
Results: Both Mdr2-/-;Cd44-/- and Mdr2-/- mice show only low numbers of HCC and the difference between groups was not significant. However, the number of foci of cellular alteration (FCA) that are considered as tumor precursor lesions, was significantly lower per liver in Mdr2-/-;Cd44-/- mice in comparison to controls (25.44 vs. 48.88; p = 0.0188). Additionally, the number of FCAs larger than 1mm (2.44 vs. 6.25; p = 0.0191) was also lower in CD44-deficient livers.
Conclusion: In the Mdr2-/- model of hepatic carcinogenenis, CD44 seems to play an important role in development and growth of tumor precursor lesions, though no effect on HCC development in this model was observed – possibly due to the low numbers of tumors overalls. Our data show that CD44 could play a key role in early hepatic tumorigenesis and could be a possible target to prevent HCC development.

P4.34 Machine Learning Highlights Association of Body Composition with Cholangiocarcinoma Mortality

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Background Cholangiocarcinoma (CCA) is a high mortality malignancy. Previous studies have largely overlooked individual differences in physiological and metabolic characteristic, limiting the ability to explain and predict the high mortality of CCA. Body composition (BC), a key manifestation of these characteristics, plays a crucial role in cancer. However, its impact on CCA mortality remains inadequately understood.
Methods All data were obtained from the UK Biobank, with CCA diagnosed based on ICD-10 codes. Proportional hazards models were used to assess potential associations between BC and CCA and its subtypes, intrahepatic (ICC) and extrahepatic (ECC). Additionally, multiple machine learning algorithms were employed to develop prognostic prediction models for CCA. And the SHapley Additive exPlanations approach was applied to improve model interpretability.
Results Fat mass in the arm (left: HR = 1.31, right: HR = 1.28, P < 0.05) and leg (left: HR = 1.31, right: HR = 1.28, P < 0.05) were positively associated with total CCA and ICC mortality. In contrast, ECC mortality was associated with leg fat-free mass (left: HR = 2.21, right: HR = 2.10, P < 0.05). Additionally, the eXtreme Gradient Boosting model, which centered on BC, outperformed all other models, achieving area under the curve values of 0.884 for total CCA, 0.865 for ICC, and 0.737 for ECC in the test set.
Conclusion This study highlights significant associations between site-specific BC and CCA mortality and develops a CCA mortality prediction model centered on BC variables. These findings provide valuable insights for personalized clinical management and prognostic interventions.

P4.35 Icer Knockout Influences the Development of Primary Liver Cancer by Promoting Macrophage Infiltration

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Introduction Inducible cAMP early repressor (ICER) modulates gene expression by binding to CREB and CREM in response to elevated cellular cAMP levels. ICER proteins can act as potent repressors of cAMP-induced gene expression. Its induction is thought to function as a negative feedback mechanism during the development of primary liver cancer. However, the specific role of ICER in liver tumor development, particularly in bone marrow-derived macrophages (BMDMs) during hepatocarcinogenesis, remains poorly understood and requires further investigation.

Methods We utilized bone marrow macrophage-specific ICER gene knockout mice to study the development of primary liver cancer after intraperitoneal injection of diethylnitrosamine (DEN). First, we compared liver cancer development between knockout and control cohorts. Next, we extracted liver tumor tissues and analyzed markers of proliferation and apoptosis. Additionally, we assessed whether ICER knockout affects macrophage infiltration in primary liver cancer tissue. Lastly, we explored potential mechanisms by which ICER influences cancer development through its regulation of macrophages.

Results Our study revealed that ICER knockout mice developed more severe primary liver cancer. Histological analysis showed a significant increase in macrophage infiltration in the tumors of ICER knockout mice, suggesting that ICER plays a regulatory role in tumor progression. Furtermore, ICER knockout altered tumor cell proliferation and apoptosis, with activation of the Wnt/beta-Catenin signaling pathway observed.

Discussion These findings underscore the critical role of ICER in hepatocarcinogenesis and suggest potential therapeutic strategies targeting ICER and its negative feedback regulation during liver cancer development.

P4.36 Adiposity and myosteatosis are prognostic biomarkers in advanced HCC patients receiving immunotherapy

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Background and purpose: Immune checkpoint inhibitor (ICI)-based treatments have become the standard first-line therapy for patients with advanced hepatocellular carcinoma (HCC). Despite significant improvements with respect to the previously established standard sorafenib, response rates remain low at around 30 %. Human metabolic phenotypes can modulate inflammation and tumor immunosurveillance. This study aimed to characterize metabolic states of patients with advanced HCC treated with ICI and assess their impact on clinical outcomes, potentially identifying novel prognostic biomarkers.

Methods: This observational, retrospective study collected data from a single center in Germany (LMU University Hospital Munich). Baseline body composition markers including BMI (< 25 vs. ≥ 25), visceral fat (high vs. low, based on median), and muscle density as a correlate of myosteatosis (yes vs. no, using Martin's cut-offs), were assessed from CT scans at the L3 vertebral level. Markers were correlated with patient survival and analyzed using log-rank test.

Results: A total of 146 patients with unresectable HCC treated with ICI were included. BMI did not significantly impact overall and progression-free survival. Patients with higher levels of visceral fat showed prolonged survival (mOS 1038 days vs. 540 days, p = 0.0142). Furthermore, the absence of myosteatosis emerged as strong prognostic marker for improved clinical outcomes (yes: mOS 240 days vs. no: mOS 709 days, p = 0.0038).

Conclusions: Body composition parameters, such as visceral fat and myosteatosis, are significant prognostic markers in patients with advanced HCC treated with ICI. These findings might help to identify patients who could benefit from nutritional interventions to improve clinical outcomes.

P4.37 Immunoregulation and MDSC-Mediated T Cell Paralysis in Hepatocellular Carcinoma Following rVSV-NDV Therapy

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Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality, characterized by a profoundly immunosuppressive tumor microenvironment that hinders effective immune responses. This study evaluates the efficacy of an oncolytic virus therapy in modulating anti-tumor immunity in HCC. Treatment with a recombinant chimeric virus, rVSV-NDV, has been shown to mediate therapeutic effects in preclinical models of HCC, although curative responses were not achieved. Here, we demonstrate robust recruitment of monocytes and effector CD8 + T cells into the liver and tumor in response to rVSV-NDV treatment in an HCC mouse model. Subsequent analyses revealed that infiltrating monocytes differentiate into myeloid-derived suppressor cells (MDSCs), coinciding with T cell infiltration and potentially neutralizing their cytotoxic effects. This transition suggests a mechanism of MDSC- mediated inhibition of T cell function within the tumor microenvironment. In vitro studies demonstrated that HCC cells could drive the differentiation of monocytes into MDSCs, which subsequently suppressed T cell activity via methylglyoxal transfer.

To validate the presence and relevance of these cells in vivo we analyzed scRNA-seq datasets from murine HCC models, not only revealing a population of MDSCs but also indicating a potential intermediate state between mononuclear phagocytes and MDSCs. Current investigations focus on elucidating the induction steps and mechanisms driving the differentiation of mononuclear phagocytes into MDSCs, with implications for understanding their role in shaping the immunosuppressive landscape of HCC and identifying potential therapeutic targets. These findings offer insights into the complex interplay between viral therapy and immune suppression, informing future strategies to overcome resistance in immunotherapy.

P4.38 LZTR1 acts as a potent tumor suppressor gene in liver cancer by safeguarding aberrant MAPK activity via posttranslational control of RAS GTPases

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Hepatocellular carcinoma (HCC) ranks among the cancers with the highest rate of mortality, yet treating this carcinoma remains challenging due to late diagnosis and poor patient stratification, thereby preventing the utilization of targeted therapeutical approaches. Using human genome sequencing data, we identified frequent deleterious alterations of Leucine-zipper-like transcriptional regulator 1 (LZTR1), which plays a crucial role in regulation of RAS-like GTPases (e.g. RIT1) and downstream pathways, such as the mitogen activated protein kinase (MAPK) pathway. Using murine in vivo as well as human in vitro models, we reveal that loss of function of LZTR1 promotes tumorigenesis in vivo as well as cell growth in vitro, an effect accompanied by elevated RIT1 expression and subsequent MAPK pathway activation. Moreover, truncated forms of LZTR1 lacking domains crucial for its interaction with RAS molecules phenocopied the effect of LZTR1 loss, further suggesting that this interaction is crucial for tumor suppression. Finally, expression of mutant RIT1 proteins rendering RIT1 non-degradable by LZTR1 in murine livers resulted in liver tumorigenesis comparable to LZTR1 loss. Thus, our findings suggest that LZTR1 safeguards MAPK signaling by controlling RAS GTPases in the liver and could therefore potentially be utilized to stratify HCC patients for usage of small molecule inhibitors targeting MAPKs, which are currently only employed in other carcinomas.

P4.39 GLUT1-Positive Immune Cells at the Tumor Interface: Uncovering a Metabolic Pathway to Enhanced Survival in Colorectal Liver Metastases

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Background: Glucose transporter 1 (GLUT1) is crucial for cellular energy regulation, and its elevated expression in tumor cells is associated with poor prognosis in several malignancies, including colorectal carcinoma. However, the role of GLUT1 expression in immune cells and its impact on antitumor responses remains underexplored. This study investigates the influence of GLUT1-positive immune cells within the infiltration margin of colorectal liver metastases on patient survival.

Materials and Methods: Immunohistochemical staining for GLUT1 was performed on colorectal liver metastasis tissue samples, and GLUT1 expression was correlated with patient survival data from a clinical database. Leukocytes isolated from the infiltration margin were analyzed via flow cytometry to differentiate between GLUT1-positive and GLUT1-negative CD8 + TEMRA cells. The cytotoxic potential of these cells was assessed based on GLUT1 expression and granzyme B levels.

Results: Increased GLUT1 expression within the infiltration margin was significantly associated with prolonged patient survival ($p = 0.011$), independent of tumor proliferation rate. This survival advantage was most notable in patients with solitary liver metastases. Flow cytometry revealed a higher frequency of GLUT1-positive CD8 + TEMRA cells, with a trend toward increased granzyme B expression, although this did not reach statistical significance ($p = 0.06$).

Conclusion: GLUT1 expression in immune cells at the tumor-host interface may enhance antitumor immune responses, possibly through increased cytotoxicity of CD8 + TEMRA cells. These findings suggest that GLUT1 could serve as a valuable prognostic marker and a potential target for therapeutic strategies aimed at boosting immune-mediated tumor suppression in colorectal liver metastases.

P4.40 Brg1 suppress DEN-induced hepatocellular carcinogenesis in mice

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Background: Hepatocellular carcinoma (HCC) is the most common primary liver cancer. Mutations in the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex are linked to various cancers. Brahma-related gene 1 (Brg1), a key SWI/SNF subunit, is essential for chromatin remodeling and gene regulation. However, its role in liver tumorigenesis remains unclear.

Materials and methods: To elucidate the role of Brg1 in liver carcinogenesis, we utilized a diethylnitrosamine (DEN)-induced HCC model in wild-type (Control) and hepatocyte-specific Brg1 knockout (Brg1 KO) mice. Mice were administered intraperitoneal DEN injections, and liver tumor burden was evaluated after 11 months. Molecular analyses were performed at various stages of tumor development.

Results: Brg1 expression was significantly upregulated in tumor tissues compared to adjacent non-tumor tissues in DEN-induced HCC in wild-type mice. Notably, DEN-injected Brg1 KO mice exhibited a substantial increase in liver tumor incidence, tumor multiplicity, and tumor volume compared to DEN-injected Control mice. These findings strongly indicate that Brg1 deficiency promotes liver tumorigenesis. Additionally, survival analysis revealed a significantly reduced lifespan in DEN-injected Brg1 KO mice compared to the Control group ($p < 0.05$). Molecular analyses identified dysregulation of key oncogenic pathways in Brg1 KO mice, underscoring the role of Brg1 in maintaining liver homeostasis and tumor suppression.

Conclusion: Our data demonstrate that Brg1 acts as a tumor suppressor in hepatocytes, and its loss accelerates hepatocarcinogenesis in DEN-induced HCC models. These findings highlight the critical role of Brg1 in chromatin dynamics and liver tumor initiation, suggesting its potential as a therapeutic target in HCC.

P4.41 Impact of Additive Chemotherapy on Survival in Stage IV Colon Cancer Patients Following Liver Metastasectomy: A Retrospective Analysis with a Focus on Chemotherapy Regime Efficacy

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Introduction: The use of additive chemotherapy following R0 liver metastasectomy is a topic surrounded by controversy. This study aims to investigate the impact of adjuvant chemotherapy on overall survival (OS).

Methods: This monocentric study at the University Hospital Regensburg investigated whether additive chemotherapy provides a survival benefit for patients over the age of 18 years with adenocarcinoma or mucinous carcinoma of the colon and synchronous or metachronous liver metastases following R0 resection. Secondary endpoints included progression-free survival (PFS) and the occurrence of adverse events.

Results: 171 patients were enrolled. 65 received adjuvant chemotherapy, and 106 did not. Both groups showed no significant differences regarding sex, risk factors, or tumor characteristics. However, the chemotherapy group was significantly younger (61 vs. 68 years, $p = 0.002$). OS did not differ significantly between groups (median: 62.9 months vs. 55.9 months, $p = 0.323$). Similarly, no significant difference was observed in PFS (median: 30.4 months vs. 23.7 months, $p = 0.157$). Subgroup analysis revealed that patients receiving capecitabine ($n = 17$) exhibited a significantly superior OS (median: 90 months) compared to those receiving FOLFOX ($n = 40$, median: 31 months, $p = 0.014$). PFS showed no significant difference (median: 14 vs. 12 months, $p = 0.446$). There were no significant differences in adverse events between the groups,

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though the chemotherapy group experienced more fatigue, constipation, and diarrhea, while thrombocytopenia and leukopenia were more common in the control group.

Conclusion: The study suggests that additive chemotherapy does not significantly improve OS in patients with colorectal cancer following liver metastasectomy, though capecitabine appears superior to FOLFOX.

