ADVANCES IN HEPATOLOGY – FROM MECHANISTIC INSIGHTS TO NOVEL THERAPEUTIC CONCEPTS

October 24-25, 2025

Symposium 242
BERLIN, GERMANY

11,5 CME CREDITS

11,5 credit hours (CME) have been awarded by the European Union of Medical Specialists (UEMS).

PREFACE

Dear colleagues and friends,

It is with great pleasure that we welcome you to our international symposium, *Advances in Hepatology*, a unique gathering that brings together leading minds from across the globe to explore the latest advancements in the understanding and treatment of liver diseases. This meeting represents a confluence of diverse expertise, from basic science to clinical practice, and offers a platform to foster collaboration, inspire innovation, and pave the way toward transformative breakthroughs in hepatology.

Liver diseases remain a significant global health challenge, with far-reaching impacts on millions of lives. The focus of this year's conference is on new mechanisms and therapies, and our program reflects this emphasis with cutting-edge sessions on topics such as liver fibrosis, cholestatic liver diseases, metabolic liver disease / MASLD, viral hepatitis, and liver cancer. These sessions will delve into the molecular and cellular mechanisms underlying disease progression, as well as emerging therapeutic strategies, including precision medicine, disease monitoring strategies, novel drug targets, and advanced technologies like organoids, single-cell omics and artificial intelligence.

We are proud to host an outstanding lineup of internationally renowned speakers who will share their groundbreaking research and clinical insights. In addition to the plenary sessions, the conference will feature interactive panel discussions, poster presentations, and networking opportunities, ensuring a dynamic and engaging experience for all participants.

This event is not only an opportunity to learn from the best but also a chance to contribute to the future of hepatology. By fostering an open exchange of ideas and building connections across disciplines, we aim to create an environment that inspires innovation and advances the care of patients with liver diseases. We are grateful to the Falk Foundation for providing us this unique platform of international exchange at the symposium.

We look forward to welcoming you to what promises to be an intellectually stimulating and highly rewarding conference in Berlin. Together, let us explore the frontiers of hepatology and work toward a healthier future.

Warm regards,

Stefan Fichtner-Feigl Tom Hemming Karlsen Sophie Lotersztajn Frank Tacke

ADVANCES IN HEPATOLOGY – FROM MECHANISTIC INSIGHTS TO NOVEL THERAPEUTIC CONCEPTS

October 24-25, 2025

Scientific Organization:
Stefan Fichtner-Feigl, Freiburg (Germany)
Tom Hemming Karlsen, Oslo (Norway)
Sophie Lotersztajn, Paris (France)
Frank Tacke, Berlin (Germany)

Congress Venue:
JW Marriott Hotel Berlin
Stauffenbergstr. 26
10785 Berlin
Germany

For admission to scientific events your name badge should be clearly visible.

Accompanying persons are not permitted during the conference at any time.

Start of Registration:
Thursday, October 23, 2025
16:00-20:00 h
at the congress office

Friday, October 24, 2025

09:00 Welcome
Stefan Fichtner-Feigl, Freiburg; Tom H. Karlsen, Oslo; Sophie Lotersztajn, Paris; Frank Tacke, Berlin

SESSION I

Current developments in hepatology

Chairs: *Robert Thimme, Freiburg; Jessica Zucman-Rossi, Paris*

09:10 Keynote lecture: Major advances in hepatology in 2025
Vlad Ratziu, Paris

09:30 Liver disease burden in 2025
Zobair M. Younossi, Washington DC

09:50 Liver biology at single-cell resolution
Sonya MacParland, Toronto

10:10 Liver disease modelling
Ludovic Vallier, Berlin

10:30 **Coffee break with ePoster session**

SESSION II

Mechanisms of injury, inflammation, fibrosis

Chairs: *Sophie Lotersztajn, Paris; Massimo Pinzani, Palermo*

11:00 Fibrosis progression and regression: An integrated view
Robert F. Schwabe, New York

11:20 Liver immunology in the era of multi-omics data
Charlotte Scott, Ghent

11:40 Metabolic reprogramming in liver injury
Catherine Postic, Paris

Poster pitches

Chairs: *Sophie Lotersztajn, Paris; Massimo Pinzani, Palermo*

12:00 Basic and translational science
(5 poster pitches)

12:30 **Lunch break with ePoster session**

SESSION III

Cholestatic liver diseases

Chairs: *Tom H. Karlsen, Oslo; Christoph Schramm, Hamburg*

14:00 Management of primary biliary cholangitis: Current algorithms
Christophe Corpechot, Paris

14:20 Management of concurrent inflammatory bowel disease and primary sclerosing cholangitis
Britta Siegmund, Berlin

14:40 The translational journey of drug development in cholangiopathies

Part 1: From bile acid pathobiology to therapeutic actions of Norucholic acid
Peter Fickert, Graz

Part 2: Clinical development and trial results with Norucholic acid
Michael Trauner, Vienna

Panel discussion

Chair: *Christoph Schramm, Hamburg*

15:10 Current management of primary sclerosing cholangitis
Verena Keitel-Anselmino, Magdeburg; Tom H. Karlsen, Oslo; Michael Trauner, Vienna

15:30 **Coffee break with ePoster session**

INTERNATIONAL HERBERT FALK AWARD

16:00 Presentation of the International Herbert Falk Award
Jürgen Schölmerich, Hofheim

16:10 International Herbert Falk Award Lecture: What hepatologists can learn from the discovery of pancreatic stellate cells
Minoti Apte, Sydney

SESSION IV

New avenues for liver diseases

Chairs: *Paolo Angeli, Padova; Thomas Berg, Leipzig*

16:30 Viral hepatitis: Challenging current dogmas on hepatitis B and on delta
Heiner Wedemeyer, Hannover

16:50 Genetic cholestasis: Diagnosis and management
Verena Keitel-Anselmino, Magdeburg

17:10 Alcohol-associated liver diseases: How can we leverage the developments from the MASLD field?
Alexandre Louvet, Lille

17:30 Xenotransplantation and artificial liver devices: New avenues for liver transplantation?
Beicheng Sun, Hefei

Saturday, October 25, 2025

SESSION V

From monitoring liver disease progression to pathways of care

Chairs: *Annalisa Berzigotti, Bern; Jochen Hampe, Dresden*

09:00	Do we need a non-invasive liver health check in the general population? *Maja Thiele, Odense*
09:20	Blood-based and imaging biomarkers for monitoring liver disease progression and treatment responses: Are we there yet? *Vincent W.-S. Wong, Hong Kong*
09:40	The microbiome as a diagnostic tool and a therapeutic target in liver diseases *Bernd Schnabl, San Diego*
10:00	Scaling up liver and metabolic health screening: LiverHealth project in China *Xiaolong Qi, Nanjing*
10:20	**Coffee break with ePoster session**

SESSION VI

Challenges in advanced liver diseases

Chairs: *Patrizia Burra, Padova; Xiaolong Qi, Nanjing*

10:50	Portal hypertension: What to expect from Baveno VIII? *Annalisa Berzigotti, Bern*
11:10	Acute-on-chronic liver failure: Evidence-based management *Paolo Angeli, Padova*
11:30	Moving boundaries in liver transplantation: Obesity, cholangiocarcinoma, alcohol *Julie K. Heimbach, Rochester*

Poster pitches

Chairs: *Thomas Berg, Leipzig; Stefan Fichtner-Feigl, Freiburg*

11:50	Clinical science (5 poster pitches)
12:20	**Lunch break with ePoster session**

SESSION VII

Hepatocellular and cholangiocellular carcinoma

Chairs: *Johann Pratschke, Berlin; Lorenza Rimassa, Milan*

13:20	Therapeutic relevance of the molecular landscape in liver cancer *Jessica Zucman-Rossi, Paris*
13:40	Functional relevance of the immunological environment in liver cancer *Mathias Heikenwälder, Heidelberg*
14:00	The therapeutic (r)evolution in managing liver cancer *Bruno Sangro, Pamplona*
14:20	Moving boundaries in surgery for liver cancer *Iswanto Sucandy, Tampa*
14:40	**Awards for best presentations (posters + poster pitches)** *Stefan Fichtner-Feigl, Freiburg; Tom H. Karlsen, Oslo; Sophie Lotersztajn, Paris; Frank Tacke, Berlin*
15:00	**Coffee break with ePoster session**

SESSION VIII

MASLD: The biggest challenge in hepatology?

Chairs: *Patrizia Burra, Padova; Münevver Demir, Berlin*

15:30 Management of obesity and type 2 diabetes: Lessons for the hepatologist
Cyrielle Caussy, Pierre-Bénite

15:50 The next generation of risk stratification algorithms in MASLD
Elisabetta Bugianesi, Torino

16:10 The evolving landscape of pharmaceutical therapies in MASLD management
Arun J. Sanyal, Richmond

Panel discussion

Chair: *Patrizia Burra, Padova*

16:30 Current medical therapies in MASLD management
Cyrielle Caussy, Pierra-Bénite; Vlad Ratziu, Paris; Arun J. Sanyal, Richmond; Frank Tacke, Berlin

16:50 Closing Remarks
Stefan Fichtner-Feigl, Freiburg; Tom H. Karlsen, Oslo; Sophie Lotersztajn, Paris; Frank Tacke, Berlin

HERBERT FALK (1924 – 2008)

Herbert Falk was born in 1924 in Müllheim, a small town in South-West Germany between Freiburg and Basle, where his father ran a pharmacy. It was here that Herbert Falk spent his early years, attending primary school and high school up to the 5th grade. His parents then moved to Freiburg, where his father had his own pharmacy. On gaining his university entrance diploma from the Rotteck high school in March 1942, he was immediately called up for military service. During the Second World War he served on the front line in North Africa as a soldier with the Africa Corps and narrowly escaped death several times. At the end of the North Africa campaign, he was captured and transferred to the USA as a prisoner of war, spending his final year of captivity in England.

On his release and return to Germany, Herbert Falk studied pharmacy then medicine at the University of Freiburg. He graduated and received his doctor's degree in both subjects. Thereafter, he took over the pharmacy in Freiburg from his father.

After several years of success as a pharmacist, Herbert Falk made the decision which would prove so crucial for his future life's journey and founded his own company, producing and marketing pharmaceuticals for application in gastroenterological and hepatological diseases. Within a few years, his abundant energy, determined pursuit of goals, untiring diligence, keen eye for promising research developments, and not least his legendary talent for organization, had turned his pharmaceutical company into a global enterprise world famous in specialist circles. Falk products are meanwhile highly acclaimed not only in Germany and other European countries but also in South America, countries of the Near and Far East, Russia, China and Australia.

Herbert Falk's contributions to research were founded not on his own scientific work but on his organization of symposia, workshops and other scientific congresses which he sponsored and promoted to an extraordinary level and with great personal dedication. International Falk Symposia, workshops and congresses have won global recognition. There are several reasons for this:

- In addition to numerous advanced medical education programs for doctors organized by the Falk Foundation, which are primarily or exclusively concerned with issues of medical practice, the foundation also organizes symposia, workshops and congresses. These feature in-depth

lectures and critical discussions on questions and findings of biomedical basic sciences as well as their application in diagnostic measures, diagnostic decision-making, disease prevention and therapy.

- Leading researchers from a particular field and clinical-medical experts are invited to Falk Symposia as speakers or discussion leaders, enabling comparison within a field at an international level. The scientific organizers have a completely free hand in their choice of topics and selection of speakers. This gives symposia participants an opportunity to acquire first-hand knowledge of the latest findings in their field.
- Falk Symposia are the ideal opportunity for representatives of biomedical basic research, clinical research and physicians working in clinic and practice to meet and exchange opinions. Participants benefit enormously from this fertile interchange of personal experiences, critical viewpoints and valuable suggestions for further work.
- Not least, Falk Symposia are of great significance for the new medical and scientific generation in Germany, since they provide an opportunity for young doctors and scientists to encounter internationally renowned scientists from the field of gastroenterology who can answer their queries and assist their further progress by offering constructive criticism, suggestions and encouragement. A frequent outcome of these encounters is the opportunity for young German scientists to spend a lengthy period abroad as guests in the laboratories or clinical institutions of foreign researchers.

It was Herbert Falk's personality which gave the symposia their unique stamp. His generous support of organizers and speakers, intuitive flair for innovative developments, extraordinary talent for organization and overwhelming hospitality have turned Falk Symposia, workshops and congresses into scientific events of international esteem and renown.

Herbert Falk received many honors and distinctions for his outstanding achievements as a sponsor of biomedical and clinical research and patron of the upcoming medical-scientific generation. These included honorary membership of numerous national and international gastroenterological and hepatological societies. He was made an honorary doctor of the medical faculties of the Universities of Cluj-Napoca (Romania), Basle and Freiburg. The German Medical Association commended him for his services by awarding him the Ernst von Bergmann Plakette. In 2004, the American Gastroenterological Association (AGA) honored him with its highest distinction: The Lifetime Distinguished Service Award.

The portrait of Herbert Falk would not be complete without mentioning some key aspects and traits of his personality. Despite his multifaceted success in the development of his pharmaceutical company and the many honors he received, Herbert Falk remained a man of great humility in his personal dealings with the people around him. His friends and co-workers could rely on him implicitly to fulfill any decision or promise which had been made. He always had an open ear for constructive criticism. His joie de vivre and positive attitude to life remain unforgettable. Especially memorable is the pleasure he took in the culinary delights of kitchen and cellar. On such festive occasions he would strike up the "Badener Lied", the hymn to his beloved native area of Baden. The unique beauty of this countryside - so dear to him from countless hikes through the Black Forest - never ceased to fascinate him. This was where he felt at home. This was where he found the strength and inspiration he needed for his work.

Herbert Falk continued to contribute to the development of his company into a ripe old age. He kept up to date with the latest international research projects in the fields of gastroenterology and hepatology, showing a keen interest, critical discernment and sure instinct for quality. He did not give up his leading role in the company until the end of 2003, when he was nearly 80 years of age.