P4.42 How physical activity affects quality of life in patients with UICC IV hepatobiliary and gastrointestinal cancer undergoing systemic therapy

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Introduction: Hepatobiliary and gastrointestinal cancer is a prevalent form of cancer, yet there is a noticeable gap in research on the effects of physical activity on patients with UICC IV undergoing systemic therapy.

Methods: This prospective observational study aimed to investigate the influence of physical activity on quality of life. With the help of pedometers and activity diaries, 52 patients (pancreatic cancer n = 16, gastric carcinoma n = 8, esophageal carcinoma n = 5, colorectal carcinoma n = 11, hepatocellular carcinoma n = 11, cholangiocellular carcinoma n = 7) documented their daily physical activity three times for two weeks at intervals of 3 months. Additionally, their quality of life was assessed by EORTC QLQ-C30 questionnaires. For the final analysis, the patients were divided into three groups according to their physical activity (low, average, high).

Results: The results showed significant changes at baseline and after 3 months for the subscales physical functioning (Baseline: H(2) = 27,54; p < 0,001, 3M: H(2) = 10,67; p = 0,005) , role functioning (Baseline: H(2) = 15,10; p = 0,001, 3M: H(2) = 13,53; p = 0,001), fatigue (Baseline: H(2) = 16,74; p < 0,001, 3M: H(2) = 8,04; p = 0,018) and appetite loss (Baseline: H(2) = 15,88; p < 0,001, 3M: H(2) = 12,54; p = 0,002) in favor for physical activity. For global health/quality of life (H(2) = 7,22; p = 0,027) and nausea and vomiting (H(2) = 6,05; p = 0,049), differences reached significant levels only at baseline.

Conclusion: This study shows that even patients with hepatobiliary and gastrointestinal cancer UICC IV undergoing systemic therapy can benefit from physical activity during their treatment. This could give these patients a sense of control by improving their quality of life. Therefore, patients need to be informed about.

P4.43 The cell polarity protein MPP5/PALS1 controls the subcellular localization of the oncogenes YAP and TAZ in hepatocellular carcinoma

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The oncogenes yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ) are potent oncogenes in the liver. Mutations in upstream regulators cannot explain the nuclear enrichment of both proteins, illustrating that other mechanisms might affect their subcellular localization and activity. In this project, we aim to understand which mechanisms support the activation of YAP/TAZ in liver cancer.

Through proteomics, we identified numerous apical cell polarity complex proteins that interact with YAP and TAZ. A subsequent functional screen revealed that the loss of MPP5 (synonym: PALS1) in liver cancer cells led to the nuclear enrichment of YAP/TAZ. Co-immunoprecipitation (co-IP) experiments showed that MPP5 physically interacts with YAP and TAZ. Subsequent co-IP analyses, after removing four distinct MPP5 protein domains, revealed that the PDZ and Gukc domains play a crucial role in YAP binding. The interaction between YAP/TAZ and MPP5 in the cytoplasm of liver cancer cells was confirmed by proximity ligation assays (PLAs). In human hepatocellular carcinoma (HCC) tissues, a reduction of apical MPP5 was observed, positively correlating with the nuclear accumulation of YAP and TAZ. Expression data analysis illustrated that MPP5 is inversely associated with YAP/TAZ target gene signatures in human HCCs. Lastly, low MPP5 levels define an HCC patient group with poor clinical outcome. The loss or improper localization of MPP5 facilitates the nuclear accumulation of the oncogenes YAP and TAZ in HCC cells. This qualifies MPP5 as a tumor-suppressor gene in hepatocarcinogenesis and explains how the loss of cell polarity can foster tumorigenesis.

P4.44 Clinical effectiveness of two courses of gemcitabine/cisplatin/durvalumab re-administration after failure of durvalumab maintenance therapy in a patient with intrahepatic cholangiocarcinoma

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Introduction: Gemcitabine/cisplatin/durvalumab followed by maintenance durvalumab is the standard treatment of locally advanced or metastatic cholangiocarcinoma (CCA). The clinical benefit of rechallenge for progressing intrahepatic CCA on durvalumab maintenance therapy is currently unknown.

Methods: We report the clinical response to rechallenge of triple therapy after progression on durvalumab maintenance in a patient with intrahepatic CCA.

Results: In August 2021, a 55-year-old female presented with a hepatic lesion in segment VIII and without evidence of metastatic disease. Biopsy-based histology revealed moderately differentiated adenocarcinoma of the intrahepatic bile ducts. The tumor marker CA19-9 was elevated at 538 U/ml. After in situ splitting, complete resection was performed in December 2021, followed by adjuvant therapy with capecitabine for six months. In September 2022, relapse occurred with new unresectable liver lesions and CA19-9 increased to 61 U/ml. After four cycles of gemcitabine/cisplatin/durvalumab followed by five cycles of durvalumab maintenance, partial remission was achieved and CA19-9 normalized. Treatment was discontinued due to grade II fatigue and dizziness, which resolved under maintenance therapy. In August 2023, progression of liver lesions occurred and CA19-9 increased to 998 U/ml. Rechallenge with triple therapy again induced a partial remission and CA19-9 decreased to 32 U/ml. In January 2024, progression of liver lesions with a CA19-9 increase to 209 U/ml was observed after three additional cycles of durvalumab maintenance and a second rechallenge with triple therapy was initiated.

Conclusions: Rechallenge with triple therapy was effective and safe in our patient. This strategy may delay the need for second-line therapy.

P4.45 Inhibition of the chemokine CXCL12 promotes liver cancer progression by modulating the inflammatory and angiogenic tumor microenvironment

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Background and Aims: The chemokine (C-X-C motif) ligand 12 (CXCL12) and its receptors C-X-C motif receptor 4 (CXCR4) and atypical chemokine receptor

3 (ACKR3, or CXCR7) have been implicated in liver fibrosis progression and tumors in several organs. Moreover, CXCL12 was shown to shape a pro-tumorigenic microenvironment by favoring immunosuppressive immune cell recruitment. This study aims at exploring the therapeutic potential of CXCL12 inhibition for the treatment of primary liver tumors, i.e. hepatocellular carcinoma (HCC), and characterizing its impact on liver inflammation.

Method: The CXCL12-neutralizing Spiegelmer NOX-A12 was used in fibrosis-associated (chronic CCl4 injections), and metabolic dysfunction-associated steatotic liver disease (MASLD) related (Western diet, WD) mouse models combined with diethylnitrosamine (DEN)-induced HCC. Tumor growth, liver injury and liver fibrosis were assessed. Blood and liver immune cell populations were analyzed by flow cytometry and multiplex immunostaining.

Results: CXCL12 inhibition increased tumor growth in both CCl4- and WD-associated HCC models. This was accompanied by reduced monocyte-derived macrophages (MoMF) and increased cytotoxic T cell numbers in tumour lesions. Moreover, NOX-A12 activated tumor microvessels, evidenced by an upregulation of CXCR4 on tumor endothelial cells and increased gene expression of angiogenic (Ang2) and anti-angiogenic (Ang1, Thbs1) genes in tumors. CXCL12 inhibition reduced eosinophils and B cells in the liver of CCl4-treated, but not MASLD livers. Concomitantly, NOX-A12 decreased CD11c + MHC-II + MoMF and increased Ly6C + MoMF accumulation.

Conclusion: This study demonstrates pro-tumorigenic effects of CXCL12 inhibition in mouse models of primary liver cancer and suggests a pivotal role for CXCL12 in modulating the tumor immune microenvironment.

P4.46 Batch-effect correction improves downstream imaging mass cytometry data quality and facilitates robust cell type identification in the liver and hepatocellular carcinoma microenvironment

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Introduction Imaging mass cytometry (IMC) enables in-depth analyses of single cells in complex tissue architectures such as the liver and the hepatocellular carcinoma (HCC) microenvironment. However, batch effects can be a significant hurdle for data analysis due to difficulty to discriminate procedural and experimental variability from biological differences. Batch-effect correction strategies aim to reduce non-biological sample-specific signals and improve overall data quality. No formal comparison on IMC data between published methods exists.

Methods We performed IMC and cell segmentation on 12 hepatocellular HCC patients. To reduce batch-effects between single patients, semi-automated background removal (SABR), percentile normalization GUI image deNoising (PENGUIN) and single-cell based correction tools (fastMNN, harmony and Seurat) were performed separately. After phonograph clustering, we compared the performance of these approaches based on the ability to identify expected cell types in the HCC and liver microenvironment, their numeric distribution and patient specificity of clusters.

Results Application of batch-effect correction tools led to a reduction of sample-specific clusters. Most expected cell types were identified after fastMNN, harmony, PENGUIN and SABR. We observed varying numbers of CD8 T cells in some patients with dense immune infiltrates. Inferring test quality criteria from ground truth comparison showed a favorable balance between sensitivity and specificity after PENGUIN and harmony.

Conclusion Batch-effect correction may enhance IMC data performance by limiting non-biological patient-specific variability and ensuring robust cell type detection using clustering algorithms in the liver and HCC microenvironment. Both, batch-effect correction on a primary data level and on a post-segmentation level can be successfully applied.

P4.47 From genotype to phenotype: how IDH1 mutations alter the landscape of intrahepatic cholangiocarcinoma

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Gain-of-function mutations in IDH1 render it with a neomorphic activity to produce an oncometabolite, 2-hydroxyglutarate (2-HG). Little is known about the relevance of this phenomenon in intrahepatic cholangiocarcinoma (iCCA), even though this gene is among the most frequently mutated genes in this tumour type. Furthermore, mutated IDH1 could serve as an important potential target for exploring novel therapeutic options for iCCA.

To elucidate the role of IDH1 in the development of iCCA and determine the functional consequences of 2-HG production, we employed a mouse model which enables introduction of genetic elements directly into the liver. Our results revealed that IDH1 mutations combined with other iCCA-driving oncogenic events shorten survival span of tumor-bearing mice. Moreover, 2-HG accumulation in tumor tissue leads not only to upregulation of methylation and induction of tumor differentiation, but also to altered stromal cell infiltration (e.g. fibroblasts, lymphatics). Further, to identify key players contributing to 2-HG-driven phenotype, we apply mass spectrometry analyses of extracellular matrix from liver cancer tissue. Additionally, to target IDH1 mutant cholangiocarcinoma cells, we screened for peptides with an immunogenic capacity and identified a novel peptide, which is suitable for mutation-specific vaccination. Further experiments are now investigating the therapeutic potential of the novel peptide for rescuing IDH1-related iCCA.

In summary, our results reveal a crucial role of IDH1 in shaping the tumor microenvironment and cell differentiation in iCCA and provide novel insights into immunotherapeutic options for targeting IDH1 as a tumor-specific neoantigen.

P4.48 Focal Adhesion Kinase (FAK)-Dependent Immune Escape in Hepatocellular Carcinoma

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Background and Aims: Overcoming resistance to immunotherapy is an unmet medical need in the treatment of hepatocellular carcinoma (HCC). Immune-excluded HCCs are often characterized by overexpression of focal adhesion kinase (FAK) due to hypomethylation or amplification of its gene PTK2. The functional role of FAK in this tumor immune escape in HCC is poorly understood.

Methods: We applied imaging mass cytometry (IMC) to characterize the immune landscape in HCC with FAK overexpression. Moreover, human HCC single-cell RNAseq data (scRNAseq, GSE151530) were studied to determine specific lineages and differentiation states of immune cell populations associated with high or low FAK expression in tumor cells. Ex vivo spheroid perturbation studies were used to test functional effects of FAK inhibition on common molecular mechanisms of tumor immune escape.

Results: Four out of 12 human HCC tumor tissues showed markedly enhanced expression of FAK in tumor cells. High dimensional immune cell profiling by IMC indicated an increased ratio of PD1 + CD4 + T cells ($p = 0.04$) and CD68 + mac-

rophages (p = 0.02) in FAKhigh HCCs. Moreover, exhausted T cells such as CD39 + CD8 + and TIM3 + CD8 + were more abundant in HCCs with high FAK expression (p = 0.04). Consistently, scRNAseq analyses revealed an enrichment of FOXP3 + Tregs and CD163 + tumor associated macrophages in FAK-overexpressing HCC tumors. Inhibition of FAK in HCC spheroids resulted in an increased expression of pro-inflammatory cytokines (e.g. CCL5) and increased MHC-class I antigen expression.

Conclusions: These data suggest FAK as a potentially targetable driver of immune escape in hepatocellular carcinoma.

P4.49 Spatial analysis of the tumor immune microenvironment in Biliary Tract Cancer

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Background: Biliary Tract Cancer (BTC) is a highly aggressive and often lethal malignancy. Immunotherapies are now regularly used for therapy, however the understanding of the BTC tumor immune microenvironment is still lacking.

Methods: Tissue Microarrays (TMA) from 21 BTC patients were analyzed using imaging mass cytometry. We employed an analysis approach to understand the immune architecture on a single-cell and spatial level, taking into account regional features such as tumor organization. Such an approach has previously allowed patient classification in HCC, and was linked to the outcome of immunotherapy.

Results: 21 BTC samples were differentiated into 3 immunotypes (IT) based on CD8T cell infiltration and relative localization in tumor stroma or parenchyma: enriched (n = 5, 23 %), compartmentalized (n = 6, 28 %) and depleted (n = 11, 52 %). Differential immune cell associations were found: M2-like Macrophages (CD204 + CD68 +) cells were higher in depleted BTC tissue as compared to compartmentalized IT (99,55/mm2 vs 72,46/mm2; p = 0,0001) and FoxP3 regulatory T cells were more abundant in depleted IT against enriched IT (17,81/mm2 vs 9,51/mm2; p = 0,0001), CD45 + CD20 + B cells were seen more in enriched IT versus the depleted IT (155,9/mm2 vs 0,39/mm2; p = 0,0001) and CD68 + CD163 + and CD68 + CD15 + macrophages were enriched in depleted versus enriched IT tissue (112,14/mm2 vs 46,34/mm2; p = 0,0001). Similarly, CD8 + CD45RO + memory T cells were present in enriched tissue more than in depleted ones (1227/mm2 vs 40,7/mm2; p = 0,0001).

Conclusion: The heterogeneity of the tumor immune microenvironment in BTC can be described using a highly multiplexed single-cell analysis of the immune architecture

P4.50 Spontaneous HCC development in mice expressing all HBV transcripts is STAT3 dependent and indicates an oncogenic effect of HBx

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Background: Although most hepatocellular carcinoma (HCC) cases are driven by hepatitis and cirrhosis, a subset of patients with chronic hepatitis B develop HCC in the absence of advanced liver disease, indicating the oncogenic potential of hepatitis B virus (HBV). We investigated the role of HBV transcripts and proteins on HCC development in the absence of inflammation in HBV-transgenic mice.

Methods: HBV-transgenic mice replicating HBV and expressing all HBV proteins from a single integrated 1.3-fold HBV genome in the presence or absence of wild-type HBx (HBV1.3/HBVxfs) were analyzed. Flow cytometry, molecular, histological and in vitro analyses using human cell lines were performed. Hepatocyte-specific Stat3- and Socs3-knockout was analyzed in HBV1.3 mice.

Results: Approximately 38 % of HBV1.3 mice developed liver tumors. Protein expression patterns, histology, and mutational landscape analyses indicated that tumors resembled human HCC. HBV1.3 mice showed no signs of active hepatitis, except STAT3 activation, up to the time point of HCC development. HBV-RNAs covering HBx sequence, 3.5-kb HBV RNA and HBx-protein were detected in HCC tissue. Interestingly, HBVxfs mice expressing all HBV proteins except a C-terminally truncated HBx (without the ability to bind DNA damage binding protein 1) showed reduced signs of DNA damage response and had a significantly reduced HCC incidence. Importantly, intercrossing HBV1.3 mice with a hepatocyte-specific STAT3-knockout abrogated HCC development.

Conclusions: Expression of HBV-proteins is sufficient to cause HCC in the absence of detectable inflammation. This indicates the oncogenic potential of HBV and in particular HBx. In our model, HBV-driven HCC was STAT3 dependent. Our

P4.51 Deciphering the Role of LSD1 in Hepatocellular Carcinoma: Implications for Cell Proliferation and Energy Homeostasis

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DOI 10.1055/s-0044-1801178

Lysine-specific demethylase 1 (LSD1) plays a pivotal role in chromatin structure regulation and transcriptional control through the demethylation of histone 3 lysine 4 or lysine 9, resulting in gene-specific activation or repression, respectively. LSD1 overexpression was shown in various cancer types, contributing to high malignancy. In our study we investigated the role of LSD1 role in hepatocellular carcinoma (HCC).

Global transcriptomics and proteomics analyses of hepatoma cells revealed significant alterations in cell cycle, mitochondrial, and lipid metabolism genes upon LSD1 inhibition. Consequently, LSD1 inhibition significantly impaired cell cycle progression, viability, and mitochondrial ATP and oxygen production. Importantly, using a metabolic-associated HCC mouse model by means of diethyl nitrosamine application and a high fat diet, we show a marked reduction in liver enzymes, fat accumulation, proliferation and tumor growth upon pharmacological LSD1 blockade. Moreover, expression profiling in clinical HCC samples of different etiologies demonstrated that LSD1 levels significantly correlated with the expression of cell cycle and the energy balance machinery. In order to prove that a wide panel of genes involved in proliferation, mitochondrial respiration and lipid biogenesis are direct targets of LSD1 histone demethylation, we performed chromatin-immunoprecipitation followed by whole genome sequencing on hepatoma cells in response to conditional siRNA LSD1 inhibition. Indeed, LSD1 mediated alterations in the histone methylation status revealed its epigenetic transcriptional control . In conclusion, this study demonstrated that LSD1 promotes HCC progression by triggering proliferation and metabolic reprogramming, highlighting its potential as a therapeutic target for HCC treatment.

P4.52 Spontanous bacterial peritonitis caused by Listeria monocytogenes – a possible indicator for Carcinoma

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Spontanous bacterial peritonitis caused by Listeria monocytogenes– a possible indicator for Carcinoma

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Introduction Listeriosis is a foodborne infection caused by Listeria monocytogenes. These bacteria frequently colconize the intestine and are responsible for severe gastroenteritis, including sepsis and neurolisteriosis. Immunocompromised patients have an increased risk of Listeria infection. However, little is known about spontaneous bacterial peritonitis caused by Listeria. Case studies in recent years have shown that patients with liver cirrhosis are more at risk. In rare cases, however, a Listeria infection can also indicate a previously unknown neoplasia.

Methods We present a 77-year-old woman who came to the emergency room with persistent diarrhea and fatigue. The initial examination revealed leukocytosis and new-onset ascites. Blood cultures were taken and an ascites puncture was performed in the presence of known liver cirrhosis. The blood cultures were negative. The ascites cultures were positive for Listeria monocytogenes. Treatment was started with ampicillin. Neurologically, there were no signs of meningitis. In summary, further cross-sectional imaging showed a suspicious echogenic structure in the area of the ovary. After further investigation and biopsy, the detected structure was confirmed as a carcinoma.

Results After diagnostics had been carried out, the listeria bacteremia revealed an underlying malignant disease, in this case a previously undetected ovarian carcinoma.

Conclusion The risk of Listeria infection is increased in patients with liver cirrhosis or immunosuppression. In rare cases, however, an infection can also indicate carcinoma.

P4.53 PD-L1 expressing circulating tumor cells to predict survival in patients with advanced hepatocellular carcinoma treated with immunotherapy: a prospective, multicenter study

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DOI 10.1055/s-0044-1801180

Background and purpose: Treatments based on immune checkpoint inhibitors (ICIs) have emerged as the standard first-line therapy for patients with advanced hepatocellular carcinoma (HCC). However, only a small subset of patients demonstrates a sustained response and suitable biomarkers are lacking. Pre-treatment tumor biopsies of PD-L1 did not prove to be predictive of ICI benefit in HCC. This study aimed to investigate the role of PD-L1 expressing circulating tumor cells (CTC) as liquid biomarkers in patients with advanced HCC undergoing immunotherapy.

Methods: This prospective, multicenter study included patients with unresectable HCC treated with ICI at three hospitals in Germany. Baseline CTC were detected in peripheral blood using CellSearch™ and correlated with clinical endpoints. PD-L1 expression of CTC was compared to PD-L1 expression of primary tumor tissue.

Results: 82 patients were included. CTC and primary tumor tissue showed distinct PD-L1 expression rates, with a significantly higher percentage of PD-L1 expression in the CTC. Patients with PD-L1 positive CTC had a reduced OS compared to patients without PD-L1 expressing CTC. This was confirmed in a sensitivity analysis excluding patients with impaired liver function and in a landmark analysis at three months. The detection of CTC in advanced HCC did not significantly impact progression-free survival or response rate.

Conclusions: PD-L1 expressing CTC were linked to poor outcomes in patients with HCC treated with ICI. Larger studies are needed to validate this biomarker.

Poster Visit Session V
VIRAL HEPATITIS AND IMMUNOLOGY
15/02/2025, 11.00am – 11.40am

P5.01 Immune activation as a hallmark in liver disease progression

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Background & Aims: Liver cirrhosis is characterized by an immune dysfunction on the one hand, and an exaggerated immune response leading to systemic hyperinflammation on the other hand. This so called cirrhosis-associated-immune dysfunction (CAID) involves innate and adaptive immune cells. In this study, we aim to investigate the role of T cells as part of the adaptive immune system in different stages of liver disease.

Z Gastroenterol 2025; 64: e1–e84

Methods: In total, 62 patients with liver disease were enrolled in this study and subdivided into patients with and without cirrhosis as well as compensated and decompensated cirrhosis. T cell phenotype and function were analyzed using flow cytometry and cytokines were measured using a bead-based multiplex assay.

Results: CD8 + T cells, but not CD4 + T cells were diminished in patients with decompensated liver cirrhosis and this further resulted in an increased CD4/CD8 T cell ratio in patients with decompensated cirrhosis. In addition, the phenotype of CD4 + and CD8 + T cells shifted towards activated and highly proliferative effector-memory and terminally differentiated cells in patients with liver cirrhosis. Furthermore, following stimulation with IL-12 + IL-18, CD4 + and CD8 + T cells from patients with liver cirrhosis responded with higher expression of pro-inflammatory cytokines and effector molecules compared with healthy controls. This was further corroborated by the presence of a pro-inflammatory cytokine milieu in these patients.

Conclusions: CD4 + and CD8 + T cells in accordance with the soluble immune landscape are skewed towards an activated and pro-inflammatory environment and reveals immune activation as a hallmark in liver disease progression.

P5.02 Th2-Associated Cytokines Display an Inverse Relationship with Hepatic Egg Load in Hamsters Infected with Schistosoma mansoni

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DOI 10.1055/s-0044-1801182

Background Schistosomiasis is a parasitic infection caused by Schistosoma species that afflicts over 250 million people worldwide. The Schistosoma mansoni species specifically targets the gastrointestinal system and triggers a Th2-type immune response through its eggs, resulting in granuloma formation. This study sought to examine whether the quantity of S. mansoni eggs influences the immune response in infected hamsters.

Methods Eight-week-old hamsters were infected with S. mansoni cercariae using the paddling technique. Bisex and monosex worm populations were generated through poly-miracidial and mono-miracidial intermediate-host infections, respectively. The hepatic and intestinal egg burdens were quantified, cytokine and mRNA expression of key egg-derived proteins were analyzed in infected animals via qRT-PCR.

Results Notably, the Th1 cytokine response to S. mansoni infection was independent of hepatic egg burden, while Th2 cytokines IL-4, IL-5, and IL-13 showed an inverse correlation in the liver. Bisex-infected animals had increased expression levels of up to 4.6-fold (IL-4), 10-fold (IL-5), and 30-fold (IL-13). Hepatic IL-4 and IL-13 levels inversely correlated with egg-derived factors like IPSE/alpha-1, kappa-5, and omega-1. In contrast, IL-4, IL-5, and IL-13 expression in the colon was unaffected by intestinal egg burden.

Conclusion Our findings indicate an inverse correlation between hepatic egg burden, soluble egg factors, and the Th2 immune response in the liver, but not in the colon. This suggests a protective mechanism in the liver to limit the Th2 response under high egg burden, likely due to prolonged embryogenesis. The absence of correlation in the colon supports this hypothesis, where eggs transit more quickly.

P5.03 The vitamin D receptor genotype is associated with Vitamin D- and Interleukin-6 concentrations in liver cirrhosis and acute-on-chronic liver failure

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Background: Vitamin D (25(OH)D3)-deficiency is highly prevalent in liver cirrhosis. Moreover, 25(OH)D3-status correlates with systemic inflammation and decompensation risk in liver cirrhosis. This study aimed to evaluate how single nucleotide polymorphisms (SNPs) of the Vitamin D receptor (VDR) influence 25(OH)D3-status and 25(OH)D3-mediated immunological effects in liver cirrhosis and acute-on-chronic liver failure (ACLF).

Method: Compensated and decompensated liver cirrhosis patients with or without ACLF were recruited from a monocentric, prospective cohort study (N = 355). Clinical data were analysed, 25(OH)D3-plasma-concentrations were quantified by ADVIA Centaur Immunoassay and cytokine levels were determined by ELISA. The VDR was examined for distinct SNPs (rs7968585, rs731236, rs7975232, rs2239179, rs2228570) using pyrosequencing.

Results: Patients mean 25(OH)D3-concentrations were 15.3ng/mL underlining the high prevalence of 25(OH)D3-deficiency. 25(OH)D3-levels decreased significantly with liver cirrhosis progression (compensated vs. ACLF: P = 0.007). Furthermore, 25(OH)D3-supplementation proved to be highly effective in compensated and decompensated liver cirrhosis, whereas 25(OH)D3-levels could not be increased significantly in ACLF by supplementation (ACLF supplemented vs. unsupplemented P > 0.99). Inflammatory markers, e.g. Interleukin-6 (IL-6) increased with cirrhosis progression (compensated vs. ACLF: P < 0.0001). Overall, 25(OH)D3- and IL-6-concentrations correlated inversely. Of note, a trend of an opposing association between IL-6-levels and the genotype of the VDR haplotype rs731236/rs7975232/rs7968585 and rs2239179 was identified in compensated liver cirrhosis and ACLF. rs2239179 was moreover associated with 25(OH)D3-status (AG vs. GG: P = 0,002) and its GG-genotype showed lower prevalence in ACLF (P = 0.0003).

Conclusion: According to this analysis the VDR-genotype may affect inflammatory molecules, 25(OH)D3-status and the success of a supplementary therapy in liver cirrhosis and ACLF.

P5.04 The anti-tumour effector function of mucosal-associated invariant T cells against hepatocellular carcinoma is impaired by fatty acids and aberrant lipid metabolism

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DOI 10.1055/s-0044-1801184

Mucosal-associated invariant T (MAIT) cells, the most abundant innate-like T cell population in the liver, harbour anti-cancer potential. However, their effector function is impaired in hepatocellular carcinoma (HCC) for reasons that are incompletely understood. Here, we aim to decipher the mechanism by which MAIT cell effector function is impaired in metabolic dysfunction-associated steatotic liver disease (MASLD), a common precondition for HCC development.

MAIT cells from peripheral blood of MASLD patients or healthy controls were stimulated ex vivo, and MAIT cells from healthy controls were challenged with fatty acids during stimulation. MAIT cell phenotype and function was analysed by multi-colour flow cytometry, metabolism was investigated by metabolic flux analysis and gene expression by RNA sequencing.

We show that MASLD MAIT cells express higher levels of activation markers and effector cytokines ex vivo, suggesting MAIT cell activation in MASLD in vivo. However, upon ex vivo restimulation, these activated MAIT cells were dysfunctional and failed to produce effector cytokines. Notably, culture with distinct fatty acid species characteristic of the MASLD microenvironment and accumulating in our MASLD patient cohort, impaired expression of effector cytokines by MAIT cells and abrogated their HCC cell killing capacity. Mechanistically, these effects were mediated by corrupted mitochondrial function, oxidative stress and aberrant lipid metabolism and could be rescued by treatment with redox regulators.