In 2008, a serious illness borne with admirable equanimity brought his life to an end. His memory, life's work and services will live on through the Herbert Falk Prize.

Wolfgang Gerok, Freiburg (†)

INTERNATIONAL HERBERT FALK AWARD 2025

The International Herbert Falk Award will be presented for the 6th time by the Falk Foundation e.V. on the occasion of Symposium 242 in Berlin in October 2025. The prize amounts to EUR 40.000,- and is awarded for outstanding contributions to gastroenterology and hepatology, including advances in diagnosis, therapy and prevention.

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M.M. Lerch, München (Germany)
A. Schoepfer, Lausanne (Switzerland)
J. Schölmerich, Hofheim (Germany)
R.C. Spiller, Nottingham (Great Britain)
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COORDINATOR OF THE INTERNATIONAL HERBERT FALK AWARD COMMITTEE:

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REGISTRATION

You can register for the event via our homepage:
www.falkfoundation.org
Registration is only possible online.

You will receive an automatic confirmation of registration by e-mail.
Please transfer the congress fee to the bank account listed in the e-mail within two weeks.

CONGRESS FEES

Scientific Program of Symposium 242	EUR 300
Students (copy of student ID required)	EUR 150

The congress fees include:
- Pre-Opening and Welcome on Thursday, October 23, 2025
- Refreshments during coffee breaks
- Lunch on Friday and Saturday, October 24-25, 2025
- A copy of the final program

CONGRESS OFFICE AND REGISTRATION

Opening Hours:

Thursday, October 23, 2025	16:00 – 20:00 h
Friday, October 24, 2025	08:00 – 17:30 h
Saturday, October 25, 2025	08:00 – 17:00 h

The Falk Foundation will take pictures during the meeting. Additionally, parts of the meeting might be recorded. By participating all attendees consent and agree with the recording and the photo shoots.

ARRIVAL

JW Marriott Hotel Berlin
Stauffenbergstr. 26
10785 Berlin
Germany

By plane
The Berlin Brandenburg Airport (BER) is about 26.5 km away from the hotel and well connected with trains departing from Terminal 1-2 every hour. You can also take a taxi which takes about 30 minutes time.

By train
Berlin Central Station (U-Bahn, S-Bahn, regional trains, ICE train)
Station Potsdamer Platz (U-Bahn, S-Bahn, regional trains)
From Station Potsdamer Platz: Head west on Potsdamer Platz/B1.
Turning right toward Sigismundstrasse. Slight right onto Sigismundstrasse. Turn left onto Stauffenbergstrasse. Destination will be on the left.

By car
On-Site Parking
Hourly: €3.00
Daily: €25.00

CONFLICTS OF INTEREST

Members of the scientific committee declare the following potential conflicts of interest:

Stephan Fichtner-Feigl: no potential conflict of interest to report

Tom Hemming Karlsen: Albireo, Boehringer, Dr. Falk Pharma, Gilead, MSD, Rectify Pharma

Sophie Lotersztajn: no potential conflict of interest to report

Frank Tacke: Abbvie, Alnylam, Agomab, Astra Zeneca, BMS, Boehringer, Dr. Falk Pharma, Gilead, GSK, Ipsen, Madrigal, MDD, MSD, NovoNordisk, Novartis, Pfizer, Sanofi

POSTER ABSTRACTS

1. Intraperitoneal administration of investigational drug VS-01 captures accumulated metabolites in patients with decompensated liver cirrhosis
   B. Alard, O. Tyc, J. Magnanensi, Z. Majd, M. McCoy, S. Klein, R. Schierwagen, S. Sayah Jeanne, S. Ferreira, D. Hum, B. Staels, K. Staufer, J. Trebicka, F. Uschner (Loos, Lille, FR; Frankfurt, Münster, DE; Zurich, CH)
2. Risk factors associated with hepatocellular carcinoma (HCC) in a tertiary gastroenterology center
   C. Atodiresei (Iasi, RO)
3. Role of CCL5 in the pathology of hepatitis delta infection
   B. Bartosch, E. Batbold, O. Khomich, J. Molle, A. Roca Suarez, X. Grand, A. Ivanov, F. Zoulim (Lyon, FR; Moscow, RU)
4. Mapping the clinical profile of chronic liver diseases in Mongolia
   B. Batkhuu, D. Yagaanbuyant (Ulaanbaatar, MN)
5. Treatment outcomes of Peg-interferon alpha-2a in patients with chronic HDV infection
   D. Bekhbold (Ulaanbaatar, MN)
6. Nitazoxanide counteracts systemic inflammation and organ failure in disease models of acute-on-chronic liver failure (ACLF)
   M. Bobowski-Gerard, C. Vanbesien, V. Legry, P. Delataille, V. Daix, Z. Majd, D. Hum, B. Staels, S. Sayah Jeanne (Loos, Lille, FR)
7. Context-dependent immunogenic effects of ferroptosis in hepatocellular carcinoma and implications for immunotherapy
   A. Bruneau, W. Werner, I. Lurje, H. Fuller, N. Hilbert, M. Kohlhepp, J. Kusnick, K. Detjen, N. Beindorff, F. Tacke, L. Hammerich (Berlin, DE)
8. Neutrophils associate with progression of primary sclerosing cholangitis in the presence of inflammatory bowel disease
   A. Bruneau, S. Wdowinski, H. El Mourabit, A. Guillot, M. Kuzminskaya, P. Horn, L. Barleben, B. Ozdirik, J. Gautheron, L. Hammerich, C. Housset, F. Tacke (Berlin, DE; Paris, FR)
9. Inhibition of ATGL shapes cholangiocyte inflammatory response in vitro
   T. Chakma, T. Claudel, E. Dixon, H. Horstmeier, G. Grabner, C. Fuchs, M. Trauner (Vienna, AT)
10. Weight changes differentially impact MASLD incidence and outcomes based on genetic and metabolic risk profiles
    L. Chen, F. Tacke, A. Guillot, G. Lv (Berlin, DE)
11. Whole genome architecture links non-coding variants to the risk of end-stage liver disease and prognosis after liver transplantation
    L. Chen, F. Tacke, A. Guillot (Berlin, DE)
12. Metabolic dysfunction-associated steatotic liver disease (MASLD) in renal transplant recipients: Relation to systemic inflammation, oxidative stress, and cardiovascular risk
    H. El Aggan, H.S. El-Wakil, S.A. Mahmoud, A.A. Saad (Alexandria, EG)
13. Expression of Toll-like receptor 7 and its downstream interferon lambda 1 and nuclear factor kappa B in hepatitis C virus-related hepatocellular carcinoma: Relation to tumor aggressiveness
    H. El Aggan, N. El Deeb, E. Hassona, A. El Gendy, M. Mohamed (Alexandria, EG)

14. From fibrosis to hepatocellular carcinoma: The hypoxia-driven continuum in MASLD/MASH
G. Fathi Rashid, C. Meier, A. Brieger, C. Schrecker (Frankfurt, DE)

15. Pancreatic steatosis as a preceding stage of liver steatosis in adult zebrafish experimental models
C. Flourou, C. Michaelides, G. Georgiou, E. Oganyan, C. Azina, N. Dietis (Nicosia, CY)

16. Inhibition of bile acid conjugation improves DDC-induced cholestatic liver injury in mice with a humanized bile acid pool
C. Fuchs-Steiner, O. Petrenko, V. Mlitz, H. Scharnagl, T. Reiberger, B. Garfinkel (Vienna, Graz, AT; Cambridge, US)

17. Bsep/Abcb11 is not required for choleretic actions norucholic acid in mice
C. Fuchs-Steiner, O. Petrenko, V. Mlitz, H. Scharnagl, M. Henricsson, A. Molinaro, T. Reiberger (Vienna, Graz, AT; Gothenburg, SE)

18. Identification of molecular targets from the interactome of primary sclerosing cholangitis and their therapeutic modulation
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1. Intraperitoneal administration of investigational drug VS-01 captures accumulated metabolites in patients with decompensated liver cirrhosis

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Introduction: Microbiota-derived metabolites may contribute to acute decompensation (AD) in patients with liver cirrhosis. VS-01 is an investigational liposomal infusion for intraperitoneal administration designed to enhance the clearance of ammonia and other disease-related metabolites. This study evaluated VS-01's ability to capture gut-derived metabolites in 9 patients with decompensated liver cirrhosis, ascites, and covert hepatic encephalopathy, as part of a Phase 1b safety clinical trial (EudraCT no.: 2018-004606-25).

Methods: Patients received a single dose of VS-01 (either 15, 30, or 45 mL/kg) following paracentesis, with a 2-hours dwell time. Peritoneal fluid and plasma samples were collected at baseline (T0), 1 hour (T1), 2 hours (T2), and 24 hours (T24). Untargeted LC/MS metabolomic analysis was performed on all samples. From the identified compounds, 103 gut-derived metabolites (based on the Gutsy Atlas) were selected for analysis. Fold changes (FC) and t-tests were computed to compare and detect significant differences ($p < 0.05$) in peritoneal samples at T0 vs T2, and in blood samples at T0 vs T24. Statistical analyses were performed using MetaboAnalyst on the peak lists containing the detected mass features of identified compounds.

Results: Of the 103 metabolites, 64 showed increased concentration in peritoneal fluid at T2 vs T0, suggesting uptake by VS-01. Twelve metabolites increased significantly (log2[FC] ranging from 1.12 to 4.47), with no significant increase in plasma at T24 vs T0. These included three xenobiotics (theophylline, norcotinine, (S)-nicotine) whose degradation occurs mainly in the liver, and four metabolites previously described as accumulating in the context of AD (5-methyluridine, allantoin, methionine, formiminoglutamic acid). The remaining five were trigonelline, prolylglycine, methionine sulfoxide, carnosine, urocanic acid.

Discussion/Conclusion: VS-01 appeared to capture gut-derived metabolites including three xenobiotics. In the context of decompensation of cirrhosis and impaired liver function, reducing metabolite accumulation might halt progression of AD and ACLF. Further analyses are warranted to confirm our findings.

2. Risk factors associated with hepatocellular carcinoma (HCC) in a tertiary gastroenterology center

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Introduction: HCC is the most common primary liver cancer and a major complication of chronic liver diseases. This study aims to identify the main risk factors for HCC in a cohort of patients analyzed retrospectively over one year.

Methods: Patients diagnosed with HCC between January 2024–January 2025 were included, based on imaging and/or histological criteria. The study evaluated the etiological factors, presence of cirrhosis, metabolic comorbidities, sex, age, disease duration, and Barcelona-Clinic Liver Cancer-BCLC staging.

Results: A total of 120 patients with HCC were included, with a mean age of 64 years and a male predominance (70%). The duration of liver disease exceeded 10 years in 60% of cases. The etiological distribution was predominantly viral: HCV – 38 patients (32%), of whom 10 (8%) had achieved sustained virologic response; HBV – 24 patients (20%), of whom 8 (7%) were under antiviral treatment; and HBV+HDV co-infection was present in 5 patients (4%). Alcoholic etiology was identified in 22 patients (18%), and MAFLD in 12 patients (10%). Type 2 diabetes (T2DM) was present in 54 patients (45%), 12 of whom also had MAFLD. Cirrhosis was present in 102 patients (85%), classified according to Child-Pugh score: Class A – 26 patients (25.5%), B – 56 patients (54.9%), and C – 20 patients (19.6%). 18 patients (15%) did not have cirrhosis.

Discussion/Conclusion: Cirrhosis was significantly associated with HCC ($p < 0.00001$). T2DM was also a significant risk factor ($p = 0.023$). BCLC staging was as follows: Stage A – 18 patients (15%), B – 36 patients (30%), C – 48 patients (40%), and D – 18 patients (15%). Viral or alcoholic liver cirrhosis and T2DM are the main risk factors for HCC. MAFLD was not significantly associated with HCC, while advanced age remains an important predictor. Monitoring patients with chronic liver disease and metabolic risk is essential for the early detection of HCC.

3. Role of CCL5 in the pathology of hepatitis delta infection

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Introduction: Liver cancer is the sixth most common cancer and the third most common cause of cancer-related deaths worldwide. The number of new HCC cases is predicted to increase by 55% by 2040. One main cause of liver cancer are hepatitis viruses. Among them, HBV and HCV are considered oncogenic viruses, but the role of HDV in hepatocarcinogenesis (HCC) is still unknown. Chronic hepatitis Delta is associated with accelerated fibrosis progression and increased HCC incidence compared to chronic HBV infection. Thus, it is crucial to understand the mechanisms underlying the pathophysiology of chronic hepatitis Delta. We have identified CCL5, expressed in a wide variety of myeloid and lymphoid

populations within the liver microenvironment, to be induced by HDV. Importantly, increased levels of CCL5 have been implicated in the progression of chronic liver disease towards HCC in the context of several different aetiologies.

Methods: Differentiated HepaRG and PHH as well as well as other liver resident cell types were infected with HDV, HBV or both, or conditioned media derived from these infections. Infection and cellular responses were monitored by RTqPCR, single cell sequencing, western blotting, ELISA and other.

Results: In single-cell RNAseq, mono-HDV or HBV/HDV co-infected HepaRG cell transcriptomes clearly differed from non-infected and HBV-infected cells. Pathway analysis in these populations revealed strong inflammatory responses to be associated with HDV infection, particularly IFN signaling. Virus-induced IFN signalling was furthermore associated with important metabolic alterations. Furthermore, a mono-HDV infected sub-cluster of HepaRG cells showed a strong upregulation of CCL5, which was induced by HDV independently of IFN signaling. Furthermore, CCL5 produced in response to HDV infection was found to be secreted and to activate stellate cells in co-culture.