Taken together, we show that impairment of MAIT cell anti-tumour effector function against HCC is mediated by metabolic signals in the hepatic microenvironment in MASLD patients that induce oxidative stress and corrupt MAIT cell metabolism.

P5.05 The pivotal role of infected hepatocytes in determining the outcome of antiviral CD8 T cell immunity in the liver

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DOI 10.1055/s-0044-1801185

Lymphocytic choriomeningitis virus (LCMV) and adenoviral infection sensitizes hepatocytes towards efficient CD8 T cell mediated killing. As hepatitis B virus (HBV) infections are a global health problem with 290 million chronic infections, we aimed to analyze, if also HBV renders hepatocytes more susceptible for enhanced cell death induction.

HBV-replicating primary human and murine hepatocytes were co-cultured with HBV-specific CD8 T cells or treated with T cell effector molecules, like Fas-ligand and tumor necrosis factor (TNF). The T cell effector function against infected hepatocytes was analyzed in real-time using impedance measurement. In vivo, we monitored viral clearance using bioluminescence imaging and ALT measurement after transfer of antigen-specific CD8 T cells in mice.

Whereas adenoviral and LCMV infections resulted in higher killing efficiency of virus-specific CD8 T cells, HBV-infected hepatocytes did not display increased susceptibility and were more resistant towards cell death induction. Increasing the number of CD8 T cells or the concentration of effector molecules we could overcome the threshold for cell death induction of HBV-infected hepatocytes. Thereby, killing efficacy of HBV-infected hepatocytes was still comparable to uninfected hepatocytes. Strikingly, co-infection with HBV reversed the virus-induced sensitivity towards immune-mediated cell death induction leading to reduced killing efficacy of HBV-infected hepatocytes.

Here, we demonstrate that HBV infected hepatocytes do not only escape the non-canonical CD8 T cell effector function but are also more resistant towards CD8 T cell mediated killing. Overcoming these immune escape mechanism of HBV bears the promise to boost immune-mediated clearance of HBV-infected hepatocytes.

P5.06 A DNA launch method for HBV infection in human hepatocyte chimeric mice enables isogenic studies of basal-core promoter and precore mutants

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Background & Aims: Studying isogenic infectious hepatitis B virus (HBV) mutations in human hepatocyte chimeric mice (huFNRGs) has remained challenging due to the low efficiency of infection with cell culture-derived virus and because clinical isolates contain mixed virus populations. We sought to develop an efficient method to launch HBV infection from recombinant HBV-DNA, thereby facilitating research on isogenic mutants, including basal-core promoter (A1762T/G1764A, BCPM) and precore mutant (G1896A, PCM) viruses.

Methods: We engineered silent mutant barcodes in and mixed these in serial dilution (ratios ranging from 1:10 to 1:10,000) with wild-type (WT) HBV-DNA to compare the efficiency of two delivery methods in huFNRGs: ex-vivo human hepatocyte transfection and re-transplantation (TRT) and direct intrahepatic injection of recombinant-cccDNA (IHI). Next, we generated isogenic virus stocks from genotype C2-3 WT, BCPM and PCM and performed infection experiments in huFNRGs.

Results: IHI is superior to TRT, initiating the launch of at least 10,000 rcccDNA molecules and yielding viremia in 90.2 % of huFNRGs across genotypes A-F (TRT: 40.6 %). We defined the unique transcriptomic profiles attributable to isogenic genotype C2-3 variants (WT, BCPM, PCM) using RNA sequencing. We furthermore found variant-specific effects on the proteomic landscape in liver tissue and, using isolated human hepatocytes from infected huFNRGs, observed variant-specific responses to interferon treatment in the proteome.

Conclusion: The rcccDNA IHI-launch technique efficiently initiates HBV infection, allowing the study of isogenic variants across genotypes. Using this approach in genotype C2-3, we were able describe distinct transcriptomic and proteomic differences that are directly attributable to BCPM and PCM.

P5.07 CRISPR/Cas9-mediated Cxcr3 gene knock-out in unstimulated murine primary CD4 + T cells

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Background: Recognition of myelin basic protein (MBP) in hepatocytes of CRP-MBP mice induces tolerance of MBP-specific CD4 + T cells and protection from MBP-driven neuroinflammatory disease. To investigate mechanisms, we aimed for a gene editing method targeting primary CD4 T cells, which are then followed in vivo after transfer to CRP-MBP mice. As current protocols rely on intermediate in vitro stimulation that can potentially confound the following in vivo experiment, we here establish a CRISPR/Cas9 protocol for unstimulated primary CD4 + T cells, using the example of the liver-homing receptor Cxcr3.

Methods: CD4 + T cells were isolated from murine spleens utilizing negative selection, subjected to electroporation with Cas9 and sgRNA, and immediately injected intravenously into CD45.1- CRP-MBP mice. Transferred cells were re-isolated after 7 days from blood, liver and spleen and analyzed by flow cytometry.

Results: Transferred T cells were vital after 7 days in vivo, and 80 % of the cells manifested Cxcr3 gene knock-out, and undetectable Cxcr3 in flow-cytometry. Cxcr3 knock-out was ineffective in the other 20 % of transferred T cells, which could thus serve as internal control. Transferred T cells with Cxcr3 knock-out manifested significantly decreased infiltration into the liver, as compared to transferred T cells without Cxcr3 knock-out.

Conclusion: The study demonstrates the feasibility of CRISPR/Cas9-mediated gene editing in unstimulated murine primary CD4 + T cells for use in adoptive transfer experiments. Thus, this technique can be used for identification and functional validation of specific molecules in T cells in vivo without potentially confounding intermediate in vitro culture.

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P5.08 Skewed HBV-specific CD8 + T cell repertoire in chronic versus acute-resolving HBV infection

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DOI 10.1055/s-0044-1801188

Background/aims: Function and quantity of CD8 + T cell responses is superior in acute-resolving versus chronic HBV infection. If epitopes are targeted differentially in these outcomes of HBV infection, is unclear.

Methods: PBMC from 80 patient with HBV infection (55 chronic; 25 resolved or acute) were screened for interferon-γ responses using overlapping peptides covering the full HBV proteome. Subsequent epitope fine-mapping and HLA-restriction analysis was performed. Additionally, autologous viral sequences of the tested and additional patients with chronic HBV infection (overall n = 532) were obtained.

Results: We found a broad HBV-specific CD8 + T cell epitope repertoire in acute HBV infection. After spontaneous resolution, the number of these responses decreased, while the broad landscape was preserved. In chronic HBV infection, the HBV-specific CD8 + T cell epitope repertoire was skewed, with a lack of functional HBsAg-specific CD8 + T cell responses, as recently described. HBx-specific responses were relatively over-represented. Interestingly, patients with chronic HBV infection showed significantly more HLA-B- than HLA-A-restricted HBV-specific CD8 + T cell responses, while the distribution in acute-resolving HBV infection was balanced. This might be explained by T cell selection pressure. Compared to HLA-A-restricted CD8 + T cell responses, HLA-B restricted responses more frequently displayed autologous viral sequences variations indicating viral escape. This trend was validated in a broader sequence dataset, where HLA-associated viral footprints were more frequently detected for HLA-B compared to HLA-A.

Conclusions: HLA-B-restricted epitopes are dominant in chronic HBV infection, but might be more prone to viral escape. This findings have implications for the development of future immunotherapeutic approaches.

P5.09 Analysis of the CXCL9-11 mediating recruitment of CXCR3 + CD4 T cells to HDV-infected livers

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Background & Aims: In this study, we characterized the induction pattern of inflammatory chemokines in HDV-infected primary human hepatocytes (PHHs) and CXCR3-mediated chemotaxis of T cells in chronic hepatitis D (CHD).

Methods: We performed qPCR, RNA in situ hybridization (ISH) and FACS analysis in liver biopsies and blood samples from patients with chronic HBV infection (CHB) and CHD. Chemokine expression was investigated in cultured HBV/HDV-infected PHHs and in livers of HBV/HDV-infected humanized mice, in the presence or absence of adoptively transferred human T cells.

Results: HDV infection highlighted CXCL9-11 as the most strongly induced chemokines. Interferon lambda-1 (IFNL1) was also strongly induced by HDV and blocking of the IFNL receptor before HDV infection resulted in reduced CXCL9-11 induction in cultured PHHs. ISH analysis of HDV-infected livers from patients and chimeric mouse revealed that PHHs substantially contribute to chemokine expression in vivo. Moreover, the corresponding chemokine receptor CXCR3 was enhanced on CD4 T cells in the periphery of CHD patients. CXCR3-upregulation was unspecific and was not detected on HDAg- or HBsAg-specific CD4 T cells by AIM assay. Adoptive transfer of human T cells in humanized mice led to the recruitment of non-HBV/HDV-specific CD4 + T cells only in the setting of HBV/HDV co-infection, but not in HBV-mono-infected mice.

Conclusions: HDV infection enhanced the expression of CXCL9-11 in hepatocytes, and such induction was augmented by IFNL1 production. The CXCL9-11 increase correlated with the accumulation of bulk CXCR3 + T cells in HDV-infected liver. This pathway may contribute to the aggravated liver inflammation in CHD patients.

P5.10 Single-nuclei RNA-sequencing of human liver samples reveals heterogeneity and compositional changes of biliary epithelial cell subpopulations during the progression of primary sclerosing cholangitis

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In primary sclerosing cholangitis (PSC), biliary epithelial cells (BECs) are central targets of inflammatory responses. However, little is known about their composition, function and role in the disease process. Within this project we aim to decipher the characteristics of BECs at different disease stages.

Human liver biopsies and samples from more than 60 individuals, including PSC patients at various disease stages, other liver diseases and healthy controls, were processed by single-nuclei RNA-sequencing. To resolve the location of cell states, spatial transcriptomic techniques were performed.

We identified seven distinct BEC states. Compared to healthy controls, BECs with a progenitor-like phenotype and those with a mature BEC phenotype showed a significant and gradual decline from early to advanced PSC stages. In contrast, BECs characterized by a reactive ductular phenotype exhibited a progressive and significant increase as PSC advanced. Spatial transcriptomic analysis confirmed the presence of this reactive cell state in the portal fibrotic scar regions. Differential gene expression analysis of BECs in PSC compared to healthy controls revealed, among other findings, a significant upregulation of genes involved in the TNF-α signaling pathway. Additionally, interactome ana-

lysis suggested enhanced interactions between BECs and macrovascular endothelial cells in PSC.
In this study, we define specific BEC states implicated in the progression of PSC. Our findings provide a comprehensive understanding of the heterogeneity of BECs in different liver disorders and how BECs might interact with other parenchymal and immune cells in the pathogenesis of PSC.

P5.11 Cytotoxic CD16 + γδ T Cells Are Associated with Virus Control in Chronic Hepatitis B Virus (HBV) Infection by Mediating Antibody-Dependent Cellular Cytotoxicity (ADCC)

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The role of the immune system in the pathogenesis of HBV infection and the correlates of functional cure are not fully understood. Antibody-dependent cellular cytotoxicity (ADCC) is a possible important mechanism for controlling viral replication. However, its role in CHB, especially the involvement of NK and γδ T cells, which are abundant in the liver, is still unclear.
This study analyzed peripheral NK and γδ T cells in individuals with acute (n = 13) and chronic HBV (n = 57) using spectral flow cytometry and single-cell RNA sequencing, alongside HBV viral markers. To assess NK and γδ T cell-mediated ADCC, isolated NK or γδ T cells from HBV patients and cord blood were stimulated with HBsAg and intravenous immunoglobulin (IVIG).
We showed that CD16 + γδ T cells but not CD16 + NK cells negatively correlate with HBcrAg, a marker of intrahepatic HBV replication in CHB. These cells expressed higher levels of cytotoxic markers (granzyme B, perforin, NKG2D), and their stimulation with HBsAg and IVIG led to increased IFN-γ, TNF-α, and CD107a expression. Ex vivo staining of CD16 + γδ T cells positively correlated with ADCC in individuals with CHB and acute HBV, while γδ T cells from cord blood, with low CD16 expression, lacked ADCC function.
In conclusion, our results emphasize the role of CD16 + γδ T cells and ADCC in the control of HBV during chronic infection. The absence or low levels of CD16 + γδ T cell-associated ADCC in cord blood may explain the high rate of CHB in the context of vertical transmission.

P5.12 Mucosal-associated invariant T (MAIT) cells possess direct anti-tumour potential, but are rendered dysfunctional within the tumour microenvironment in HCC

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Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide. Innate-like mucosal-associated invariant T (MAIT) cells are protective against HCC in murine models but often dysfunctional in human HCC patients for reasons that are incompletely understood. Here, we aim to unravel molecular mechanisms of MAIT cell cytotoxicity and dysfunction within the tumour microenvironment in HCC in human patients.
MAIT cells were isolated from human liver tissue and peripheral blood. Primary MAIT cells were co-cultured with various HCC cell lines in vitro and MAIT cell phenotype and function was analysed by multi-colour flow cytometry. MAIT cell cytotoxicity was tested by real-time viability assays using xCelligence.
We uncover a so far unrecognised direct cytotoxic capacity of human MAIT cells against HCC cells employing an in vitro co-culture system. Mechanistically, MAIT cell cytotoxicity is dependent on signalling via death receptors of the tumor necrosis factor superfamily as well as effector cytokines secreted by MAIT cells. In HCC patients, MAIT cells are systemically reduced in frequency and excluded from HCC tumour tissue. Importantly, tumour-educated MAIT cells express a dysfunctional phenotype, which is induced by HCC cells in a cell contact-dependent manner. Importantly, MAIT anti-tumour capacity could be enhanced by targeting the death receptor – cytokine axis we have identified.
Our results demonstrate a direct cytotoxic capacity of MAIT cells against HCC cells and suggest that enhancing the anti-tumour potential of MAIT cells could be harnessed to improve immunotherapeutic strategies against HCC.

P5.13 No evidence for viral escape mutations in immunodominant CD4 HCV-specific epitopes

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Hepatitis C virus (HCV) infection provides a valuable model for studying immune responses under viral persistence and clearance. About 70 % of infections become chronic, while 30 % resolve spontaneously. Viral adaptation to CD8 T cell pressure is linked to viral persistence. However, immune escape in CD4 T cells is less understood.
This study aimed to compare HCV-specific CD4 T cells in patients with chronic infection, patients who resolved HCV via direct-acting antiviral (DAA) therapy, and individuals with spontaneous resolution, including potential CD4 immune escape mechanisms.
Therefore, we analyzed HCV-specific CD4 T cells using MHC class II tetramers in peripheral blood mononuclear cells (PBMCs) from 139 patients with chronic and spontaneously resolved HCV. CD4 T cells in resolved individuals showed higher CD127 expression and lower CD95 and PD-1 expression compared to chronic HCV patients. For in-depth analysis of immunodominant viral epitopes, viral isolates were sequenced, and mutations were analyzed in relation to HLA-DRB1 alleles using Fisher's exact test. Found mutations were genotype-specific and not associated with HLA-DRB1-alleles. CD4 T cell recognition was tested using epitope-specific T cell clones stimulated with mutated and non-mutated epitopes, followed by cytokine secretion analysis. Importantly, HCV-specific CD4 T cell clones recognized both mutated and non-mutated epitopes equally.
In conclusion, we identified phenotypic differences in CD4 T cells between chronic and resolved HCV cases. There was no evidence for viral escape in the analyzed CD4 epitopes.
These findings offer important insights into the immune mechanisms of HCV persistence and resolution, with potential implications for CD4 T cell-targeted therapies.

P5.14 Association of fibronectin serum levels with loss of hepatitis B surface antigen in patients with chronic hepatitis B during nucleos(t)ide analogue treatment

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Background: Fibronectin is an essential part of the extracellular matrix, and its binding to the surface antigen (HBsAg) of the hepatitis B virus (HBV) has been linked to viral propagation. We aimed to correlate fibronectin serum levels with viral biomarkers in patients with chronic hepatitis B (CHB) during nucleos(t)ide analogue (NUC) therapy.

Method: In this study, 54 patients with HBeAg-positive chronic HBV infection were enrolled. The median duration of NUC therapy was 36 months. The cohort included 17 patients with HBsAg loss, 6 patients with HBeAg loss and 31 HBeAg-positive patients without serologic response. Serum levels of fibronectin, HBV DNA, total HBsAg and the three HBsAg components large (L) HBs, middle (M) HBs and small (S) HBs were measured before and during therapy at months 6, 12 and 24.

Results: The median fibronectin level was lower in patients with HBsAg loss compared to patients without seroconversion at baseline (348.4 µg/mL vs. 203.5 µg/mL, p = 0.100), at month 6 (318.2 µg/mL vs. 276.7 µg/mL, p = 0.001) and at month 24 (413.3 µg/mL vs. 295.5 µl/mL, p = 0.003). There was an increase in median fibronectin levels in patients without serologic response from baseline to month 24 (323.8 µg/mL vs. 407.4 µg/mL, p = 0.068). Correlations of fibronectin with HBsAg, HBV DNA, LHBs and MHBs were recorded at month 6 and 24.

Conclusion: Fibronectin serum levels are significantly lower in patients with subsequent HBsAg loss undergoing NUC therapy and correlate with the composition of HBsAg. Further studies are needed to clarify the role of fibronectin in functional cure.

P5.15 Disrupting the intracellular MK2/3-TTP interaction reduces inflammation but preserves antiviral mechanisms in CMV infection

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Acute viral infections trigger robust immune responses in the liver, which are characterized by the activation of resident cell populations and the subsequent recruitment of additional cells of innate and adaptive immunity. Here, the expression of inflammatory cytokines by liver macrophages plays a central role. However, excessive inflammation and immunopathology must be prevented. The intracellular MK2/3 kinase system is a key molecular mediator as it controls cytokine expression mainly through tristetraprolin (TTP)-dependent post-transcriptional regulation. However, it also controls a negative feedback loop involving type I interferons (IFN-I) and IL-10. Thus, this kinase system is a linchpin in the initiation and resolution of inflammatory mechanisms.

In this study, we infected macrophages in vitro or mice in vivo with the murine cytomegalovirus (MCMV). Liver and serum were isolated for further analysis. MCMV is an accepted model for human CMV infections, which lead to severe organ diseases and increased morbidity or mortality especially in individuals with an immature or compromised immune system. Therefore, investigating the immune responses induced by CMV is of high relevance.

Our data reveal that the deletion of the MK2/3 kinase system resulted in an abrogation of two distinct MCMV-induced cytokine responses: 1) TTP-dependent inflammation including TNF-α and IL-10, 2) TTP-independent antiviral IFN-I. Consequently, loss of IL-10- and TNF-α-mediated signaling in macrophages improves the production of immune cell-activating cytokines, such as IL-12 or CXCL9.

In conclusion, targeting the MK2/3-TTP interaction is a potential strategy to limit inflammation while maintaining antiviral responses associated with CMV infections.

P5.16 Important roles of HBe and HBs antigens in the evasion of endogenous innate immune responses in Hepatitis B Virus infection

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Hepatitis B virus is a DNA virus with no apparent cytotoxicity, but can cause persistent infection. Despite the development of an effective vaccine, an estimated 2 billion people worldwide have evidence of past or present HBV infection; 300 million people are chronic HBV surface antigen carriers and are at high risk of developing hepatocellular carcinoma and liver cirrhosis. 20-30 % of the chronically infected patients will develop complications associated with HBV infection, causing more than 700,000 deaths annually. The persistence of HBV in patients is due to an inadequate host immune response with an absent or weak HBV-specific cytotoxic T lymphocyte response. It is therefore proposed that HBV controls or evades endogenous immune responses, whereas activation by exogenous stimuli results in an effective antiviral signalling. Immune evasion occurs not only through pattern recognition receptor signalling, but also through control of cytokine and interferon responses.

Aim: The aim of this project is to determine HBsAg- and HBeAg-mediated immune evasion of potential HBV-sensing pattern recognition receptors (TLR2, TLR3, RIG-I/MDA5, STING and cytosolic DNA sensors). In this context, key host proteins interacting with HBsAg or HBeAg will be identified and their contribution to immune evasion will be investigated. The impact of HBsAg or HBeAg on cytokine- and interferon-mediated responses and viral effects on regulatory inflammatory networks in the liver will also be investigated.

P5.17 Bulevirtide in combination with pegylated interferon alfa-2a shows a sustained off-treatment response in the liver

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Background: Bulevirtide (BLV) is a first-in-class entry inhibitor approved for chronic hepatitis D (CHD). The phase-2b study MYR204 evaluated safety and efficacy of BLV with or without pegylated interferon alfa-2a (PegIFNα). This sub-study aimed to assess intrahepatic virological and host changes 24w after end of treatment (EOT).

Method: 174 CHD patients were randomized (1:2:2:2) to receive (A) PegIFNα for 48w; (B) 2mg BLV + PegIFNα or (C) 10mg BLV + PegIFNα for 48w, both followed by 48w monotherapy with BLV 2mg or 10mg, respectively; (D) 10mg BLV for 96w. Paired liver biopsies at baseline and 24w after EOT from a subset of patients were assessed by qPCR (n = 42) and immunohistochemistry (n = 44) for HDV, HBV and host parameters.

Results: Intrahepatic HDV-RNA levels and HDAg-positive cells decreased from baseline, with the largest reductions in the combination arms. At follow-up, 57 % of patients in arm B and 73 % in arm C were HDV-RNA negative. Intrahepatic changes of HDV-RNA mirrored serological HDV-RNA changes (r = 0.82; p < 0.0001). Intrahepatic HBV parameters did not change significantly apart from sharp declines in some patients receiving combination treatments. Decreases in infection-related genes, e.g., CXCL10, strongly correlated with the reduction of intrahepatic HDV-RNA (r = 0.67; p < 0.0001) and ALT levels (r = 0.75; p < 0.0001), suggesting ameliorated liver inflammation.

Conclusion: Paired BL and post-treatment biopsy analyses demonstrated a strong correlation between intrahepatic and serum HDV-RNA reductions. Reduced expression of infection-related genes accompanied the decline in HDV.

The highest off-treatment virological response in the liver was observed in the arm that received BLV 10mg + PegIFNα combination.

P5.18 Tolerance induction by liver sinusoidal endothelial cells is preserved in liver fibrosis

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Background Liver sinusoidal endothelial cells (LSECs) are major inducers of immune tolerance. Previously, we have shown that targeting of autoantigen peptides to LSECs using nanoparticles (NP) can be used for therapy of autoimmune diseases. In liver fibrosis, LSECs capillarize and are believed to acquire enhanced immunogenicity. Here, we explore whether in fibrosis, LSECs maintain their ability to induce tolerance to ingested autoantigen peptides.
Methods To investigate LSEC tolerance induction in liver fibrosis, the CCl4 and Mdr2KO mouse models were used. Targeting of NP to liver cells was examined by injection of Cy5-labelled NP, and the ability of LSECs to cross-present antigens was tested using an antibody recognising SIINFEKL-peptide on MHC-I molecules. Furthermore, Treg conversion assays were performed using LSECs from fibrotic livers as antigen presenting cells. Treatment of autoimmune diseases with autoantigen-coupled NP in the context of liver fibrosis was tested in two mouse models: experimental autoimmune encephalomyelitis (EAE) and autoimmune cholangitis.
Results In liver fibrosis, autoantigen-coupled NP were predominantly targeted to LSECs with similar efficacy as in non-fibrotic controls. LSECs from fibrotic livers had similar abilities to cross-present antigen and to induce Tregs as normal LSECs. Furthermore, NP-mediated targeting of autoantigen-peptide to LSECs in mice with established liver fibrosis was effectively preventing CD4 + T cell-driven EAE and CD8 + T cell-driven autoimmune cholangitis.
Conclusion The ability of LSECs to induce specific immune tolerance to autoantigen peptides was not impaired by liver fibrosis, indicating that their tolerance-inducing function is less susceptible to fibrotic changes than previously thought.

P5.19 Molecular pathways defining human CD8 T cell auto-aggression in immune-mediated liver diseases

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Introduction Immunopathology in immune-mediated liver diseases such as autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) or metabolic-dysfunction associated steatohepatitis (MASH) is considered to be caused by cytotoxic CD8 T cells but the molecular mechanisms remain incompletely understood. Here, we report the identification of auto-aggressive CD8 T cells (aaCD8 T cells) in liver tissues of these patients that developed in response to IL-15-stimulation and efficiently killed hepatocytes in the absence of MHC-restricted antigen recognition.
Methods: Single-cell RNA-seq of CD8 T cells (ex vivo/in vitro), flow cytometry and cytotoxicity assays were performed to study phenotype and function of human aaCD8 T cells.
Results: scRNA-seq of IL-15 activated human CD8 T cells in vitro identified CD8 T cells with an auto-aggression signature that was characterized by high levels of HLA type II molecules and granzymes. Using bioinformatic approaches, we found CD8 T cells with an auto-aggression gene signature to be enriched in tissues of patients with AIH and PSC. Mechanistically, aaCD8 T cells that were activated by extracellular histones eliminated target cells dependent on the release of granzymes and the surface expression of c-type lectin receptors Clec2B and D. Blockade of SYK signaling downstream of Clec2B/D completely prevented CD8 T cell auto-aggression whereas killing of target cells by NK cells or antigen-specific CD8 T cells was unaffected.
Conclusion: We defined molecular pathways of MHC-unrestricted CD8 T-cell auto-aggression in tissues of patients with immune-mediated liver diseases that could open new avenues for the treatment of immune-mediated diseases in the liver and in other organs.

P5.20 Mucosal-associated invariant T (MAIT) cells are functionally impaired and metabolically altered in patients with chronic HBV infection

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Chronic infection with hepatitis B virus (CHB) affects more than 250 million people worldwide and represents a major global health burden. In CHB patients, conventional virus-specific CD8 + T cells are rendered dysfunctional. In contrast, the functionality of mucosal-associated invariant T (MAIT) cells, innate like T cells enriched in the liver, in CHB remains unclear. Here, we investigate the functionality and metabolic regulation of MAIT cells in patients with CHB.
MAIT cells were isolated from peripheral blood of CHB patients with or without nucleos(t)ide analogue (NUC) treatment or controls. Phenotype, functionality and metabolic features of MAIT cells were analysed by multi-colour flow cytometry.
MAIT cells were detected in similar frequencies in patients with CHB and healthy controls. Phenotypic analysis demonstrated an activated phenotype of MAIT cells in CHB patients with and without NUC treatment. However, following ex vivo re-stimulation, MAIT cells from CHB patients without NUC treatment expressed lower levels of effector molecules, such as Granzyme B and IFN□□ compared to MAIT cells from NUC-treated CHB patients. Metabolic analyses revealed defects in glucose uptake and higher mitochondrial mass in MAIT cells from CHB patients compared to controls. While effector cytokine expression by MAIT cells of controls required glycolysis, expression of granzyme B and TNF by CHB MAIT cells was independent of glycolysis.
Our data demonstrate functional and metabolic alterations of MAIT cells in CHB patients that may be targeted to improve therapeutic strategies against HBV.

P5.21 Improvement in liver histology is observed in most patients with chronic hepatitis delta after 48 weeks of bulevirtide monotherapy

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Aims: Patients with chronic HDV treated with bulevirtide (BLV) in study MYR301 showed superior responses at week48 vs controls based on virological and biochemical response. We now explore the relationship between virologic, biochemical, and histologic change through 48W.