Discussion/Conclusion: Our study describes the characterization of the transcriptional profiles of HBV- and HDV-infected mono- or co-infected cell populations. It furthermore shows upregulation and secretion of chemokine CCL5 to be induced specifically in HDV mono-infected cells. HDV-induced CCL5 is secreted from hepatocytes and thus may play an important part in driving fibrosis progression. Translational studies in the future will allow to address these findings in vivo and to ask whether CCL5 may also play a role in the excessive inflammatory phenotype and increased HCC incidence, known to be associated with chronic hepatitis Delta.

4. Mapping the clinical profile of chronic liver diseases in Mongolia

Barkhas Batkhuu, Dahgwahdorj Yagaanbuyant (Ulaanbaatar, MN)

Introduction: Mongolia has among the highest global prevalence of viral hepatitis, with HCV at 8.1% and HBV at 9.4%. Among HBV-infected individuals, 60–65% are co-infected with HDV—placing Mongolia first worldwide. As a result, Mongolia also leads in hepatocellular carcinoma (HCC) incidence and mortality. A comprehensive clinical profile is urgently needed.

Objective: To describe the clinical characteristics of chronic liver diseases and HCC based on data from the DETECT-HCC study in Mongolia.

Methods: We analyzed data from 1,378 participants (51.1% male) enrolled between October 2023 and April 2025. Hepatitis status was assessed using qHBsAg/qAnti-HCV (HISCL5000); viral loads with GeneXpert (HBV/HCV) and Agilent PCR (HDV). Tumor markers (AFP, PIVKA-II) were analyzed on Sysmex BX3010. Fibrosis and steatosis were evaluated by FibroScan 630-Expert; imaging via ultrasound (ESAOTE-Mylab) and contrast-enhanced MRI/CT (Primovist, Siemens Essenza 1.5T), interpreted using LI-RADS 2018. Data were captured in NEVIOM EDC.

Results: Of the participants, 475 had HCC (57.3% male; mean age: 59.5/64.6), 305 had cirrhosis, 299 had chronic hepatitis, and 299 were relatively healthy. Among HCC cases, 46.9% had HBV-HDV co-infection, 34.1% had HCV (48.7% active replication), and 37.2% were in early stages (BCLC 0-A). Diagnostic cut offs: AFP 5.8 ng/mL (AUC = 0.84), PIVKA-II 44.5 mAU/mL (AUC = 0.925)

Discussion/Conclusion: HBV-HDV co-infection is the dominant burden across all disease stages. Active HCV in 14.3% supports the need for national elimination efforts. PIVKA-II showed superior diagnostic performance. LI-RADS-based imaging enables early detection with clear clinical value.

Keywords: LI-RADS, PIVKA-II, HCC, HDV, Primovist

5. Treatment outcomes of Peg-interferon alpha-2a in patients with chronic HDV infection

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Introduction: Hepatitis D virus (HDV) is the most severe form of viral hepatitis and rapidly progresses to cirrhosis and hepatocellular carcinoma. Despite the approval of bulevirtide for HDV treatment, its high cost and limited efficacy (around 20%) remain major barriers.

Objective: To evaluate the clinical and virological efficacy, as well as side effects, of pegylated interferon (Peg-IFN) therapy in patients with chronic HDV infection.

Methods: A total of 39 patients with chronic HDV infection treated with Peg-IFN were included. The mean age was 42.2 ± 7.4 years; 79.4% were male. Clinical status, side effects, blood tests, viral load, and liver fibrosis (via Fibroscan) were monitored.

Results: Five patients discontinued treatment (1 due to side effects, 4 for other reasons), leaving 34 patients who received 24–72 weeks of Peg-IFN therapy. At baseline, fibrosis staging was F1 in 29.4%, F2 in 11.7%, F3 in 41.1%, and F4 (cirrhosis) in 17.6%. By week 24, fibrosis improved in 71.3% of F3 patients and 33.3% of F4 patients. ALT levels decreased significantly from 104.07 ± 72.5 U/L to 61.01 ± 33.1 U/L ($p = 0.0004$). Quantitative HBsAg decreased in 63.6% of patients ($p = 0.0003$). HDV-RNA decreased from 6.1 ± 0.7 to 2.6 ± 1.9 log10 IU/mL; 14.7% had undetectable HDV-RNA, and 52.9% showed ≥ 2 log10 reductions. Common side effects included fever (50%), fatigue (up to 14.7%), leukopenia (8.8%), and hair loss (5.8%).

Discussion/Conclusion: Peg-IFN demonstrated notable antiviral and antifibrotic effects in patients with chronic HDV infection, with a manageable safety profile. It remains a viable treatment option, especially in resource-limited settings.

Keywords: HDV-RNA – Hepatitis D viral load, q-HBsAg – Hepatitis B surface antigen, HDV – Hepatitis D virus, HBV – Hepatitis B virus

6. Nitazoxanide counteracts systemic inflammation and organ failure in disease models of acute-on-chronic liver failure (ACLF)

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Background and Aims: ACLF is a life-threatening condition in patients with chronic liver disease, characterized by systemic inflammation and multi-organ failure, with limited therapeutic options. Systemic inflammation, triggered by bacteria or endotoxins such as lipopolysaccharide (LPS), is a primary driver of ACLF. We aim to evaluate the efficacy of the FDA-approved anti-parasitic drug nitazoxanide (NTZ) in rat models of ACLF.

Methods: ACLF was induced by LPS (1–10 µg/kg, i.p.) in rats with advanced liver injury resulting from bile duct ligation (BDL) or chronic carbon tetrachloride (CCl_4) exposure. NTZ was orally administered 1 h before, concomitantly or 15 min after LPS challenge. Serum and tissues were collected at 3 h or 24 h post-LPS injection. Brain damage was evaluated by measuring cerebral water content.

Results: In the CCl_4 + LPS model, administration of NTZ 1 h before LPS challenge improved hepatic function (total bilirubin -103%, $p < 0.0001$; total bile acids -130%, $p = 0.03$; AST -100%, $p = 0.003$; GGT -99%, $p = 0.014$) and restored renal function (creatinine -99%, $p = 0.03$; urea -96%, $p = 0.0005$), while reducing hepatic macrophage infiltration (CD68 cells -57%, $p = 0.0014$), in comparison with vehicle.

In BDL rats, LPS triggered an intense systemic inflammatory response associated with renal impairment and brain edema; hallmarks of ACLF. When administered concomitantly to LPS, NTZ reduced serum levels of pro-inflammatory cytokines (IL6 -99%, $p = 0.0006$; TNFα -94%, $p = 0.003$; IL1β -87%, $p = 0.06$), restored kidney function (cystatin C -85%, $p = 0.004$), and inhibited circulating RIPK3 (-89%, $p = 0.002$), a marker of necroptosis, when compared to the vehicle group. NTZ also resolved cerebral edema by -149% ($p = 0.003$). Interestingly, beneficial effects on inflammation and organ function (liver and kidney) were observed in this model when NTZ was adm

Discussion/Conclusion: NTZ protects against systemic inflammation and liver, kidney and brain failure in disease models of ACLF. These data support the investigation of NTZ treatment as a promising approach to alleviate systemic inflammation and multi-organ injury in ACLF.

7. Context-dependent immunogenic effects of ferroptosis in hepatocellular carcinoma and implications for immunotherapy

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Purpose: Immune-checkpoint-inhibitors (ICI) have transformed cancer therapy, yet response rates in hepatocellular carcinoma (HCC) remain unsatisfactory, potentially aggravated by underlying liver disease. Inducing immunogenic cell death (ICD) offers a promising approach to enhance immune activation within the tumor microenvironment (TME) and improve ICI therapy. Ferroptosis, an iron-dependent form of programmed cell death characterized by lipid peroxidation, is frequently dysregulated in cancer and may possess immunogenic properties. Here, we investigate how ferroptosis remodels HCC TME and how this may be leveraged to boost effectiveness of ICI therapy.

Results: Murine and human HCC cell lines were sensitive to ferroptosis induction. Ferroptotic cell death was accompanied by high mobility group box 1 (HMGB1) release and calreticulin translocation - both hallmarks of ICD – and associated with programmed death-ligand 1 (PD-L1) upregulation. Co-culture of ferroptotic HCC cells or their conditioned media with primary immune cells activated both myeloid and T cell populations. Ex vivo multiplex immunofluorescence revealed that untreated human and murine HCC tumors displayed cold TME with low immune cell infiltration. BSO treatment of diethylnitrosamine (DEN)-induced HCC-bearing mice with CCl4-induced liver fibrosis enhanced lymphoid and myeloid immune cell infiltration, delayed tumor growth and improved survival compared to untreated controls. Conversely, BSO primarily promoted infiltration of tumor-associated macrophages and failed to provide survival benefit in DEN-induced HCC-bearing mice with diet induced steatosis. While ICI monotherapy failed in both fibrosis- and steatosis-associated models, combination therapy with BSO conferred a survival benefit in steatotic- HCC. Notably, ICI addition did not enhance the therapeutic effect of BSO in fibrotic HCC.

Discussion/Conclusion: Ferroptosis induces immunogenic alterations in HCC, reshaping the TME and enhancing antitumor immune responses. Its therapeutic efficacy is influenced by the underlying liver disease, highlighting a context-dependent synergy with ICI therapy. Further investigation is warranted to elucidate the mechanisms driving this etiology-specific response to ferroptosis in HCC.

8. Neutrophils associate with progression of primary sclerosing cholangitis in the presence of inflammatory bowel disease

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic liver disease frequently associated with inflammatory bowel disease (IBD). Increasing incidence, limited therapies and progression to cirrhosis or tumors indicate an urgent need for new pathogenic insights. The prevalence of elevated anti-neutrophil cytoplasmic antibodies among PSC patients suggest a role for neutrophils, but their contribution to PSC, especially associated with colitis, remains under-

studied. Here, we explore the interplay between neutrophil activity, intestinal inflammation, and hepatic fibrosis.

Methods: Wild-type (WT) and FVB-mdr2-/- mice (a spontaneous PSC model) were treated with 3% DSS for 5 days to induce acute colitis and sacrificed immediately or after 7 days of recovery, or 5 cycles of 2% DSS for 5 days followed by 12 days of water (chronic). Disease severity was assessed using standard biochemical methods. Inflammation was assessed by multiplex immunohistochemistry, flow cytometry and bulk RNA-seq. Peripheral immune cells from PSC patients with and without IBD (n = 67), were characterized by flow cytometry.

Results: Acute colitis does not worsen liver fibrosis compared to untreated mdr2-/- mice, but rather heightens inflammation in the liver and colon, which is sustained even after 5 days of recovery. In the presence of chronic colitis, hepatic fibrosis is exacerbated in the mdr2-/- mouse model. In both conditions, we observe an increase of neutrophils in WT and mdr2-/- mice after DSS treatment. In mdr2-/- mice with chronic colitis, neutrophils show an activated (MPO+ctH3+) phenotype, indicating that neutrophil recruitment and activation following colitis may play a key role in the progression of PSC. Similar results are also observed in cohorts of PSC patients with or without IBD. Specifically, PSC patients display strong phenotypical changes in their neutrophil populations only when they have associated IBD, suggesting neutrophil activation might be induced by gut-derived signals.

Discussion/Conclusion: Neutrophils may play a major role in PSC progression and could be a promising therapeutic target.

9. Inhibition of ATGL shapes cholangiocyte inflammatory response in vitro

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Introduction: Adipose triglyceride lipase (ATGL) is the rate limiting enzyme in intracellular lipolysis, generating free fatty acids (FAs) that regulate key cellular processes. While ATGL has been linked to inflammation in hepatocytes, its role in cholangiocytes is largely unknown. In this study, we seek to investigate whether ATGL inhibition impacts inflammation in cholangiocyte and how this shapes their response to injury.

Methods: H69 cells were exposed to pro-inflammatory cocktail consisting of 10 ng/ml IFN-γ, 10 ng/ml TNFα and 10 ng/ml LPS for 24 h and 48 h (to model acute inflammation) in the presence or absence of ATGL inhibitor. Gene expression changes were analyzed by qPCR.

Results: Cholangiocyte surface marker CK19 was upregulated ($p = 0.0003$) in cells exposed to pro-inflammatory cocktail for 24 h compared to control. Conversely, treatment with the inhibitor suppressed its expression to baseline ($p = 0.0002$). Acute inflammation induced by pro-inflammatory cocktail exposure

was associated with a significant upregulation in cholangiocyte inflammation and reactive phenotype markers such as IL6, IL8 and VCAM1 at 24 h ($p = 0.0008$; $p < 0.0001$; and $p < 0.0001$ respectively) and 48 h ($p < 0.0001$; $p < 0.0001$; and $p = 0.0005$ respectively). In the presence of the inhibitor, this effect was ameliorated for IL8 and VCAM1 but not IL6 at 24 h ($p = 0.0056$ and $p = 0.0009$ respectively) and for all the markers at 48 h ($p = 0.0022$; $p = 0.0026$; and $p = 0.00095$ respectively). Notably, an induction in PPARG signalling was observed at 24 h ($p = 0.006$) and 48 h ($p < 0.0001$). This effect decreased in the presence of the inhibitor at both time points ($p = 0.0236$ and $p = 0.0224$ respectively).

Discussion/Conclusion: We show that ATGL inhibition attenuates cholangiocyte inflammation partly through nuclear receptor (PPAR) signalling. Ongoing investigations in H69 and human cholangiocyte organoids will help to unravel the underlying molecular mechanisms.

10. Weight changes differentially impact MASLD incidence and outcomes based on genetic and metabolic risk profiles

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is driven by environmental (e.g., nutrition), metabolic and genetic factors, leading to heterogeneous subgroups with liver- vs. cardiovascular-related adverse outcomes. Weight management is crucial in preventing MASLD and related adverse events, but the effect of weight loss on MASLD subgroups is unclear. We designed a prospective cohort from the UK biobank to assess the associations of body weight dynamics with MASLD incidence, MASLD-associated hepatic progression and cardiovascular diseases (CVD).