Method: Patients were randomized to 144W of BLV 2mg or 10mg or control with additional 96W of follow-up after end of treatment. Liver biopsy was performed at Baseline and W48. Analysis focused on patients with paired biopsies. Viral response categories at W48 included VR, partial response or non-response. Histologic parameters included histologic activity index and Ishak fibrosis score.

Results: Of 150 patients 55 % had paired biopsy data. At BL: mean age 42 years, 52 % males, 33 % with compensated cirrhosis and 61 % on concomitant NUC-therapy. Mean HDV RNA and median ALT, HAI, and Ishak fibrosis score was 5.1 log10 IU/mL, 92 U/L, 9, and 2. At W48, 80 %, 11 % and 9 % of patients treated with BLV achieved VR, PR, and NR while no control achieved VR. Similar median change in ALT was observed across viral response group. Decrease in ALT was observed in 89 % of BLV treated patients of those 80 % had HAI improvement. Higher likelihood of improvement in HAI category and greater decrease in median HAI from BL was observed with VR: 69 % and PR: 83 %. ALT normalization didn't have correlation with degree of HAI improvement. Improvement in fibrosis occurred in VR: 58 %, PR: 33 %, NR: 25 % and control: 30 %. Histological improvement occurred in VR: 69 %, PR: 83 %, NR: 25 %, controls: 33 %

P5.22 Granzyme profiles in CXCR6 + PD-1 + CD8 + T cells differentiate acute and chronic hepatitis flares and may reflect intrahepatic immune imprints

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Previously, we demonstrated that circulating CXCR6 + PD-1 + CD8 + T cells correlate with liver damage in patients with ALT flares (GASL 2024). Further understanding of these cells' phenotypic and transcriptional profiles may reveal their role in disease pathogenesis.

We analyzed blood CD8 + T cells in 63 patients with ALT levels ≥ 5x ULN, including 24 with acute viral hepatitis (16 HBV), 16 with chronic viral hepatitis (15 HBV), and 23 non-viral cases (mainly autoimmune hepatitis). Public single-cell RNA sequencing data (blood and liver CD8 + T cells) from HBV-infected patients were reanalyzed to investigate transcriptional patterns.

Circulating CXCR6 + PD-1 + CD8 + T cells exhibited distinct granzyme expression. Acute hepatitis was associated with high GZMB expression while resolving acute and chronic hepatitis showed high GZMK levels. UMAP analysis revealed that intrahepatic CD8 + T cells predominantly transcribe GZMK while circulating CD8 + T cells mainly transcribe GZMB. A subset of circulating cells, marked by high CXCR6, HLA-DRA, and PDCD1 transcription, shared transcriptional similarities with intrahepatic cells. This subset exhibited high co-transcription of immunomodulatory and checkpoint genes, activation markers, CREM, and GZMK. Trajectory analysis identified an intermediate state of CXCR6 + CD8 + T cells transitioning between liver and blood, characterized by a shift in granzyme expression between GZMB and GZMK.

In conclusion, CXCR6 + PD-1 + CD8 + T cells show different granzyme profiles in ALT flares between acute and chronic hepatitis. We suggest that the initial inflammatory response is dominated by the expression of GZMB, followed by a transcriptional shift towards GZMK, reflecting the developing intrahepatic immune dynamics (i.e. CREM expression).

P5.23 Influence of the Chemerin signaling pathway on NK cell function and migration

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Introduction: Chemerin, encoded by the gene Rarres2, is a secreted, proinflammatory adipokine which is highly expressed in the liver. Its cognate receptor ChemR is expressed on NK cells and has been shown to play a role in NK cell migration and co-localization with dendritic cells. We aim to investigate the Chemerin-ChemR axis to elucidate its impact on NK cell function and localization at steady state and in inflammation.

Methods: Using in vivo and in vitro approaches, we analyze Chemerin expression across different tissues as well as the effects of ChemR downstream signaling on NK cells on a phenotypic, transcriptional and functional level.

Results: We find highly organ-specific chemerin expression patterns in mouse and human. On NK cells, ChemR is exclusively expressed on mature subsets and is discretely regulated by cytokines and microenvironmental influences. Finally, inflammatory signals leading to chemerin induction result in tissue-specific NK cell accumulation.

Conclusions: Our findings indicate that the Chemerin-ChemR axis plays a crucial role in regulating organ-specific NK cell migration and function. Further work will show deeper mechanistic insights, potentially revealing novel therapeutic targets aimed at manipulating NK cell migration.

P5.24 Previous hepatitis B virus infection and the risk of liver-related complications in patients after HCV cure – Data on more than 6000 patients from the German Hepatitis C-Registry (DHC-R)

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Background: Previous exposure to hepatitis B virus (HBV) is often unrecognized and may influence the risk of developing hepatocellular carcinoma (HCC) and other liver-related events (LRE) in particular in patients after HCV cure. Previous studies are not conclusive and there are only few large studies from Europe.

Methods: We analyzed clinical endpoints (≥ 3-point increase in MELD score, esophageal variceal bleeding, ascites, encephalopathy, liver transplantation, death, with/without HCC; HCC alone) in patients cured from HCV. Data were obtained from the German Hepatitis C Registry. Patients after organ transplantation, a history of HCC, or HIV co-infection were excluded. Statistical analyses included Kaplan-Meier curves to analyze the influence of HBV serological markers and logistic regression to identify predictors of clinical endpoints.

Results: A cohort of 6,355 patients fulfilled inclusion criteria, the median time of follow-up was 2.5 years (range 0.04 – 8.01). Serological evidence of previous HBV exposure was present in 1,889 patients (HBsAg negative/anti-HBc positive) while 157 patients had active hepatitis B (HBsAg positive). Univariate analysis identified age 50-70 years (odds ratio [OR], 2.04), sex (OR, 1.38), cirrhosis (OR, 4.88), anti-HBc-positivity (OR, 1.49) and diabetes mellitus (OR, 2.71) as risk factors for LRE. Multivariate analysis confirmed male sex, older age, cirrhosis and diabetes as independent risk factors.

Conclusions: The clinical impact of previous HBV in HCV patients after SVR requires further investigation. We suggest that occult HBV infection should be considered a contributing factor for potential adverse disease outcomes also in Caucasian patients.

P5.25 Mucosal-associated invariant T (MAIT) cells exert direct anti-viral effector function against HBV

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Chronic infection with hepatitis B virus (CHB) represents a major global health burden affecting more than 250 million people worldwide. Conventional virus-specific CD8 + T cells can clear hepatitis B virus (HBV), but often become dysfunctional in CHB. Here, we aimed to determine whether mucosal-associated invariant T (MAIT) cells, innate like T cells enriched in the liver, possess anti-viral effector function against HBV.

Primary human MAIT cells isolated from peripheral blood of CHB patients with or without nucleos(t)ide analogue (NUC) treatment or controls were activated and co-cultured with HepG2-NTCP cells infected with HBV. MAIT cell cytokine expression, HBe-antigen and cccDNA were quantified by ELISA and qPCR. MAIT cell cytotoxicity was tested by real-time viability assay using xCelligence.

Following ex vivo activation, MAIT cells killed HBV-infected HepG2-NTCP cells and limited HBV replication in HepG2-NTCP cells, indicating a direct anti-viral effector function of MAIT cells against HBV. Notably, MAIT cell anti-viral effector function required T cell receptor-mediated stimulation. Employing a transwell system revealed that MAIT cells limit HBV replication in a cell-contact independent, cytokine-mediated manner. Importantly, MAIT cells from patients with CHB without NUC treatment expressed markedly lower levels of the effector cytokines IFNy and TNFa and lost their capacity to limit HBV replication.

Our data uncover a direct antiviral effector function of innate-like MAIT cells against HBV that is impaired in patients with CHB and could be targeted to improve the anti-viral immune response against HBV.

P5.26 Metabolic reprogramming of HBsAg-positive hepatocytes after stimulation with Schistosoma mansoni egg antigens

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Introduction: Schistosomiasis is a parasitic tropical disease caused by trematodes, affecting over 250 million people worldwide. S. mansoni eggs induce inflammation, granuloma formation and portal hypertension. In endemic regions, co-infections of S. mansoni with hepatitis B virus (HBV) occur frequently. Individuals chronically infected with HBV and S. mansoni exhibit a more severe course of illness and greater liver damage. The effect of co-infection on hepatocellular metabolism remains unclear. Our goal was to characterize hepatocellular carbohydrate metabolism in a cell culture model for co-infection with the use of HBV surface proteins (HBsAg) and Schistosoma mansoni egg antigens.

Methods: Human hepatoma cells (HepG2) and primary mouse hepatocytes were transfected with HBsAg and/or stimulated with purified soluble egg antigens (SEA) obtained from infected hamsters. Metabolism and transcription factors were analyzed using Western blotting, viability assay, immunohistochemistry and a glycogen assay. Group differences were evaluated using one-way ANOVA ($p < 0.05$).

Results: A higher activation of glucokinase (GK), pyruvate kinase 1 (PKM1), glucose-6-phosphate dehydrogenase (G6PDH), and lactate dehydrogenase (LDH) was observed in the S. mansoni + HBsAg groups. Furthermore, the transcription factor and proto-oncogene c-Jun was induced by the individual agents and particularly in the double-stimulated group compared to the controls. The absolute amount of hepatocellular glycogen remained unchanged.

Conclusion: In our model, we demonstrate an increase in cellular stress, as well as an induction of glucose metabolism. The enhanced fermentation of pyruvate to lactate suggests a metabolic reprogramming of hepatocytes to a "Warburg-like glycolysis." This form of ATP production is associated with malignant

P5.27 Distinct gene pathways and cell types define peribiliary disease states in PSC

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Background and Aims: Primary sclerosing cholangitis (PSC) is a cholangiopathy of unknown etiology featuring peribiliary infiltration and fibrosis. To identify novel PSC pathways, we analyzed liver explants using spatial and single-nuclei transcriptomics (snRNA-seq) and compared differential expressed genes (DEGs) across biliary regions in early and advanced PSC.

Methods: Fresh-frozen liver explants from PSC patients (4 recurrent cholangitis, 7 dysplasia,12 cirrhotic) and cirrhotic controls (4 ALD, 3 MASH) were analyzed by spatial transcriptomics (Visium,10X Genomics). Sixteen of the same explants (12 PSC, 4 controls) were assessed by snRNA-seq (Chromium 3', 10X Genomics). Spatial and snRNA-seq transcripts were clustered using Seurat v5.0.0 (Satija Lab, Broad Institute/MIT) and all DEGs reported reached statistical significance (P-adj < 0.001).

Results: To identify unique PSC pathways, we first classified liver regions as early or advanced disease using histology features and fibrosis markers detected by spatial transcriptomics (COL1A1/2 + COL3A1, COL6A2). Local profiling of biliary regions (KRT19 + FXYD2 +) by spatial transcriptomics revealed robust expression of metallothionein genes MT1E, MT1G and MT1H (14.9-fold) and inflammatory SAA1 and SAA2 (8.4-fold) by peribiliary hepatocytes at the interface between early and advanced PSC compared to controls. snRNA-seq identified 9 distinct liver cell types and showed highest metallothionein expression in PSC hepatocytes. Moreover, elevated metallothionein correlated with features of liver decompensation and cholestasis, including decreased serum sodium and elevated serum bilirubin.

Conclusions: Metallothionein is highly overrepresented in peribiliary regions at all stages of PSC suggesting that metallothionein may be triggered by early cholangiopathy in PSC livers.

P5.28 High proportion of complicated treatment courses in patients with chronic hepatitis E infection:

Men and older patients may have higher risk for viral relapse, real life data from single centre

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Background and aims: Hepatitis E is an RNA-virus infection affecting millions globally. In Europe, zoonotic genotype 3 is predominant. Chronic Hepatitis E occur in immunocompromised patients, requiring reduction of immunosuppression and/or ribavirin treatment. This study analysed all chronic hepatitis E cases (viremia over 12 weeks) from 2016 to 2024 at the University Hospital Duesseldorf to characterize the cohort, describe the different disease courses, and identify relapse-associated characteristics.

Methods: A retrospective analysis was conducted following ethics committee approval. Statistical analysis was performed using Prism Graph Pad.

Results: A total of 41 patients with chronic HEV infection were identified (10 female, median age 54, BMI 24.2, ALT 118 U/l, HEV-RNA 546,055 IU/ml). Among them 21 had prior solid organ transplantation, 13 had stem cell transplantation, and seven had other forms of immunosuppression. Four patients died before HEV treatment, while 30 were treated with ribavirin. Only two organ transplant recipients did not require ribavirin compared to four non-transplant patients. Fourteen patients (46 %) treated with ribavirin experienced recurrent HEV-viremia and required prolonged treatment. Male sex and age > 50 years is associated with recurrent viremia ($p = 0.034$, $p = 0.04$). Ribavirin dosage, GFR, ALT and HEV-viral load showed no association with HEV relapse ($p = 0.9$, $p = 0.4$, $p = 0.59$, $p = 0.51$). Eight patients had undetectable HEV-IgG. Three cases of viral mutations were identified, with two patients experienced persistent HEV infection despite multiple treatment courses.

Conclusion: Chronic HEV-infection remains a clinical challenge, especially for organ or stem cell transplant patients. Relapse and prolonged treatment is common, highlighting the need for new treatment approaches.

P5.29 Intrahepatic T cell responses modulate thermogenic adaptation in adipose tissues

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Background: Activation of brown and white adipocytes occurs in response to pharmacological stimuli or cold exposure, while underlying mechanisms and metabolites remain poorly understood. Some metabolites, including bile acids, have been described to influence energy metabolism and thermogenesis in white (WAT) and brown adipose tissue (BAT). Recently, we have shown that both production and release of these metabolites into the systemic circulation are modulated by inflammation in the liver. In this study, we aim to investigate thermogenic adaptation in adipose tissues in the context of acute liver inflammation.

Methods: Using the K14-OVAp mouse model, which expresses an ovalbumin peptide sequence (SIINFEKL) on biliary epithelial cells, acute cholangitis was induced via adoptive transfer of OVA-specific OT-1 CD8 + T cells. Mice were housed at different temperatures. Detection of serum transaminases, energy expenditure, mRNA expression, lipidomics as well as flow cytometric based immunophenotyping, were used to assess functional and molecular changes.

Results: Transferring OT-1 CD8 + T cells triggered portal inflammation in K14-OVAp mice, demonstrated by elevated transaminase levels and increased histological inflammation (mHAI). FACS analysis confirmed recruitment of OT-1 CD8 + cells to the liver and spleen. Hepatic inflammation resulted in elevated total lipid concentrations in plasma. In WAT thermogenic and lipogenic markers, like Ucp1 and Elovl3, were reduced, while BAT displayed increased energy uptake shown by significantly upregulated CD36 and Lpl gene expression.

Conclusion: Acute liver inflammation alters thermogenic responses in adipose tissue, decreasing thermogenesis in WAT and increasing energy uptake in BAT. This suggests that liver inflammation significantly impacts systemic energy metabolism.

P5.30 Schistosoma mansoni egg-derived antigens stimulate metabolic activity in the liver and colon by engaging insulin-like growth factor-1 receptor signaling pathways

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Background: Schistosomiasis, a parasitic disease affecting over 250 million people, is mainly driven by tissue damage caused by schistosome eggs rather than adult worms. The mechanism by which egg antigens transmit signals into host cells is unclear. This study explores whether S. mansoni egg antigens regulate the metabolic activity of hepatocytes and enterocytes via the insulin/IGF-1 receptor pathway.

Methods: Eight-week-old mice were infected with S. mansoni cercariae using the paddling technique. We employed RT-PCR array, western blotting, and immunohistochemistry to analyze markers of insulin/IGF-1 receptor signaling in liver and colon. We performed functional experiments on colon epithelial cell lines, including western blotting and AP-1 promoter activity assessment.

Results: S. mansoni infection significantly upregulated genes like Igf2, Dok, Aebp1, Leptin, and Akt3, with Serpine1 being the most induced, while downregulating Sos1, Irs1, and Gck, with G6pc most reduced. The insulin/IGF-1 receptor was notably activated in human perigranulomatous hepatocytes. Using the inhibitor BMS 536924, mechanistic experiments showed that S. mansoni egg antigens activated the insulin/IGF-1 receptor signaling cascade, including c-Jun activation.

Conclusions: In conclusion, our findings demonstrate that S. mansoni soluble egg antigens modulate the insulin/IGF-1 receptor signaling pathway in both murine and human hepatocytes and enterocytes, leading to an inhibition of gluconeogenesis. Thus, the parasite's soluble egg antigens may enhance insulin sensitivity in the host. However, the concurrent activation of the proto-oncogene c-Jun through this signaling pathway raises the possibility of potential morbidity associated with this mechanism.

P5.31 Multimodal characterization of autoimmune hepatitis morbidity and metabolic phenotype

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Background and Aims: Autoimmune hepatitis (AIH), as a chronic inflammatory liver disease posing significant diagnostic challenges due to its varied clinical manifestations and overlap with other liver diseases. We aim to elucidate the complex disease network associated with AIH using PheWAS analyses, as well as metabolic and serological alterations in patients with AIH.

Methods: 392 participants with AIH and 784 propensity score (age, sex, BMI, ethnicity) matched controls without liver diseases were included in the study. Comorbidities of individuals with AIH were studied using PheWAS. Moreover, we performed a comprehensive serological and metabolomic profiling comparing AIH patients with matched controls.

Results: Apart of direct liver-related complications (cirrhosis and portal hypertension), we also found a significant association of different autoimmune (systemic lupus erythematous HR: 18.9; KI95: 4.5-79.1), neoplastic (cancer of bronchus / lung HR: 4.1; KI95: 2-8.7), endocrine (type-2 diabetes HR: 2.5; KI95: 1.7-3.7), respiratory (pulmonary fibrosis HR: 11.3; KI95: 3.5-39) as well as extrahepatic gastrointestinal diseases with AIH. In lipidomic and metabolomic analyses among others the concentration of large HDL (HR: 1.04/SD) and VLDL diameter (HR: 0.96/SD), as well as tyrosine (HR: 1.02/SD) were significantly associated with AIH.

Conclusion: This study offers an in-depth view of the morbidity associated with AIH, which may improve patient counseling. Additionally, the identified metabolomic signature may provide insight into the complex pathophysiological mechanisms driving the development, progression, and related morbidity in AIH. Further we aim to validate our findings externally on a cohort from Hannover, to assure generalisability and validity.

P5.32 Circulating CD8 T cells are sentinels for intrahepatic T cell responses during HBV infection

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Chronic hepatitis B (CHB) is characterized by scarcity and dysfunction of virus-specific CD8 T-cells, for which immune-therapies, such as the therapeutic vaccination TherVacB, aim to generate virus-specific T-cells to control infection. This study sought to identify whether circulating HBV-specific CD8 T-cells reflect the intrahepatic T-cell response against infected hepatocytes and to identify biomarkers on circulating HBV-specific CD8 T-cells that predict immune control.

Using pre-clinical models of HBV as well as patient samples during an acute-resolving or chronic infection, we studied the dynamics of virus-specific T-cell response by flow cytometry and single-cell RNA sequencing.

Single-cell transcriptomic and protein-level analysis detected the generation of CD8 T-cells in the liver which were characterized by expression of CXCR6 and, during acute-resolving infection, were potent effector cells, whereas CD8 T-cells during persistent infection were dysfunctional and showed a CREM signature. Strikingly, scRNAseq analysis revealed close similarity between circulating and intrahepatic HBV-specific CD8 T-cells. We defined signatures that discriminate between lymphoid-tissue derived HBV-specific CD8 T-cells compared to HBV-specific CD8 T-cells, which had seen their antigen in the liver, thereby enabling the evaluation of intrahepatic HBV-specific CD8 T-cell responses in peripheral blood. Notably, the ability to predict T-cell immunity in infected organs was restricted to hepatotropic infections, as circulating CD8 T-cells did not reflect the T-cell response in the lung following influenza A virus infection. Importantly, we confirmed the presence of the immune signatures (termed “liver immunity index”) that predict immune control in HBV-specific CD8 T-cells from patients with acute as compared to chronic hepatitis B.

P5.33 First-in-human Clinical Results of a Novel HBV-specific TCR T Cell Therapy (SCG101) in Patients With HBV-related Hepatocellular Carcinoma (HCC)

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SCG101, a first-in-class autologous HBV-specific TCR-T cell therapy that utilizes a natural, high-affinity TCR, has been evaluated for its antiviral and antitumor activities in patients with HBV-related HCC in an investigator-initiated phase I trial.

Six HLA-A * 02:01(+), serum HBsAg(+), and HBeAg(-) patients with advanced HBV-related HCC (BCLC B/C), who had received 1-3 prior systemic therapies, were enrolled. All patients received a single dose of SCG101 at 5 x 10E7 or 1 x 10E8 cells/kg intravenously three days after lymphodepletion. Safety, pharmacokinetics, pharmacodynamics, and efficacy of SCG101 were evaluated.

Overall, SCG101 treatment was well-tolerated, with no dose-limiting toxicity or neurotoxicity observed. The most common treatment-related adverse events were elevated liver enzymes, cytokine release syndrome, and cytopenia. After infusion, SCG101 showed dose-dependent proliferation. Serum HBsAg levels dropped in all six patients; four (66.7 %) had a reduction > 1 log10, with three of them maintaining < 10 IU/mL. Transient ALT elevation was observed concurrently in all patients, indicating on-target activity of SCG101. Tumor control was observed in all four patients with HBsAg reduction > 1 log10, with two exhibiting a partial response (PR) and two a stable disease (SD) per mRECIST. The median progression-free survival (mPFS) in patients with HBsAg reduction > 1 log10 was longer than those without (mPFS: 5.9 vs 0.7 months).

SCG101, as a monotherapy for patients with HBV-related HCC, demonstrated antiviral and antitumor activities alongside a manageable safety profile. The persistence of SCG101, reduction of serum HBsAg, and tumor response collectively underscore its on-target activity.

P5.34 Impaired liver regeneration in obesity is driven by IFNAR signaling in Kupffer cells

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Liver regeneration is essential for restoring hepatic function after surgical resection or transplantation. Obesity and metabolic-driven chronic liver inflammation (metaflammation) are recognized as major inhibitors of liver regrowth. In a murine model of partial hepatectomy (HpX), we identified Kupffer cells (KCs)—rather than monocyte-derived macrophages—as the key mediators of liver regeneration. Transcriptomic and proteomic analyses of KCs during the early phase of regeneration revealed that in lean mice, resident KCs commit to tissue regeneration by suppressing innate and IFNAR-associated transcriptional programs to meet the metabolic demands for the activate liver regeneration programs. Conversely, KCs from obese mice exhibited a pronounced interferon-alpha/beta receptor (IFNAR) and innate immunity-associated signature, coupled with impaired clonal expansion and reduced metabolic fitness. Obesity-induced gut dysbiosis and microbial translocation exacerbated hepatic inflammation and inhibited regeneration by inducing type I interferon (IFN-I) signaling in KCs. Systemic inhibition or genetic deletion of IFNAR in KCs restored their proliferative capacity and metabolic fitness, leading to liver regeneration in obese mice comparable to that in lean mice. This study highlights the

critical role of KCs in liver regeneration, the deleterious effects of obesity-driven chronic IFN-I signaling, and the potential of targeting this pathway to enhance liver regeneration in obese individuals.

P5.35 S. mansoni infection of HBsAg-transgenic mice elicits hepatocellular damage, hepatic decompensation and carcinogenesis

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Background Schistosomiasis, a parasitic helminth infection, affects over 250 million people worldwide. The blood-borne S. mansoni eggs either penetrate the gut lumen, or become trapped in the liver sinusoids.

Hepatitis B virus (HBV) is a DNA virus, causing hepatic inflammation and necrosis and ultimately hepatocellular carcinoma (HCC).

Coinfections of S. mansoni and HBV occur disproportionally often in endemic areas. This project aimed to investigate their combined effects on hepatic carcinogenesis and metabolism.

Methods Transgenic (tg) mice expressing the large form of the HBV surface proteins (collectively called HBsAg) were infected with S. mansoni at the age of 43 weeks. After nine weeks of infection, the animals were sacrificed. Liver-to-body weight ratios, ALT, glucose, and albumin levels, hepatic tumor numbers and sizes were determined and compared to infected wt-mice, as well as non-infected wt- and tg-control animals.

Results S. mansoni-infected mice showed a larger liver-to-bodyweight ratio than non-infected animals, while also exhibiting higher serum ALT levels. Glucose levels of infected tg-mice were significantly lower compared to both infected wt- and non-infected tg-animals. Infected tg-mice show lower albumin levels than wt- and tg-mice. Furthermore, infected tg-animals presented larger tumors and increased numbers of atypical nucleoli.

Conclusion The observed increase in liver-to-bodyweight ratios and ALT levels suggest an additive effect on hepatocellular damage in S. mansoni infected, HBsAg-tg-mice compared to the individual disease models. Furthermore, decreases in serum glucose and albumin levels indicate hepatic decompensation. Tumor size and atypical nucleoli strongly suggest enhanced **carcinogenesis in this co-infection model.**

P5.36 Silencing of HBV and PD-L1 synergistically enhances the efficacy of therapeutic vaccination in high-titer HBV carrier mice

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Therapeutic vaccination represents a promising treatment of chronic hepatitis B; however, high levels of hepatic HBV antigens impede vaccine-mediated immunity. Reducing HBV levels before vaccination by HBV-specific siRNAs (siHBV) enhanced the immunogenicity and antiviral efficacy of our clinical candidate protein-prime/MVA-boost therapeutic vaccine, TherVacB, in high-titer HBV-carrier mice. Non-responsiveness to vaccination was associated with high PD-1 expression on vaccine-elicited CD8 T-cells. We hypothesized that combining siHBV with silencing PD-L1 could further broaden the applicability of TherVacB in high-titer HBV carrires.

We therefore established high-titer persistent HBV infection in C57BL/6J mice using AAV-HBV, resulting in over 80 % of HBV-positive hepatocytes. We pretreated mice for eight weeks with siHBV before TherVacB and applied siPD-L1 during the two protein priming immunizations. We followed up with the mice for 7.5 months after the MVA boost.

Mice receiving TherVacB or TherVacB + siPD-L1 demonstrated only a minor decrease in serum HBsAg shortly after treatment. Without vaccination, siHBV + siPD-L1 reduced HBsAg, but the antigen load eventually returned to the baseline values, and no induction of HBV-specific immunity was observed. Combining siHBV + TherVacB reduced HBsAg to undetectable levels for eight weeks, but finally resulted only in a 1-log10 decrease. By contrast, mice receiving siHBV + TherVacB + siPD-L1 cleared HBsAg for 24 weeks; 3/5 mice remained negative for 7.5 months. Overall, the siHBV + TherVacB + siPD-L1 treatment resulted in a ≥ 3-log10 reduction in HBsAg and a 70 % reduction in HBV + hepatocytes.

Our data demonstrate that complementary siRNA-mediated silencing of HBV and the immune checkpoint PD-L1 helps to further enhance the efficacy of therapeutic vaccination in high-titer HBV carriers.

P5.37 HBsAg-specific CD4 T cell response in HBV vaccinated individuals

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Background: The global implementation of prophylactic hepatitis B virus (HBV) vaccination in 1984 led to a significant decrease in HBV infections. It also offers the opportunity to study immunological mechanisms of immune memory maintenance. While most individuals develop strong anti-HBs responses, these titers are not universally maintained. Although the role of CD4 T cells in supporting antibody development and maintenance is well established, they have not been thoroughly investigated in this specific context.

Methods: We screened our biobank for samples from anti-HBs + /anti-HBc- individuals carrying the HLA DRB1 * 0101 or DRB1 * 0701 alleles. For ex vivo detection of HBsAg-specific CD4 T cells, we used peptide-loaded MHC class II tetramers restricted to the aforementioned alleles. In addition, we performed in vitro stimulation with overlapping peptides spanning the HBsAg for 10 days followed by an intracellular cytokine staining.