Methods: A metabolic risk group was defined by lipid accumulation product, and two MASLD subgroups (i.e., hepatic progression and systemic progression) were defined by genetic risk scores. A Cox proportional model was constructed to delineate the range of weight loss in the general population and subgroups. A proteome analysis unveiled weight change-associated proteins, which were tested to predict the risk of future MASLD.

Results: 51,123 participants were enrolled with a median 12.12 years of follow-up (568 incident MASLD, 168 related CVD and 15 related hepatic progression). Weight loss can reduce the risk of MASLD occurrence and prevent MASLD-related CVD in general population and subgroups, independently of initial body mass index. Intriguingly, the recommended weight loss goal was determined as 14% for “hepatic MASLD”, but only 9 % for “systemic MASLD”. Efficacy of weight loss further differed between men and women. Weight change-associated proteins in the circulation can independently predict the risk of future MASLD.

Discussion/Conclusion: Weight loss has differential impacts on reducing MASLD incidence and related CVD according to the genetic and metabolic risk profile of individuals.

11. Whole genome architecture links non-coding variants to the risk of end-stage liver disease and prognosis after liver transplantation

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Introduction: Liver transplantation (LT) is the only curative therapy for end-stage liver disease (ESLD). The genetic factors driving ESLD are incompletely understood. In addition, the whole genomic architecture of LT recipients, donors or their mismatch that determine outcome after LT are currently unknown.

Methods: We prospectively established a LT cohort (n = 427 patients) and selected 316 recipients and paired donors with whole blood samples available for whole genome-sequencing (WGS) to decipher the genetic architecture of ESLD, especially comparing the impacts of coding and non-coding variants. The genetic mismatch scores, including both overall mismatch and single nucleotide polymorphism (SNP) mismatch, were constructed to assess the impact of genetic mismatch on recipients' overall survival and acute rejection after LT.

Results: A total of 295 recipients and 301 donors were eligible for WGS analysis after quality control on sequencing and samples. WGS analysis unveiled key genes associated with ESLD, and downstream analyses (e.g. the Mendelian randomization analysis) highlighted CDKN1A as a potential target to alleviate liver injury. Unexpectedly, the non-coding variants (98%) substantially contributed to the genetic risk profile of ESLD. Besides, the copy number variants and structural variants were also associated with ESLD. Whole genome mismatch did not impact the recipients' overall survival. However, SNP-level mismatch was strongly associated with poorer survival and top 10 SNPs were all non-coding variants where the mismatch of SNP rs2049048, rs138960437 and rs79222239 were suggested to lead to increased risk of acute rejection.

Discussion/Conclusion: This study suggests that non-coding variants are determinant in the pathogenesis of liver diseases and implicates that genetic testing should be adopted to improve prognosis of LT.

12. Metabolic dysfunction-associated steatotic liver disease (MASLD) in renal transplant recipients: Relation to systemic inflammation, oxidative stress, and cardiovascular risk

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Introduction: Renal transplant recipients (RTRs) often have metabolic abnormalities like obesity, diabetes, and dyslipidemia, which are also key drivers of metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD potentially increases the risk of cardiovascular disease (CVD) and decreases graft survival by amplifying systemic inflammation and oxidative stress. The present study was designed to study the association between MASLD and renal transplantation and its relation to systemic inflammation, oxidative stress, and cardiovascular risk.

Methods: Thirty renal transplant recipients (RTRs) with a mean duration of transplantation 7.97 ± 5.01 years were enrolled in the study. MASLD was diagnosed by the presence of hepatic steatosis and at least one cardiometabolic risk factor (CMRFs), exclusion of other causes of hepatic steatosis, and no or mild alcohol consumption. Anthropometric measurements included body mass index (BMI) and waist-hip ratio (WHR). Liver function tests, lipid profile, fasting blood glucose (FBG), and fasting serum insulin (FSI) were assayed and the homeostatic model assessment for insulin resistance (HOMA-IR) was calculated. Renal function was evaluated by serum creatinine (s.Cr), estimated glomerular filtration rate (eGFR), and urinary protein/creatinine (Pr/Cr) ratio. Systemic inflammatory markers included serum high sensitivity C-reactive protein (hs-CRP) and neutrophil-to-lymphocyte ratio (NLR). Oxidative stress was assessed by measuring serum levels of malondialdehyde (MDA) and total antioxidant capacity (TAC). CVD was diagnosed using 2D transthoracic echocardiography and by estimating cardiovascular risk (CVR) score.

Results: Post-transplant MASLD was diagnosed in 18 (60%) patients. CMRFs included overweight/obesity in 21 (70%) patients, diabetes in 6 (20%) patients, hypertension in 12 (40%), and dyslipidemia in 19 (63.3%) patients. RTRs with MASLD showed significantly higher BMI, WHR, serum levels of liver enzymes, FBG, FSI, triglycerides, low density lipoprotein-cholesterol, s.Cr, hs-CRP, and MDA, NLR, and HOMA-IR, and a significantly lower eGFR, serum high density lipoprotein-cholesterol level and TAC than RTRs without MASLD ($p < 0.05$). Left ventricular mass and CVR score showed significant increases with the presence MASLD in RTRs ($p = 0.003$ and $P = 0.013$ respectively). The frequency of MASLD was significantly higher in RTRs who developed chronic allograft dysfunction than in RTRs with stable renal function ($p = 0.025$).

Discussion/Conclusion: Post-renal transplantation MASLD is associated with metabolic derangements and increases the risk of CVD and allograft dysfunction, possibly related to systemic inflammation and oxidative stress. Screening RTRs to detect MASLD followed by proper management may reduce the incidence of adverse CVD events and improve graft survival.

13. Expression of Toll-like receptor 7 and its downstream interferon lambda 1 and nuclear factor kappa B in hepatitis C virus-related hepatocellular carcinoma: Relation to tumor aggressiveness

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Introduction: Hepatitis C virus (HCV) is a major risk factor for the development of hepatocellular carcinoma (HCC). Compelling evidence suggests that a dysregulated innate immune responses may contribute to hepatocarcinogenesis. Toll-like receptor 7 (TLR7) is an intracellular pattern recognition receptor of the innate immune system that primarily senses single-stranded RNAs including viruses like HCV. Stimulation of TLR7 results in the induction of type III interferon, known also

as interferon lambda (IFNL), as well as the activation of nuclear factor kappa B (NF-κB) to stimulate proinflammatory genes. The present work was conducted to study the expression of TLR7 and its downstream effectors IFNL1 and NF-κB in HCV-related HCC and their relation to tumor aggressiveness.

Methods: Twenty patients with HCV-related cirrhosis and HCC who underwent surgical resection of the tumor were included in the study. The severity of liver disease was assessed according to Child-Pugh classification, Model for End Stage Liver Disease 3.0 (MELD 3.0) score, and albumin-bilirubin (ALBI) score. HCC stage was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging system. Tumor burden and tumor aggressiveness index (TAI) were calculated. Representative samples of HCC and the surrounding non-neoplastic liver tissue were examined. HCC was graded according to Edmondson and Steiner's criteria. The surrounding non-neoplastic liver tissue was assessed as regards the histological activity grade and fibrosis stage according to METAVIR scoring system as well as steatosis grade. Immunohistochemical examination was performed using antibodies against TLR7, IFNL1, and NF-κB/p65 and the staining intensity was scored semi-quantitatively (Score 0–3) as a percentage of the total liver tissue area.

Results: Positive cytoplasmic immunostaining for TLR7 and IFNL1 was detectable in the tumor cells of 60% of HCCs and 95% of the surrounding non-neoplastic liver tissues. Positive nuclear immunostaining of NF-κB was detectable in the tumor cells of all HCCs and in 70% of the surrounding non-neoplastic liver tissues. The TLR7 and IFNL1 staining scores showed significant decreases while NF-κB staining score showed a significant increase in HCC tissues compared with the surrounding non-neoplastic liver tissues ($p = 0.012$, $p = 0.002$, and $p = 0.005$ respectively). The intratumoral TLR7 and IFNL1 staining scores were positively correlated ($p < 0.001$) and both showed inverse correlations with serum HCV RNA levels, ALBI score, serum AFP levels, HCC maximum diameter, BCLC stage, tumor burden, TAI, and HCC histological grade ($p < 0.05$). The NF-κB expression in HCCs was positively correlated with serum ALT levels, HCC maximum diameter and HCC histological grade but not with TLR7 and IFNL1 expression ($p < 0.05$).

Discussion/Conclusion: Down-regulation of the TLR7 signaling may play an important role in the development and progression of HCV-related HCC mainly through impairment of IFNL1 production but was not enough to suppress the NF-κB pathway, which may be activated by other non-TLR-7-mediated pathways.

14. From fibrosis to hepatocellular carcinoma: The hypoxia-driven continuum in MASLD/MASH

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Introduction: Metabolic-associated steatotic liver disease (MASLD) and its progressive form, metabolic-associated steatohepatitis (MASH), are increasingly recognized as major contributors to liver fibrosis, which can progress to

cirrhosis and hepatocellular carcinoma (HCC). Emerging evidence suggests that hypoxia contributes to fibrogenesis and genomic instability, potentially through immune-mediated mechanisms. This study investigates the role of hypoxia in MASLD/MASH progression and explores whether therapeutic targeting of hypoxia-induced pathways can modulate fibrotic remodeling, prevent cirrhotic transformation, and mitigate oncogenic risk.

Materials and methods: Hepatic stellate cell lines (LX-2 and HSC-T6) were cultured under normoxic and hypoxic conditions to evaluate the expression of fibrotic activation markers COL1A1 and ACTA2 (α-SMA) via qPCR, Western blotting, and immunofluorescence. Collagen deposition was assessed using Sirius Red staining in vitro in cell cultures and in formalin-fixed MASH liver tissue. In parallel, two HCC cell lines, HepG2 and Huh7, were subjected to chronic hypoxia over several months and compared with cells maintained under normoxia. Subsequently, microsatellite instability (MSI) was analyzed by fragment analysis, and mismatch repair (MMR) protein expression was assessed by Western blotting. Ongoing experiments aim to characterize hypoxia-induced immune responses by analyzing the expression of key pro-inflammatory cytokines, immune checkpoint molecules, and chemokines in hepatic stellate cells and HCC cell lines.

Results: Exposure of LX-2 cells to hypoxia resulted in a robust upregulation of α-SMA and Collagen I protein levels, consistent with the activation of a pro-fibrotic phenotype. These in vitro findings were corroborated by enhanced collagen deposition in hypoxic regions of MASH liver tissue, reinforcing the role of hypoxia to fibrogenic remodeling. In HCC models, chronic hypoxic exposure induced microsatellite instability, accompanied by alterations in MMR protein expression, suggesting that sustained hypoxic stress compromises genomic integrity, may contribute to malignant progression in the context of chronic liver disease.

Discussion: Collectively, these data support a model in which hypoxia acts as a central pathogenic driver of both fibrogenesis and genomic instability during MASLD/MASH progression. We further postulate that hypoxia contributes to disease advancement by fostering an immunologically active, fibrogenic microenvironment – characterized by the upregulation of pro-inflammatory cytokines and immune checkpoint molecules involved in immune cell recruitment and retention. The concordance between in vitro activation of hepatic stellate cells and histological evidence of collagen accumulation in hypoxic liver regions underscores the biological relevance of oxygen deprivation in sustaining fibrotic remodeling.

Concurrently, the emergence of MSI and MMR dysregulation in hypoxia-exposed HCC cells reinforces the concept that hypoxia undermines genome maintenance mechanisms, thereby facilitating oncogenic transformation.

Our ongoing work focuses on delineating and therapeutically targeting hypoxia-driven metabolic alterations as well as immune pathways and responses, with the aim of reversing fibrogenesis, mitigating genomic instability, and intercepting the progression from MASH to HCC. This integrated approach is expected to provide a mechanistic foundation for developing novel, precision-based therapies targeting hypoxia-driven fibrotic and oncogenic processes in chronic liver disease.

15. Pancreatic steatosis as a preceding stage of liver steatosis in adult zebrafish experimental models

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Introduction: Metabolic dysfunction associated with steatotic liver disease (MASLD) is the most common chronic liver disease in the western world. MASLD prevalence is on the rise along with the obesity and metabolic syndrome epidemic. Obesity is leading to liver steatosis but also to intrapancreatic fat deposition. The correlation between pancreatic steatosis and MASLD has not been studied. Zebrafish have emerged as valuable model organisms for studying human diseases due to similarities in structure, function and regeneration with human liver and pancreas. Therefore, we aimed to assess this correlation in obese adult zebrafish (Danio rerio) experimental models.

Methods: Adult zebrafish were in an environment at 28.5°C with a periodic rhythm of 14 h of light and 10 h of darkness. Animals were divided in three dietary groups of 12 fish each. The control group (CTR) received a standard commercial diet with flakes with a fat concentration of 10%, twice a day for eight weeks. The High Fat Diet Group 1 (HFD group 1) was fed with egg yolk powder (55.8% fat, 34.2% protein, 17.2% saturated fatty acids) 70 mg per adult fish per day for eight weeks. The High Fat Diet Group 2 (HFD group 2) separated in two subgroups, the first was fed as the HFD group 1 for four weeks and the second group for eight weeks. Euthanasia was performed at the end of feeding period. Morphological traits, length and weight were recorded. Body Mass Index – BMI and Fulton K factor were calculated to characterize animals in three categories: underweight, normal, overweight. Histological assessment with haematoxylin and eosin staining (H&E) of pancreatic and liver parenchyma was performed.