Results: This is an ongoing study and additional results will be presented at the conference. So far, we analyzed 47 individuals. 32 % (15/47) had detectable HBsAg-specific CD4 T cells directly ex vivo. The highest frequencies were observed in individuals with anti-HBs titers > 100 IU/l. Phenotypic analyses for different memory subpopulations are currently ongoing. Following in vitro HBsAg stimulation, we identified cytokine-producing CD4 T cells in 70 % of the individuals (n = 10, experiments ongoing).

Conclusions: Our preliminary results suggest that the frequency of HBsAg-specific CD4 T cells is associated with the anti-HBs titers in vaccinated individuals. Whether this is driven by specific memory subsets and in how far this correlates with individual vaccine history is currently being investigated.

P5.38 T cell hyporesponsiveness distinguishes Autoimmune Hepatitis from Drug-Induced Liver Injury

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Autoimmune hepatitis (AIH) and drug-induced liver-injury (DILI) have overlapping features and are difficult to distinguish. Both conditions are presumably driven by a T cell response to hepatocyte antigens – autoantigens in AIH and

neoantigens in DILI. Since AIH and DILI require different management, improved understanding of common and distinctive immune features is needed.
We analysed clinical and histological features of untreated AIH (n = 11) and DILI (n = 9) patients and immune cells in blood and liver by flow cytometry. Immune profiling was repeated after disease remission.
Untreated AIH and DILI patients manifested similar serum ALT levels (AIH: 779 U/l, DILI: 839 U/l), mHAI scores (AIH: 8, DILI: 9), and numbers of liver-infiltrating CD3 + T cells. Both conditions showed a marked increase in hepatic CD8 + T cells with an activated phenotype (CD38, ICOS, PD-1), as compared to MASLD (n = 5). However, AIH showed distinctively lower levels of effector molecules (IFNg, FASL, IL-2) in hepatic T cells or in blood T cells. Moreover, the numbers of migrating CCR7 + Foxp3 + CD25 + Tregs was significantly increased in AIH blood (AIH = 4,28; DILI: 2,55 %; p = 0,01). After disease remission, the T cell phenotype persisted in treated AIH, whereas the activated T cell phenotype normalised in DILI.
Conclusion: Clinically and histologically AIH and DILI were indistinguishable. However, AIH was characterised by distinctive markers of hypo-responsiveness in effector T cells and increased migratory capacity of Tregs. Although both AIH and DILI patients presented with acute clinical disease, the observed immune adaptations in AIH suggest a more long-standing immune response with extended preclinical phase.

P5.39 Deconvoluting the spatial immune landscape in the Hepatitis B Virus infected human liver at single-cell resolution

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Chronic hepatitis B virus (cHBV) infection remains a major global health problem due to risk of progression to cirrhosis and hepatocellular carcinoma. However, the interactions of immune cells and virally infected parenchymal cells, in particular that mediate immune escape, remain poorly understood. We thus set out to generate a spatially resolved cell atlas of the cHBV-infected liver.
To this end, we applied multiplexed ion beam imaging by time-of-flight (MIBI-TOF) to profile the expression of 38 proteins at sub-cellular resolution in liver tissue from a first cohort of 4 patients diagnosed with cHBV infection.
Our panel enabled the simultaneous detection of liver parenchymal cells, immune cells, stromal cells, and HBV antigens within the liver microenvironment. Cells were organized into distinct microenvironmental niches, each associated with specific functions. Niches compositions varied across liver zonation. HBV-infected hepatocytes were concentrated in Zone 3. Proximity analysis identified CD103 + tissue-resident memory T cells (TRM), macrophages, and NK cells as the closest immune cells to HBV-infected hepatocytes, suggesting these cells as key mediators for HBV clearance. Patients were stratified into two groups based on liver enzyme levels: mid immune-active and high immune-active. High immune-active patients exhibited an increased density of PD-1-CD103 + TRM cells, while PD-1 + CD103 + TRM cells were higher in the mid immune-active group. The different expression pattern of additional exhaustion markers between these two TRM subsets revealed they may have distinct functional roles in the immune response to HBV.
These findings suggest that spatial profiling can reveal immune interactions contributing to disease progression during cHBV infection.

P5.40 Acid ceramidase of macrophages traps herpes simplex virus in multivesicular bodies and protects from severe disease

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DOI 10.1055/s-0044-1801220
Macrophages have important protective functions during infection with herpes simplex virus type 1 (HSV-1). However, molecular mechanisms that restrict viral propagation and protect from severe disease are unclear. Here we show that macrophages take up HSV-1 via endocytosis and transport the virions into multivesicular bodies (MVBs). In MVBs, acid ceramidase (aCDase) converts ceramide into sphingosine and increases the formation of sphingosine-rich intraluminal vesicles (ILVs). Once HSV-1 particles reach MVBs, sphingosine-rich ILVs bind to HSV-1 particles, which restricts fusion with the limiting endosomal membrane and prevents cellular infection. Lack of aCDase in macrophage cultures or in Asah1-/- mice results in replication of HSV-1 and Asah1-/- mice die soon after systemic or intravaginal inoculation. The treatment of macrophages with sphingosine enhancing compounds blocks HSV-1 propagation, suggesting a therapeutic potential of this pathway. In conclusion, aCDase loads ILVs with sphingosine, which prevents HSV-1 capsids from penetrating into the cytosol.

P5.41 Generation and functional analysis of spacer-modified HBV-specific chimeric antigen receptors

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T-cell therapy using chimeric-antigen-receptors (CARs) is an established immunotherapeutic strategy for treating cancers, but also interesting for chronic viral infections. Our study aimed to optimize CAR constructs to exclude target-independent tonic signaling and realize recognition of HBV envelope protein (HBVenv) merely on HBV-positive cells, but not as soluble antigens.
We constructed S-CARs containing the HBV S-specific single-chain antibody C8 as the binding domain, CD28-CD3 intracellular signaling domains, and various spacers. We transduced human T cells with single S-CARs or logic-gated HER2-synNotch-inducible S-CARs and characterized the function of S-CAR-T cells on HBVenv-positive hepatoma cells.
S-CARs containing IgG1-CH2CH3, IgG4-CH3Hinge, IgG2-CH3, or zEGF spacers of 119-225 amino acids in length specifically activated T-cells to secrete cytokines and eliminate HBVenv transgenic hepatoma cell lines. Moreover, the S-CAR-T cells showed antiviral activity and significantly decreased the level of viral antigens, intracellular HBV DNA, and HBV cccDNA in HBV-infected HepG2-NTCP cells. HER2-synNotch-inducible CAR-T cells expressed the S-CAR upon HER2-synNotch activation only when HER2 was recognized on target cells. Unlike S-CAR transduced T cells, they were not activated when incubated with soluble HBsAg and selectively killed dual antigen (HER2 + HBVenv +) HepG2 cells but not cells only positive for HBVenv or HER2.
Taken together, our study demonstrates that after spacer-modification of the S-CAR unwanted, ligand-independent tonic signaling is eliminated, while the antiviral function of S-CAR-T cells is maintained. Inducing the S-CAR by the synNotch strategy improves CAR T-cell efficacy and specificity. Thus, our optimized CARs are interesting therapeutic candidates for treating chronic hepatitis B and HBV-associated hepatocellular carcinoma.

P5.42 Virulent Enterococcus faecalis from individuals with Primary Sclerosing Cholangitis crosses the intestinal barrier and induces liver inflammation in Mdr2 -/- mice

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Primary Sclerosing Cholangitis (PSC) is characterized by bile duct inflammation and scarring, with alterations in microbiota thought to be involved in disease progression. Notably, biliary Enterococcus species are associated with transplantation-free survival, but mechanistic insights remain unclear. We aimed to investigate E. faecalis strain diversity and its potential role in PSC.

Bile and stool from individuals with PSC and controls were collected. 146 E. faecalis isolates were retrieved and sequenced. Virulence factors were annotated using DIAMOND in BLASTP mode and the VFDB as reference. For functional assays, H69 human cholangiocytes were challenged with E. faecalis lysates, and Interleukin-6 concentration was measured by ELISA. Selected strains were administered to antibiotic pre-treated Mdr2 -/- mice with sclerosing cholangitis. We assessed bacterial translocation to the mesenteric lymph nodes and liver, liver inflammation was assessed by RT-qPCR and flow cytometric analysis.

Genomic analysis highlighted diverse patterns of virulence in bile and stool E.faecalis. The presence of the genes esp and gelE correlated with IL-6 production in vitro. Virulent E. faecalis colonized the mesenteric lymph nodes of Mdr2 -/- mice more frequently than non-virulent E. faecalis, and induced increased expression of proinflammatory chemokines and increased frequencies of TNF producing CD4 + T cells in the liver.

E. faecalis virulence genes from patient derived bacteria associated with its inflammatory and translocation potential in Mdr2 -/- mice. These results support the notion that E. faecalis could be relevant in PSC pathogenesis. Further work is needed to assess whether these findings translate into the context of human bile ducts.

P5.43 Myeloid reprogramming of T cells: a mechanism to maintain peritoneal homeostasis

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Peritoneal leukocytes are essential for immunoregulation, tissue homeostasis and repair. When homeostasis is disturbed leukocytes are recruited to restore balance. Previously, we described the reprogramming of liver-resident CD8 + T-cells upon interaction with neighbouring myeloid cells (Pallett_etal.,Nature_2023). Upon interaction, resident CD8 + T-cells 'steal' plasma-membrane fragments, acquiring constitutive immunomodulatory features at rest and enhanced antiviral/antitumour capacity. These 'super-responder' myeloid-instructed CD8 + T-cells can be detected by co-staining for CD8/CD14. In advanced chronic liver disease, fluid (ascites) can build up in the peritoneal cavity. We hypothesise that myeloid cells within the cavity reprogramme CD8 + T-cells to help maintain peritoneal homeostasis, providing local antiviral/anti-tumour immunosurveillance. Co-staining for CD8/CD14 shows myeloid-instructed CD8 + T-cells accumulating in ascites, correlating positively with acute-phase-protein (CRP) and negatively with disease severity (MELD). Myeloid-reprogramming enhances responsiveness to TCR-stimulation, increasing antimicrobial cytokine/chemokine production within their tissue niche. We also demonstrate that CD14 + CD8 + T-cells respond to viral peptide stimulation, with increased polyfunctional dual-cytokine producing (IFNg + TNFa +) cells. Furthermore, these cells produce more autocrine IL-2, likely to support their own proliferation and retention of a memory phenotype and can better mobilise cytotoxic granules upon antigenic encounter. Stealing of the LPS-receptor from myeloid cells also allows CD14 + CD8 + T-cells to respond directly to bacteria. We confirmed LPS-receptor internalization, indicating some cells may be 'seeing' LPS in vivo. CD14 + CD8 + T-cells take up significantly more LPS than their CD14-negative counterparts in an LBP-dependent manner, indicating a role for the LBP rich physiological environment. By their polyfunctional role, myeloid-instructed CD8 + T-cells may contribute to the maintenance of immune homeostasis, representing an important immune sentinel providing critical antiviral/antitumour and antibacterial immunosurveillance.

P5.44 Hepatitis C virus alters hepatocyte's response to interleukin-1♌ by modulation of IκBα-mediated signaling

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Despite the availability of antiviral treatments, Hepatitis C virus (HCV) persists a considerable risk factor for the development of chronic liver diseases and hepatocellular carcinoma (HCC). Previous work from our research group indicates that HCV reprograms intercellular communication in the host by modulating the expression of growth factors. Furthermore, we have observed that patients with HCV infection exhibit elevated plasma levels of IL-1β, independent of viral eradication. This suggests that HCV induces persistent modifications in host cellular functions, which contribute to liver disease progression. Therefore, this study aims to investigate the impact of HCV on the host cellular response to IL-1β.

Human hepatoma cell line harboring the HCV genotype 1b subgenomic replicon (Huh9-13) and Huh7 controls, were treated with IL-1β. Subsequently, we assessed the levels of IL-1β target protein IκBα using western blot analysis. Additionally, the phosphorylation profile of IκBα (Ser32/36) was evaluated. Next, Huh7.5 cells infected with the strain JC1 (HCVcc) were used to further investigate the effects of chronic HCV infection on IκBα signaling.

Our findings indicate that HCV reduces basal IκBα protein levels and impairs its recovery following IL-1β stimulation in both the replicon and chronic infection systems. Notably, the phosphorylation profile analysis revealed that Huh9-13 cells exhibit an accelerated rate of IκBα phosphorylation, and degradation, as well as a reduced recovery after 120 minutes compared to the control.

Conclusively, HCV alters IL-1β-induced signaling through modulation of IκBα, leading to enhanced expression of NFκB-regulated genes and subsequent alterations in the host immune response to HCV.

P5.45 Identification of amino acids restricting HBV receptor function in porcine NTCP

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With 254 million chronically infected patients, hepatitis B virus (HBV) continues to be a severe health threat. While animal models play a crucial role in developing new therapies, the availability of preclinical HBV models is highly restricted, underlining the urgent need for novel in vivo infection models.

The bona fide HBV receptor, sodium-taurocholate cotransporting polypeptide (NTCP), determines the species and cell-type specificity of HBV. Recent studies have indicated that the expression of human NTCP is the only limiting factor for HBV infection in selected species, such as macaques or pigs.

Here, we confirm HBV infection of pig hepatocytes expressing human NTCP and demonstrate that porcine NTCP does not support HBV binding. By gradually humanizing porcine NTCP and site-directed mutagenesis, we identified amino acids 158 and 167 in porcine NTCP to be the crucial residues limiting HBV interaction. In a proof-of-concept experiment, we showed that the expression of porcine NTCP with humanized amino acids 157-167 renders primary porcine hepatocytes fully susceptible to HBV.

These results pave the way for generating transgenic pigs with humanized porcine chimeric NTCP as a novel, fully immunocompetent infection model for developing and validating new curative HBV therapies.

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