Results: Mean BMI was higher in HFD group 1. K-Factor characterized 57.2% of animals in HFD group 1 as overweight and 42.8% as normal weighted (Diagram 1). In HFD group 2, 33.3% and 66.7% were overweight in subgroup 1 and 2 respectively (Table 1). Histological assessment revealed normal liver and pancreatic parenchyma in CTR group. In HFD group 1, severe pancreatic and liver steatosis with ballooning and visceral fat accumulation was observed (Figure 1). In HFD group 2, subgroup 1 where feeding was 4 weeks, severe pancreatic steatosis was observed without liver steatosis and in comparison (Figure 2), with subgroup 2 where the feeding continued for other 4 weeks, the pancreatic steatosis was progressed with combined liver steatosis (Figure 3).

Discussion/Conclusion: In adult zebrafish, a high fat diet induced steatosis in both pancreas and liver. It is important to mention that pancreatic steatosis was observed prior to liver steatosis, in 4 weeks, in contrast to liver steatosis which was observed in 8 weeks. At the same time, all animals which had liver steatosis had also pancreatic steatosis. This is evidence that pancreatic steatosis is a possible

preceding stage to liver steatosis and MASLD. To date, this is the first study that mentioned it and this correlation contributes to the early detection and treatment intervention of MASLD.

16. Inhibition of bile acid conjugation improves DDC-induced cholestatic liver injury in mice with a humanized bile acid pool

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Introduction: Intrahepatic accumulation of bile acids (BAs) results in liver and bile duct injury in cholestasis. We hypothesized that inhibition of BA conjugation, subsequently increasing levels of non-amidated BAs in the BA pool and changing BA composition, may induce bile flow, thus improving cholestatic liver and bile duct injury.

Methods: Male FVB/N wildtype (Wt) mice received 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) over 4 weeks to induce sclerosing cholangitis and cholestasis with/without siRNA to silence Cyp2c70 (siCyp2c70) to humanize the BA pool. DDC fed mice with/without siCyp2c70 were treated with siRNA to inhibit BACL (siBACL) and subsequently BA conjugation. Liver injury was assessed biochemically and histologically/immunohistochemically. Bile flow measurements, bile acid profiling from serum and bile as well as biliary glutathione levels, hepatic hydroxyproline content were also investigated. RNA sequencing from bulk liver tissue as well as mRNA profiling by RT-PCR and immunoblotting were performed.

Results: Silencing Bacl in DDC siCyp2c70 animals reduced biliary levels of conjugated BAs, with cholic acid being the most prominent unconjugated BA in DDC siCyp2c70+siBacl animals, associated with a 2-fold and 3-fold increase in bile flow and biliary glutathione output, respectively. siBacl application in DDC siCyp2c70 mice, improved biochemical and histological features of liver and bile duct injury. While hepatic inflammation was only partly improved, hepatic fibrosis improved in DDC siCyp2c70 siBacl (vs. DDC siCyp2c70 animals), as reflected by reduced fibrogenesis gene expression (e.g. Col12e1, Col14a1, Col4a2, Fbn1) and lower hydroxyproline levels (reduced to 50% by BACL inhibition). CK19 (bile duct proliferation) and Vcam (reactive cholangiocyte phenotype) protein levels were significantly reduced in DDC+siCyp2c70 siBacl mice. RNA sequencing showed increased hepatic levels of Gsta1, Gsta3, Gsta5, Gstm2 and Gstm3 (all involved in ROS detoxification) among the top upregulated genes in the DDC siCyp2c70 siBacl group.

Discussion/Conclusion: Our data indicate that inhibition of BA conjugation improves liver and bile duct injury, at least in part, by increasing bile flow and biliary glutathione levels as well as ROS detoxification

17. Bsep/Abcb11 is not required for choleretic actions norucholic acid in mice

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Introduction: Choleretic properties of conjugation resistant Norucholic acid (NCA) are associated to its capability to undergo cholehepatic shunting, thereby inducing a bicarbonate (HCO3-) rich choleresis. It has been shown that the apical sodium-dependent bile acid (BA) transporter (Asbt), organic solute transporter-α (Ostα), and organic anion transporting polypeptide 1a/1b (Oatp1a/1b) transporters are not relevant for NCA induced bile flow and biliary HCO3- secretion. However, the necessity of the hepatic BA transporter bile salt export pump (Bsep/Abcb11) was not investigated. As such, within this study the role of Bsep for the choleretic actions of NCA was investigated.

Methods: Eight weeks old male FVB/N wild type (wt) and Bsep-/- mice were fed with a 0.5%NCA containing diet for 4 weeks. Liver injury was assessed biochemically and by (immuno)histology. Bile flow measurements and BA profiling from bile were also investigated. RNA sequencing from bulk liver tissue as well as mRNA profiling by RT-PCR were performed.

Results: NCA feeding in wt animals increased bile flow from 1 µL/min/g liver to 3 µL/min/g liver. Accordingly, HCO3- output was increased 3-fold (45 nmol/min/gL in wt mice vs. 150 nmol/min/gL in NCA-fed wt mice). While Bsep-/- mice had no measureable bile flow at baseline, in NCA-fed Bsep-/- mice 0.5 µL/min/g liver and a HCO3- output of 14 nmol/min/gL was dedected. NCA feeding led to increased biliary concentrations of unconjugated NCA (760 µM in wt versus 70 µM in Bsep-/-), while the amount of taurine-conjugated NCA was 100-fold higher in wt compared to Bsep-/- mice (5220 µM in wt versus 50 µM in Bsep-/-). RNAseq identified Sult2a1, Sult2a2, Sult2a4, Sult2a5 as well as Abcc3 and Abcc4 among the most up-regulated genes in Bsep-/- mice fed with NCA, indicating increased BA sulfation/hydroxylation and alternative BA efflux into the blood. Of note, although serum ALT and AST levels were increased in Bsep-/- mice after NCA feeding, (immuno)histological stainings and gene expression profiling did not illustrate any signs of liver inflammation and/or fibrosis.

Discussion/Conclusion: Our data indicate that bile acid transport via Bsep/Abcb11 is not essential for choleretic effects of unconjugated NCA. In contrast, taurine conjugated NCA transport into bile requires Bsep/Abcb11.

18. Identification of molecular targets from the interactome of primary sclerosing cholangitis and their therapeutic modulation

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Introduction: Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease marked by chronic bile duct inflammation and fibrosis, culminating in life-threatening liver cirrhosis. The cellular and molecular drivers of PSC progression remain poorly defined. In this study, we profiled the PSC liver interactome at single-cell resolution to identify disease-specific molecular targets, supported by multiomics evidence, and demonstrate their therapeutic modulation via predicted small molecule ligands.

Methods: We recruited three patients diagnosed with PSC cirrhosis (MedUni Vienna EC 2318/2019) scheduled for liver transplantation. Non-parenchymal cells were isolated from explanted livers via combined mechanical and Liberase tissue dissociation. We performed scRNA-seq on isolated NPCs and paired snRNA-seq, integrating data with healthy and non-PSC cirrhotic controls using scVI. Differential interactions were identified using MultiNicheNet. We validated top ligand-receptor pairs via imaging mass cytometry (IMC) and whole-tissue proteomics (with/without scaffold enrichment; n = 3 per group), cross-referencing significant transcriptomic changes in Mdr2-/- mice (16-week fibrosis, n = 7/group). Selected molecular targets underwent in silico ligand screening with AutoDock Vina, followed by in vitro validations with the predicted small molecules on primary PSC cholangiocyte organoids model.

Results: We obtained 35,501 single-cell transcriptomes from PSC liver samples, identifying cell types via established markers (e.g., ITGAX/CD1C for dendritic cells, DC; KRT19/CFTR for cholangiocytes). PSC-specific interactions included NRP1-VEGF between stellate and sinusoidal cells and THBS1-CD36 between DC and other immune cells. IMC confirmed increased THBS1+ DC in fibrotic areas, also highlighting SLIT2-positive PSC ductuli. PSC proteomics and Mdr2-/- transcriptomics further showed significant dysregulation of THBS1, NRP1, and SLIT2. In silico screening identified their ligands BGB-283 and RAF-265, which downregulated NF-kB signature expression in PSC organoids. GW-493838 combined with BMS270394 notably downregulated both TGF-beta and Notch signatures.

Discussion/Conclusion: We discovered perspective molecular targets in PSC and showed the impact of their predicted small molecule ligands on transcriptomes of primary PSC cholangiocyte organoids.

OP and CF share first authorship

MT and TR share senior authorship

19. Chronic alcohol consumption after eradication hepatitis C virus infection: Effects on progression liver damage

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Introduction: The aim of this study was to evaluate the effect of chronic alcohol consumption on liver damage in patients whom chronic HCV infection was eradicated three years ago.

Methods: Our prospective study was conducted on 88 patients of which 54 had chronic HCV infection, eradicated three years ago. The A group consist of 29 heavy alcohol drinkers (intake-over 80g ethanol/day for more than 10 years, confirmed for the last three years) in patients with sustained virological response (SVR) after direct-acting antiviral (DAA) treatment. The B group contains 34 heavy alcohol drinkers with alcoholic liver disease (ALD) without HCV and the C group composed of 25 non-alcoholic patients with eradicated chronic HCV. We monitored and assess the clinical manifestations, alcohol consumption, biochemical parameters, liver function tests, Fibro scan, FIB-4 score and APRI score at baseline, after 12, 24 and 36 months.

Results: After HCV eradication, mean level of alcohol intake was similar in A and B group (116.25 g/day vs. 109.03 g/day). In C group all patients was non-alcoholic in the last three years, but 17 patients are history of medium or low alcohol consumption. At baseline and after 12 months, the mean value of AST/ALT ratio was < 1 in A group, > 2 in B group and between 1 and 1.2, in C group. This level of AST/ALT ratio maintained whole period. In the A group transaminases levels was higher than in the group of alcoholic patients without chronic HCV ($p = 0.002$). After 12 months, the steatosis was present in all groups, but most frequent in the A group (89.65% of cases), comparative with B group (73.5%) and C group (72.0%). At 24 and 36 months, the steatosis grade was significantly higher in A group and indicate a quickly progression of steatosis. The score of fibrosis was more severe in patients with eradicated HCV chronic infection and alcohol intake. The incidence of cirrhosis after three years was significantly increased in alcoholic patients: 37.93% in the A group, 47.05% in B group and 16.00% in C group. The mean value of BMI in patients who developed cirrhosis was significantly higher (39.7 kg/sqm vs. 32.1 kg/sqm) which suggest that association between alcohol consumption and obesity had severe consequences after eradicated HCV infection. HCC was developed in 9 cases (10.22% of whole group), but significantly higher incidence was observed in patients with chronic hepatitis C infection: 6 cases in the A group and 3 in C group.

Discussion/Conclusion: The risk of quickly progression of steatosis and fibrosis was higher in patients which associated alcohol abuse and obesity after eradication HCV infection.

20. Comprehensive bioinformatic analysis identifies SPEF1 and SPEF2 as novel potential biomarkers in primary hepatocellular carcinoma

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Introduction: Hepatocellular carcinoma (HCC), the most common primary liver cancer, is a major cause of cancer-related deaths worldwide. Early detection greatly improves outcomes, with biomarkers playing a key role in diagnosis, prognosis, and treatment monitoring. Cancer-testis antigens (CTAs), due to their limited expression in normal tissues and high immunogenicity, are promising candidates. This study explores for the first time the potential of SPEF1 and SPEF2 as novel HCC biomarkers, building on prior research linking them to other cancers and premalignant lesions. Notably, SPEF1 was identified in a rare ciliated foregut cyst of the hepatic duct, and its mRNA is upregulated in various cancers across stages, sexes, and ethnicities, suggesting diagnostic relevance. In this study, we investigate for the first time the potential role of SPEF1 and SPEF2 as novel biomarkers for HCC.

Methods: We analyzed the expression of SPEF1 and SPEF2, their clinical and prognostic significance, and their association with the immune microenvironment in liver hepatocellular carcinoma (LIHC) using data from the TCGA, GEPIA, UALCAN, KM Plotter, and TIMER databases.

Results: SPEF1 and SPEF2 expression levels were significantly elevated in hepatocellular carcinoma (HCC) tissues ($p = 3.63 \times 10\text{-}12$ and $p = 1.62 \times 10\text{-}12$, respectively). SPEF1 transcript per million (TPM) values varied significantly across tumor stages, especially between stages 1 and 4 ($p = 3.10 \times 10\text{-}3$), 2 and 3 ($p = 5.44 \times 10\text{-}4$), and 2 and 4 ($p = 2.38 \times 10\text{-}3$). Age-stratified analysis showed lower SPEF1 expression in patients aged 21–40 compared to those aged 41–60 ($p = 6.02 \times 10\text{-}3$) and 61–80 ($p = 7.75 \times 10\text{-}5$). Patients with extreme obesity (BMI > 40) had significantly higher SPEF1 expression than those of normal weight ($p = 2.50 \times 10\text{-}3$). However, no significant differences were seen across race, gender, tumor grade, nodal metastasis, tumor histology, or TP53 mutation status. SPEF2 expression also varied with tumor stage, notably between stages 1 and 3 ($p = 1.98 \times 10\text{-}2$). It differed significantly between TP53-mutant and non-mutant groups ($p = 4.40 \times 10\text{-}2$), and among histological subtypes, with marked differences between hepatocellular carcinoma and hepato-cholangiocarcinoma ($p = 2.75 \times 10\text{-}6$), and fibrolamellar carcinoma vs. mixed type ($p = 2.57 \times 10\text{-}2$). SPEF2 expression also differed by race and gender: Caucasian vs. African American ($p = 2.08 \times 10\text{-}2$), African American vs. Asian ($p = 3.00 \times 10\text{-}3$), and male vs. female ($p = 1.77 \times 10\text{-}2$). An age-related difference was found between the 41–60 and 61–80 age groups ($p = 2.79 \times 10\text{-}2$). Kaplan-Meier analysis revealed that high SPEF1 expression was associated with poorer outcomes in overall survival (OS), relapse-free survival (RFS, $p = 0.07$), progression-free survival (PFS, $p = 4.9 \times 10\text{-}5$), and disease-specific survival (DSS, $p = 0.0012$), except for OS where the association did not reach statistical significance ($p = 0.18$).Similarly, high SPEF2 expression was significantly associated with worse outcomes in all survival metrics: OS ($p = 0.0052$), RFS ($p = 0.045$), PFS (p

= 0.00042), and DSS (p = 0.00016). Immune correlation analysis revealed SPEF1 was associated with B cells and macrophages, while SPEF2 correlated with CD4 T cells, B cells, and macrophages.

Discussion/Conclusion: In this study, we explored for the first time the potential role of SPEF1 and SPEF2, two proteins involved in the structure and function of motile cilia, unique organelles capable of autonomous movement, as biomarkers for primary HCC. Acknowledging the limitations inherent to in silico analyses, our findings indicate that both SPEF1 and SPEF2 are significantly upregulated in HCC tissues compared to adjacent non-tumorous tissues. Moreover, their expression levels are associated with key clinical characteristics, and higher expression correlates with poorer patient outcomes. These findings prompted further investigation of SPEF1 and SPEF2 expression through a stepwise approach, from in silico analysis to tissue microarray validation and clinical series evaluation. Moreover, they contribute to a deeper understanding of HCC's molecular and immunological profile, potentially guiding the development of more targeted therapeutic strategies.

21. Tumour, immune, and parenchymal cell neighbourhoods correlate with survival after intrahepatic cholangiocellular carcinoma resection

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Introduction: Intrahepatic cholangiocellular carcinoma (iCCA) originates from the bile ducts and accounts for 10–15% of primary liver cancers, with an overall 5-year survival < 20%. The poor survival is explained by a late diagnosis, limited treatment options and poor understanding of the disease-relevant pathological mechanisms involved. This project aims at better defining the cellular landscape in iCCA and identifying prognosis-related histological features that could help in patient stratification, improving patient management and identifying relevant therapeutic targets.

Methods: We assembled a cohort of 132 patients from multiple centres who underwent iCCA resection. Formalin-fixed paraffin embedded (FFPE) liver sections were subjected to a tailored, multiplex (> 15 markers) immunostaining protocol. Machine-learning based algorithms were used for digital image (> 15 mm2 tissue) segmentation and clinical data integration. Spatial clustering was performed to define cellular neighbourhoods (CN).

Results: We observed a strong accumulation of immune cells at the tumour border with macrophages particularly densely located adjacent to the tumour. CD45+ leucocytes and in particular CD20+ B cells were almost absent in the tumour area and their numbers increased towards normal liver tissue. In contrary

to our expectations and based on comprehensive analysis of single cell-resolved and clinical data, we found only weak correlations between immune cell-related characteristics and prognosis. The CN-based image segmentation successfully distinguished between tumour, parenchymal, tumour border, and portal areas, thus supporting the relevance of a multicellular-based digital image analysis. In particular, a CN that encompasses a scattered CK7+ cell distribution and altered lymphoid and myeloid cell accumulation within 300 micrometres from the tumour border was associated with a poor prognosis.

Discussion/Conclusion: Multiplexed immunohistochemistry together with advanced bioinformatics profoundly expand our horizon for disease-driving mechanism investigations. The exact cellular composition within iCCA resections is associated with prognosis, suggesting that multiplex immunostaining may be suitable to guide personalized treatment decisions after surgery.

22. Modeling the reactive cholangiocyte phenotype in cholangiopathies using human biliary organoids for evaluation of novel therapeutic compounds

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Introduction: Cholangiocytes actively participate in biliary inflammation during cholestatic disorders such as primary sclerosing cholangitis (PSC) by acquiring the so called “reactive cholangiocyte phenotype”. Multifactorial pathways involving bacterial metabolites, accumulating bile acids (BAs) or proinflammatory cytokines play significant roles in cholangiocyte activation. This study aims to (i) characterize the molecular pathways underlying cholangiocyte reactivity using human organoid cultures, (ii) explore the therapeutic effects of the novel hydrophilic, therapeutic BAs norucholic acid (norUDCA/NCA) and tetrahydroxylated BAs (THBA) on activated cholangiocytes.

Methods: Extrahepatic human cholangiocyte organoids (ECOs) were challenged either with a mixture of 10 ng/mL Lipopolysaccharide (LPS) and 100 U/L interferon-γ (IFNγ) or 50 ng/mL IL-17A and 2 ng/ml TNFa for various time periods (1–24 h). To evaluate the therapeutic potential of hydrophilic BAs, ECOs were treated with 250 µM norUDCA/NCA or 0.1 µM THBA alone, or in combination to the inflammatory trigger. Gene expression profiles of inflammatory mediators (Ccl2, Cxcl2, Cxcl10, Ccl20, IL-8) and transcription factors (EGR-1, NFκB1/2, REL, RORγT) were analyzed by qPCR.

Results: mRNA-expression profiling demonstrated that the combination of IL-17A and TNFα exerted synergistic effects, elevating Ccl20 128-fold, significantly above single cytokine (7-fold IL-17a; 21.1-fold TNFα) treatments ($p < 0.0001$). Co-treatment with 0.1 µM THBA significantly attenuated the IL-17A/TNFα-mediated inflammatory response, reducing Ccl2 (by 23%, $p = 0.013$), Cxcl2 (60%, $p = 0.015$) IL-8 (53%, $p = 0.039$) and Ccl20 (40%, $p = 0.027$) expression. NCA also demonstrated anti-inflammatory effects, decreasing Ccl2 (22%, $p = 0.015$), and

Cxcl2 (45%, p = 0.05). LPS/IFNγ stimulation induced pro-inflammatory chemokine expression in ECOs (5-fold Cxcl2 [p = 0.005], 12.3-fold Ccl2 [p = 0.003], and 764.9-fold Cxcl10 [p = 0.0008]). Co-treatment with 0.1 µM THBA demonstrated anti-inflammatory effects by reducing Ccl2 (p = 0.0019) and Cxcl2 (p = 0.0198) back to near-baseline levels and Cxcl10 by about 50% (p = 0.001).

Discussion: The BAs THBA & NCA can ameliorate the reactive cholangiocyte phenotype induced by LPS/IFNγ and IL-17A/TNFα, arguing for potentially therapeutic effects in cholestatic liver diseases such as PSC.

23. Dynamics in portal hypertension after recompensation in alcohol-related cirrhosis and role of non-invasive tests

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Introduction: Sustained alcohol abstinence can enable hepatic recompensation in patients with decompensated alcohol-related cirrhosis. However, dynamics in portal hypertension after recompensation and the applicability of non-invasive tests (NITs) in this setting remain unclear.

Methods: This study included 29 patients with recompensated alcohol-related cirrhosis who underwent a same-day hepatic venous pressure gradient (HVPG) and NIT assessment at the Vienna General Hospital. Recompensation was defined according to Baveno VII criteria as resolution of ascites and hepatic encephalopathy (off-therapy), absence of variceal bleeding, and restoration of hepatic function with abstinence. Nineteen patients had paired HVPG/NIT measurements in a decompensated state and after recompensation.

Results: At a median 4.1 months after recompensation, HVPG was 11 (8–17) mmHg, and clinically significant portal hypertension (CSPH) resolved in 41% of patients. HVPG decreased significantly after recompensation compared with the decompensated stage (median -44%; p < 0.001), accompanied by ameliorated biomarkers of systemic inflammation, fibrogenesis and hyperdynamic circulation. Liver stiffness measurements (LSM) decreased by 54% (p < 0.001) after recompensation, correlated with changes in HVPG (rho = 0.55; p = 0.022) and accurately diagnosed CSPH persistence (AUROC 0.892). LSM ≥ 25 kPa reliably ruled-in CSPH with 100% positive predictive value/specificity (CSPH in n = 13/13), while LSM ≤ 15 kPa ruled-out CSPH with 75% negative predictive value and 88% sensitivity (CSPH in n = 2/8). Platelet count (median -7%; p = 0.895) and spleen size (median -2%; p = 0.255) remained unchanged after recompensation, with AUROCs for CSPH of 0.554 and 0.696. The AUROC of spleen stiffness (SSM) for CSPH was 0.857. Von Willebrand factor (vWF) antigen decreased by 37% after recompensation (p < 0.001) with an AUROC for CSPH of 0.726.

Discussion/Conclusion: HVPG decreases significantly after recompensation in alcohol-related cirrhosis, and CSPH may resolve in a considerable proportion of patients. LSM, SSM and vWF maintained their high discriminative ability for non-invasive CSPH detection in recompensated cirrhosis, while platelet count and spleen size had limited value.

24. Molecular and transcriptomic insights into the role of adipose triglyceride lipase (ATGL) in liver fibrogenesis and portal hypertension

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Introduction: Adipose triglyceride lipase (ATGL) is the key lipase hydrolysing intracellular triglycerides to glycerol and free fatty acids (FFA) and thereby regulates hepatic energy balance, and cellular crosstalk. However, the role of ATGL-mediated lipolysis as potential disease modulator in liver fibrosis and resulting portal hypertension remains to be characterized.

Methods: We generated hepatocyte- specific ATGL knockout (Pnpla2fl/flAlb-Cre+) mice and controls (Pnpla2fl/flAlb-Cre-) and subjected them to a choline-deficient, aminoacid-defined high-fat diet (CDAHFD) or a matched control diet for 12 weeks to induce metabolic-associated steatohepatitis and liver fibrosis. Upon endpoint, portal pressure was measured invasively prior to organ harvest. Fibrosis severity was assessed by serum biochemistry and histology, whereas the liver immunophenotype was profiled using flow cytometry. A sub-cohort of mice (n = 4/group) underwent liver perfusion for hepatocyte, cholangiocyte and non-parenchymal cell isolation. After cell pooling and fixation, scRNA-seq using the 10x ChromiumFlex platform was performed.

Results: Targeted ATGL-KO under CDAHFD resulted in hepatic lipid loading, a pronounced increase in liver-to-bodyweight ratio [7.25% ± 0.37 vs. 13.59% ± 0.64; $p < 0.0001$] and reduced serum FFA levels [0.52 mmol/L ± 0.04 vs. 0.39 mmol/L ± 0.03; $p = 0.018$]. Moreover, disrupted lipolysis exacerbated fibrosis with an increased collagen proportionate area [2.17% ± 0.31 vs. 4.35% ± 0.55; $p = 0.002$] elevated portal pressure [6.64 mmHg ± 0.24 vs. 7.63 mmHg ± 0.30; $p = 0.028$] as well as an increase in spleen-to-bodyweight ratio [0.47% ± 0.03 vs. 0.56% ± 0.19; $p = 0.02$] and serum AST levels [279.3 U/L ± 22.9 vs. 429.3 U/L ± 35.3; $p = 0.0002$]. The hepatic immune cell composition remained unaffected by hepatocyte ATGL-KO in progressive fibrosis. The generated scRNA-seq dataset revealed high-quality transcriptomes across all hepatic compartments, allowing detailed insights into all hepatic cellular compartments.

Discussion/Conclusion: Our data supports a previously established crucial role for ATGL in hepatic fibrogenesis and portal hypertension. Moreover, ATGL activity

critically determines the fibrotic and portal hypertensive disease phenotype. Providing the first scRNAseq dataset on hepatic ATGL-KO, subsequent in-depth analysis will bridge an important gap in the knowledge of endogenous lipolysis in liver disease.

25. Therapeutic implication of probiotics in liver diseases

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Introduction: It is widely accepted that metabolic dysfunction-associated steatotic liver disease (MASLD) is multi-factorial and insufficiently understood condition, frequently believed to be a part of metabolic syndrome with both incidence and prevalence rising globally. The role of pro- and anti-inflammatory cytokines in pathogenesis of MASLD is generally well established, but growing evidence suggests the important role of gut microbiota and its dysbiosis in the pathogenesis of MASLD, including the cytokines-related pathways. Alterations in gut microbiota composition, dysregulated gut permeability, translocation of pro-inflammatory factors trigger liver inflammatory and fibrosis, exacerbate hepatic inflammation; dysbiosis is capable of disrupting the gut-liver axis, an important phenomenon, which regulates barrier, metabolic, and immune functions of the digestive tract and liver. However, influence of diet and dietary interventions including probiotics in MASLD remains unclear and confusing. Recent reviews have identified intestinal microbiome changes associated with MASLD, which may pave the way for new potential therapeutic strategies targeting gut dysbiosis in MASLD. Therefore, we hypothesized that different probiotic compositions may have different impact not only on intestinal microbiota but also significant influence on immunity and inflammation in MASLD, which may support raining concept of its use for therapeutic purposes.

Methods: Sixty patients with verified MASLD participated in the study (42 men and 18 women, mean age 57.9 ± 4.8 yrs). All patients were randomly divided into the following groups: 1st group included data of all patients before treatment, 2nd group – 23 patients after standard unmodified treatment (EASL/EASD/EASO, 2024), 3rd group – 17 patients after additional treatment with oral probiotic (composition of the Bifidobacterium longum and Enterococcus faecium), 4th group – 20 patients after additional treatment with another oral probiotic mix (Bacillus subtilis and Bacillus licheniformis). Control group included 17 practically healthy subjects. For research purpose pro- and anti-inflammatory cytokines transforming growth factor beta (TGF-β), tumour necrosis factor alpha (TNF-α) and IL-1β were typified (ELISA) before and after 60 days of treatment in all groups.

Results: Both IL-1β and TNF-α levels before treatment were almost twice higher than in practically healthy subjects; TGF-β level was generally 2.8 times higher than in control. IL-1β (pg/ml) levels were 92.1 ± 2.8 (1st group, $p < 0.001$); 70.9 ± 3.5 (2nd group, $p < 0.001$, $p1 < 0.05$); 65.6 ± 4.2 (3rd group, $p < 0.001$, $p1 < 0.05$);

72.2 ± 3.7 (4th group, p < 0.001, p1 < 0.05); 50.7 ± 3.6 (control, P value compared to control; P1 compared to the 1st group data). TNF-α (pg/ml) levels were 86.1 ± 2.2 (1st group, p < 0.001); 71.7 ± 3.5 (2nd group, p < 0.001, p1 < 0.05); 83.3 ± 3.5 (3rd group, p < 0.001, p2 < 0.05 compared to the data of the 2nd group); 93.7 ± 4.2 (4th group, p < 0.001, p2 < 0.05), and 46.3 ± 4.3 (control). TGF-β: 150.4 ± 5.0 (1st group, p < 0.001); 142.1 ± 7.4 (2nd group, p < 0.001); 72.0 ± 3.9 (3rd group, p < 0.001, p1 < 0.05, p2 < 0.05); 63.5 ± 4.1 (4th group, p1 < 0.05, p2 < 0.05), and 53.1 ± 3.6 control. In 2nd group IL-1β and TNF-α levels decreased 22.9% and 16.8% accordingly, with still higher values compared to control group's results. TGF-β level did not statistically differ in the 2nd group after the standard treatment. Probiotic administration in 3rd group caused IL-1β level decrease by 28.7%, TGF-β level reduced 2.1-fold with regard to 1st group, but all data was still higher than in control group – 29.4%, 35.6%, accordingly, especially TNF-α level – 79,9%. Probiotic administration in the fourth group caused IL-1β level reduction by 21.6%, TGF-β level decreased 2.4 times and did not differ reliably from the control group; TNF-α level became certainly higher, comparatively to second and control groups.

Discussion/Conclusion: MASLD and standard therapy causes significant lowering of the IL-1β and TNF-α levels concentration without certain influence on TGF-β level. However, the oral probiotic administration leads to the statistically reliable reduction of the IL-1β and TGF-β levels, with non-significant changes of the TNF-α concentration. The idea of different pre-, eu- and probiotic compositions study in MASLD and other liver diseases looks promising.

26. Progressive fibrosis in human MASLD is associated with spatially linked transcriptomic signatures of metabolic reprogramming and senescence

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Introduction: Granular detail about the location and nature of liver cell interactions and the metabolic, inflammatory and fibrogenic pathways driving progressive fibrosis in metabolic dysfunction-associated steatotic liver disease (MASLD) is needed to deliver novel therapeutic targets.

Methods: We generated Visium spatial transcriptomic data from 33 human liver biopsies across the spectrum of MASLD. Gene expression data were overlaid with histological annotations to integrate spatial molecular and histopathological insights to interrogate disease progression. Differential gene expression and pathway, cellular deconvolution and ligand-receptor interaction analyses were conducted for each annotated anatomical category, with specific protein expression validated using CODEX spatial proteomics and immunohistochemistry staining.

Results: Unsupervised clustering based on gene expression data classified the annotated spots into 2 main clusters enriched for fibro-inflammatory vs. parenchymal regions. Transcriptomic cellular deconvolution aligned well with manually annotated histopathological features. Fibrotic regions were enriched for genes involved in extracellular matrix/receptor interactions and inflammatory pathways, underscoring known pathological mechanisms. We also identified immunoglobulin gene induction in late-stage fibrosis, which was spatially associated with a senescence signature, as has previously been reported in aging tissues. Dynamic changes in metabolic gene expression from early to late fibrosis were observed, suggesting MASLD progression is accompanied by a decline in normal liver metabolic function and reprogramming of metabolic fuel utilisation from oxidative to glycolytic metabolism, which may be both a cause and a consequence of senescence.

Discussion/Conclusion: Taken together, our data highlight the complex crosstalk between metabolic perturbations and inflammation underpinning fibrosis progression in MASLD.

27. Role of early antibiotic use and household animal exposure in PSC: Biochemical and microbiota perspectives

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Introduction: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease marked by progressive inflammation and fibrosis of intra- and extrahepatic bile ducts. Although its etiology remains unclear, increasing evidence implicates gut microbiota dysbiosis as a central factor in disease pathogenesis. Altered microbial composition compromises gut barrier function, facilitating translocation of microbial components such as lipopolysaccharides, which activate hepatic immune responses via Toll-like and NOD-like receptors, sustaining biliary inflammation and fibrosis. In contrast, early-life exposure to household pets may promote microbial diversity and immune tolerance, potentially reducing PSC risk, in line with the hygiene hypothesis. Ursodeoxycholic acid (UDCA) is commonly used in the treatment of PSC to improve bile flow and reduce liver enzyme levels. It is typically administered at moderate doses (13–15 mg/kg/day).

Methods: In this case-control study, 37 patients with PSC and 30 with metabolic dysfunction-associated steatotic liver disease (MASLD) were recruited from the Clinic for Gastroenterohepatology, University Clinical Center of Serbia (October 2024–February 2025). Epidemiological data were obtained via a structured questionnaire. Clinical, biochemical, immunologic, and radiographic parameters were analyzed. All PSC patients were receiving UDCA therapy (13–15 mg/kg/day).

Results: Inflammatory bowel disease (IBD) was present in 73% of PSC patients. Antibiotic use in the first two years of life was significantly associated with PSC (p

= 0.005; OR = 8.36). Conversely, early-life contact with animals had a protective effect (p = 0.036). PSC patients also exhibited elevated alkaline phosphatase (ALP) (p = 0.002) and reduced albumin (p = 0.023) compared to controls.

Discussion/Conclusion: Early antibiotic exposure may increase PSC risk, while contact with household animals appears protective, likely through effects on gut microbiota. Distinct biochemical profiles, including elevated ALP and reduced albumin, further characterize PSC. These findings support the role of early environmental factors and gut–liver axis interactions in disease pathogenesis and underscore the need for further investigation into microbiota-targeted prevention and therapy.

28. A UK based District Hospital Retrospective Audit evaluating the role of post-operative colloid and crystalloid infusions in preventing post-ERCP pancreatitis

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Introduction: Post-ERCP pancreatitis (PEP) is a well-recognised complication of endoscopic retrograde cholangiopancreatography and carries a significant clinical burden. Incidence rates of up to 5% have been reported, with a subset developing severe or fatal pancreatitis. Various strategies have been explored to mitigate this risk, including post-operative intravenous fluid administration. However, the comparative effectiveness of colloid versus crystalloid solutions and the role of infusion duration remain unclear.

Methods: A retrospective audit was conducted in a UK District General Hospital between September 2022 and July 2023. Data from 199 ERCP procedures were analysed after excluding 10 cases due to failed intubation or biliary cannulation. Patients were grouped according to the post-procedure infusion prescribed by two different operators: Operator A (predominantly crystalloid) and Operator B (predominantly colloid). Infusion duration was recorded as either 2 hours or more than 2 hours. Demographic data, procedure urgency, need for pre-cut sphincterotomy, and post-procedure pancreatitis incidence were collected. Statistical analysis was performed using the Student's t-test for numerical data and the Chi-square test for categorical data, with significance set at $p < 0.05$.

Results: Of the 199 patients, 99 were treated by Operator A and 100 by Operator B. The overall incidence of PEP was 3.03% in the Gelofusin group and 4.00% in the normal saline group. Infusion durations were comparable across both groups. Statistical analysis showed no significant association between the type of fluid and PEP incidence (p = 0.703), nor between age and PEP (p = 0.401). Infusion duration also showed no significant effect.

Discussion/Conclusion: The incidence of PEP in this study aligns with published standards by the European Society of Gastrointestinal Endoscopy (ESGE) and supports the safety of ERCP practice in the unit. No significant difference in PEP incidence was found between Gelofusin and normal saline, nor between different

infusion durations. This supports our practice in opting for a cheaper infusion solution and reduced post-operative observation period. Larger, prospective studies are needed to better clarify the impact of post-ERCP hydration strategies.

29. Postbiotics reduce the hepatic fat content in MASLD patients

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Introduction: The aim of this study was to evaluate the short-term efficacy of postbiotics on hepatic fat content measured by basic serum parameters, including biochemical markers of steatosis according to the new EASL-EASD-EASO criteria, as well as by magnetic resonance imaging (MRI)-estimated proton density fat fraction (PDFF) and ultrasound in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

Methods: A total of 39 patients met the inclusion criteria. The screening period lasted 1 week. The next 3 months consisted of a treatment period, during which participants received orally twice daily 1 capsule of postbiotics/metabiotics of the probiotic strain L. rhamnosus DV – NRRLB-68023 at a dose of 100 mg or placebo capsules.

The outcomes were changes in biochemical markers of steatosis: fatty liver index (FLI), hepatic steatosis index (HSI), and triglyceride-to-glucose index (TyG), change of hepatic fat content measured by MRI-PDFF in %, ultrasound attenuation coefficient (ACM), and hepatorenal index (HRI).

Results: We observed a significant decrease in liver fat content after treatment period, which was confirmed by laboratory indicators – FLI (from 78.23 ± 14.47 to 71.95 ± 21.62; p = 0.016), HSI (from 44.55 ± 4.44 to 42.75 ± 4.98; p = 0.003), TyG (from 4.92 ± 0.39 to 4.84 ± 0.34; p = 0.081) and the results of instrumental examinations – MRI-PDFF (from 15.02 ± 2.33 to 10.84 ± 2.63%; p = 0.045), ACM (from 2.63 ± 0.07 to 2.54 ± 0.06 dB/cm; p = 0.043) and HRI (from 1.33 ± 0.05 to 1.24 ± 0.04; p = 0.011) respectively.

Discussion/Conclusion: This study demonstrated that postbiotic supplementation can reduce hepatic fat content in MASLD patients. These results support the potential of postbiotics as a safe and effective treatment for MASLD.

30. Hepatobiliary manifestations and complications in patients with IBD

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Introduction: Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). As it is a multifactorial disease involving immune dysregulation, organs other than the gastrointestinal tract may be affected. These extraintestinal manifestations (EIM) and complications can seriously affect the patient's prognosis, cause morbidity, and reduce quality of life. While a typical hepatobiliary extraintestinal manifestation is the primary sclerosing cholangitis (PSC), there are a number of other diseases arising from various anatomical or metabolic abnor-

malities caused by IBD or its treatment. These include cholelithiasis (CL) fatty liver disease (NAFLD), primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), hepatic granulomatosis, and hepatic amyloidosis.

Methods: In the years 2005–2024, 1228 patients with IBD (average age of 58.1 years), 688 with UC, 540 with CD were monitored at the Internal Clinic II. In the monitored group, liver tests were performed once a year in all patients and sonographic examination of the hepatobiliary tract was performed every two years. In case of abnormal findings, other laboratory and imaging methods were used to diagnose liver disease. After the diagnosis was established, patients were monitored according to current recommendations.

Results: During the twenty-year period, the following diagnoses were made in the above-mentioned group: NAFLD in 421 cases (34.2%), CL in 198 cases (16.1%), PSC in 41 cases (3.3%), AIH in 11 cases (0.9%), PBC in 6 cases (0.5%). We did not observe hepatic granulomatosis or hepatic amyloidosis in the group.

Discussion/Conclusion: Hepatobiliary manifestations are relatively common in IBD patients and therefore they should always be considered. Their early diagnosis and appropriate follow-up of the patients lead to early detection of these complications that can often be more serious than the course of IBD itself. The timely and effective therapy requires a multidisciplinary approach.

31. Serum sterols as markers of liver injury in primary biliary cholangitis (PBC)

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Introduction: Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease. While ursodeoxycholic acid (UDCA) remains the standard first-line therapy, PBC presents with considerable clinical heterogeneity. Previously we showed that patients with gallstone disease are characterised by altered cholesterol synthesis and absorption (Krawczyk et al. Hepatology 2012 and Liver Int. 2022). In this study, we analyse the association between PBC cholestatic phenotypes and serum sterol profiles, as markers of altered cholesterol metabolism and the progression of the disease.

Methods: A total of 219 patients with PBC (age 22–83 years; 201 women; 87 with liver cirrhosis) were included in the study and were followed-up for a median of 5 (range, 1–9) years. During this time 37 patients developed de novo cirrhosis, and 54 underwent liver transplantation. Biochemical response to UDCA therapy was evaluated at inclusion based on the Barcelona criteria. Serum sterol concentrations were quantified using gas chromatography coupled with mass spectrometry (GC/MS). We applied Machine Learning Classification (MLC) models to assess the utility of sterols as biomarkers of PBC progression and outcomes.

Results: Patients with liver cirrhosis demonstrated significantly (all $p < 0.05$) higher serum levels of phytosterols (i.e., sitosterol, campestanol and sitostanol), compared to patients without cirrhosis. In contrast, levels of cholesterol precursors, such as lathosterol and dehydrolanosterol, were significantly (all $p < 0.05$) lower in patients with cirrhosis. We detected significant positive correlations between phytosterols and markers of cholestasis (ALP and GGT). Patients without cirrhosis exhibited significantly higher phytosterol-to-cholesterol ratios (i.e. stigmasterol:cholesterol, sitostanol:cholesterol and brassicasterol:cholesterol, all $p < 0.001$). Multivariate logistic regression analyses identified gender and plant sterols as independent predictors of response to UDCA: sitosterol and campesterol were associated with treatment response (OR = 0.57, 95% CI: 0.34–0.96, $p = 0.036$ and OR = 0.57, 95% CI: 0.36–0.92, $p = 0.021$, respectively). MLC models using non-collinear sterol features accurately predicted cirrhosis progression (median AUC 0.94) and liver transplantation (median AUC 0.80).

Discussion/Conclusion: Serum sterol profiles reflect alterations in cholesterol homeostasis associated with disease progression in PBC. These findings support the need for further studies to clarify the mechanistic role of cholesterol metabolism in cholestatic liver diseases.

32. Flt3L-based in situ vaccination induces infiltration and activation of CD8+ T cells in fibrotic and metabolic hepatocellular carcinoma models

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Introduction: Hepatocellular carcinoma (HCC) is one of the most lethal cancers worldwide with increasing incidence, often arising from chronic liver diseases such as fibrosis or metabolic dysfunction-associated steatotic liver disease. Patients are frequently diagnosed at advanced stages, when local therapies are no longer feasible and systemic treatment options offer limited benefit. The immunosuppressive tumor microenvironment (TME) of HCC is a major contributor to treatment resistance and presents a promising target for immunotherapy.

In situ vaccination (ISV) with FMS-like tyrosine kinase 3 ligand (Flt3L) aims to turn the immunosuppressive TME of HCC into an inflamed one by recruiting and activating conventional dendritic cells (cDC1), thereby enhancing tumor antigen presentation and inducing a cytotoxic CD8 T cell response.

Methods: This study evaluated the impact of ISV with Flt3L on T cell infiltration patterns and underlying liver disease in murine steatosis-driven and fibrosis-driven HCC models, which reflect clinical heterogeneity. Histological staining (trichrome, Oil Red O) was used to assess fibrosis and steatosis. Multiplex immunofluorescence staining was performed to analyze CD4 T cells, regulatory T cells (Treg), and CD8 T cells, as well as their activation status based on PD-1 expression.

Results: ISV did not exacerbate fibrosis or steatosis in the respective models. While CD4 T cells and Treg remained largely unaffected, CD8 T cells were dramat-

ically expanded in both tumor and non-tumor regions, with a notable increase in activated intratumoral CD8PD-1 T cells. This effect was especially pronounced in mice with hepatic steatosis.

Discussion/Conclusion: These findings suggest that ISV with Flt3L can induce a targeted immune response and increase CD8 T cell infiltration in HCC without exacerbating liver disease, making it a promising therapeutic approach for patients with advanced HCC of different etiologies.

33. Serum biomarkers of liver injury in children with paracetamol intoxication – A preliminary study

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Introduction: Paracetamol is one of the most widely used drugs, with a well-recognized efficacy and safety profile. However, its overconsumption can lead to liver failure and even death. The purpose of this study was to examine the effects of paracetamol intoxication on markers of hepatocyte injury in a pediatric population.

Methods: The prospective study included children admitted to the hospital between 2022 and 2024 for acute paracetamol poisoning. Patients were evaluated at two time points - on admission (T0) and after 24–72 hours (T1). Blood samples were collected once at T0 from 51 participants, and at both T0 and T1 from 35 participants. Serum levels of thrombospondin-1 (THBS-1), thrombospondin-2 (THBS-2) and growth differentiation factor 15 (GDF-15) were determined using enzyme-linked immunosorbent assays.

Results: There were significant differences in GDF-15 levels on admission between the study group and healthy controls ($p = 0.007$). At T0, THBS-1 and THBS-2 were positively correlated with aspartate aminotransferase activities, while GDF-15 showed positive correlations with total bilirubin, creatinine, and the international normalized ratio. After 24–72 hours, significant changes in activities of alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and concentrations of creatinine and THBS-1 were observed. In receiver operating characteristic analysis, GDF-15 at T0 allowed for the differentiation of patients with and without paracetamol poising (AUC = 0.701, $p = 0.001$). In a linear regression model, after adjusting for age, sex, body mass index, serum paracetamol concentration, and total paracetamol intake, only the amount of ingested drug was a significant predictor of GDF-15 concentration on admission ($\beta = 0.583$, $p = 0.001$).

Discussion/Conclusion: Our results show that paracetamol intoxication in children is associated with changes in both conventional and novel markers of liver injury, with GDF-15 in particular potentially reflecting the severity of toxic exposure.

34. Can gremlin-1 be considered a non-invasive serum marker of liver steatosis and fibrosis in children with metabolic dysfunction-associated steatotic liver disease?

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver pathology in children, which is associated with excessive accumulation of visceral adipose tissue. Adipose tissue is an endocrine organ that produces numerous adipokines. One of the new adipokines is gremlin-1. Few studies suggest its association with liver pathology in patients with MASLD. The aim of our study was to evaluate the serum level of gremlin-1 in children with MASLD.

Methods: The prospective study included a group of 109 obese/overweight children (aged 7–18 years). MASLD was diagnosed according to the criteria developed by numerous scientific societies (JPGN 2024). Children with concomitant viral, autoimmune, metabolic, toxic liver diseases and diabetic patients were excluded. Transient elastography (CAP, LSM) was performed to asses liver steatosis and fibrosis. Simple surrogate biochemical-anthropometric indexes of liver steatosis (HSI, FLI, LAP) and fibrosis (APRI) were calculated according to mathematical formulas. Gremlin-1 was measured by ELISA. The control group consisted of healthy children with normal body weight.

Results: We found that children with excessive body weight (n = 109) and with MASLD (n = 74) had higher level of gremlin-1 compared to 30 controls (p = 0.045, p = 0.05 respectively). Patients with MASLD had significantly higher level of ALT, GGT, insulin, uric acid, value of BMI, waist circumference, CAP, LSM, HSI, FLI, LAP and APRI compared to non-hepatopatic obese patients (n = 35). The gremlin-1 level didn't differ significantly in patients with MASLD compared to non-hepatopatic children. No correlation was found between gremlin-1 and CAP and LSM on elastography and biochemical-anthropometric indices of liver steatosis and fibrosis.

Discussion/Conclusion: Higher level of gremlin-1 in overweight/obese children with MASLD confirms its role in the pathogenesis of this disease. However, lack of correlation with CAP and LSM on elastography and biochemical-anthropometric indices of liver injury suggests that gremlin-1 cannot be considered a useful non-invasive biomarker of steatosis and fibrosis in children with MASLD.

35. Efficacy of apoptosis signal-regulating kinase 1 (ASK1) inhibitor SRT-015 in liver failure and pathogen-associated molecular patterns (PAMPs)-induced disease models

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Introduction: Patients with liver cirrhosis are highly susceptible to infections and sepsis-related mortality due to impaired hepatic function, altered gut permeability and severe immune dysfunction. Immune dysregulation leads to systemic inflammation, characterized by elevated circulating cytokines (e.g., TNFα, IL-6, IL-1β), which plays a major role in the progression to acute-on-chronic liver failure (ACLF). ASK1, a redox-sensitive kinase activated by oxidative stress and PAMPs, is a key mediator of the inflammatory response, regulating cytokine production and cell death. This study aimed to evaluate the efficacy of SRT-015, a new investigational drug inhibiting ASK1, in rodent models of acute liver failure (ALF) and sepsis, as well as in human blood immune cells stimulated with PAMPs.

Methods: ALF was induced in mice by intraperitoneal injection of acetaminophen (APAP, 300 mg/kg) or a combination of D-galactosamine (GalN, 700 mg/kg) and lipopolysaccharide (LPS, 25 µg/kg), followed by intravenous administration of SRT-015 (0.75–1 mg/kg) 30–60 min post-induction. Sepsis was induced by cecal ligation and puncture (CLP), followed by oral SRT-015 administration (10 mg/kg, BID) for 6 days. Additionally, fresh whole blood from healthy volunteers was stimulated with PAMPs (TLR2, TLR4, or TLR5 agonists) for 4 hours, with or without SRT-015 (2–15 µM) incubation.

Results: In APAP mice, SRT-015 reduced ALT (825 vs. 3046 U/L, $p = 0.01$) and bilirubin (0.03 vs. 0.12 mg/dL, $p = 0.003$). In GalN/LPS mice, SRT-015 lowered ALT (1959 vs. 4618 U/L, $p = 0.03$), TNFα (7.0 vs. 15.8 pg/mL, $p = 0.02$), and IL-6 (264 vs. 812 pg/mL, $p = 0.006$). In CLP mice, SRT-015 improved 7-day survival (65% vs. 15%, $p = 0.004$) as compared to placebo. Finally, SRT-015 dose-dependently reduced TLR-induced cytokine release, including TNFα (up to -62%), IL-6 (up to -33%), and IL-1β (up to -91%) in human blood cells.

Discussion/Conclusion: These results demonstrate that SRT-015 alleviates liver injury and counteracts systemic inflammation and sepsis in preclinical models, supporting its therapeutic potential in ACLF.

36. Establishment of human intrahepatic and extrahepatic biliary organoids as a model for cholestatic liver diseases

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Introduction: Chronic cholestatic liver diseases (CLD) such as primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and other fibrosing cholangiopathies are characterized by the destruction of bile duct epithelial cells, the cholangiocytes. The underlying pathogenic mechanisms of these cholestatic diseases, however, are still incompletely understood. Established therapeutic options are therefore limited and may halt progression but cannot cure the disease. Therefore, it is mandatory to better understand the pathogenesis of chronic cholangiopathies and we urgently need novel preclinical model systems to unravel the molecular mechanism.

So far, our insight into the pathogenesis of CLD and the underlying mechanism that protect cholangiocytes against bile salt-, cytokine- induced toxicity and how

failure of these mechanism contributes to CLD remains limited due to missing in vitro systems that recapitulate biliary tree function.

In this project, we aim to characterize the role of regulated cell death in the biliary epithelium in the context of dysregulated bile acid metabolism, bacterial exposure and its potential contribution in to the onset and progression of CLD.

CLD are associated with inflammatory bowel disease (IBD).

Due to impaired barrier function, bacteria and microbial particles can access the systemic circulation and enter the gut-liver-axis. This can lead to further inflammation and cell death. In order to proof the impact of microbial particels on biliary epithelial cell homeostasis, we exposed biliary organoids to outer membrane vesicles (OMV) isolated from E. coli.

Discussion/Conclusion: In summary we were able to establish a novel preclinical in vitro model system to better understand the pathogenesis of CLD and to investigate gut-liver communication in vitro.

37. Toll-like receptor (TLR)5 mediates deleterious effects of lipid injury and fibrogenic responses in metabolic dysfunction-associated steatohepatitis (MASH) and clinical outcomes

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Introduction: Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive inflammatory liver condition characterised by hepatocyte lipotoxicity, infiltration of inflammatory and immune cells and stellate cell activation leading to fibrosis. The gastrointestinal tract is an important source of inflammatory mediators which activate hepatic Toll-like receptor (TLR) signalling. Stool from patients with MASH have increased proportions of flagellated bacteria (Firmicutes and Proteobacteria phyla). Flagellin is a direct agonist of TLR5 and we test the hypothesis that activation of TLR5 mediates the pathology observed in MASH and fibrosis.

Methods: Plasma flagellin and stool Flic gene load (shotgun metagenomics sequencing) were measured in samples from 69 MASLD patients and 11 controls. Lipotoxicity was modelled in vitro using oleic (1 mM) and palmitic (0.5 mM) acid in primary hepatocytes and stellate (LX2) cells. Hepatic TLR5 mRNA expression and linked healthcare outcomes were extracted from SteatoSITE 1 ($n = 668$ MASLD, 39 controls).

Results: Compared to controls, plasma flagellin is increased in advanced MASH fibrosis (F3–4) but not earlier stages of disease (538.3 vs. 745.8 pg/ml, $p < 0.01$) or in hepatitis B virus infection) which normalises in samples taken median 83 days following bariatric surgery ($n = 20$, $p < 0.01$). Stool Flic gene expression and hepatic TLR5 (but not TLR2 or TLR4) expression are increased in MASH, along with markers of intestinal permeability (FABP2, D-lactate). In vitro, TLR5 inhibition does not alter lipid accumulation (BODIPY) or beta oxidation, but attenuates lipotoxicity-mediated IL8 protein expression ($p < 0.01$, vs. control) in primary

hepatocytes. TLR5 is not expressed in stellate cells and flagellin does not activate LX2 cells (nor do toxic lipids). However, lipid-injured hepatocyte-conditioned media induces 1.4-fold increase in TGFb1 gene expression in LX2 cells compared to control ($p = 0.01$), and Th1 cell differentiation; both of which are reduced through TLR5 inhibition on the hepatocytes prior to media transfer (1.6-fold, $p < 0.01$). High hepatic TLR5 expression is associated with greater hepatic decompensation events and all-cause mortality.

Discussion/Conclusion: TLR5 mediates key pathology in the progression of human MASH and fibrosis, reverses following bariatric surgery and is associated with mechanisms of lipid-mediated inflammation and stellate cell activation. This pathway has potential as a novel therapeutic target in MASH fibrosis.

38. Outcomes of treatment with atezolizumab and bevacizumab in hepatocellular carcinoma patients with and without liver cirrhosis: A single-center retrospective analysis

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Introduction: Hepatocellular carcinoma is the fifth most common cancer worldwide and ranks among the leading causes of cancer-related mortality. The introduction of immunotherapy, particularly the combination of atezolizumab and bevacizumab, has improved clinical outcomes in patients with advanced HCC. This study aimed to assess the efficacy and safety of this therapy in patients with and without liver cirrhosis in a real-world setting.

Methods: We retrospectively analyzed 16 patients with HCC treated with atezolizumab and bevacizumab during 2024 at a tertiary center. Data collected included demographics, treatment duration, adverse events, disease progression and survival. Subgroup analysis compared outcomes between patients with and without cirrhosis.

Results: During the observation period, the median duration of therapy was 10.5 months. Treatment-related adverse events occurred in 25% of patients. Disease progression leading to initiation of second-line therapy – such as sorafenib – was observed in another 25% of patients. Death occurred in 12.5% of patients during follow-up. One patient discontinued treatment due to complete remission. The majority of patients tolerated therapy well, and severe adverse events were infrequent.

No statistically significant difference was found in median therapy duration between patients with and without cirrhosis (5 vs. 12 months, $p = 0.304$), though duration was numerically shorter in cirrhotic patients. Likewise, complication rates did not differ significantly between groups ($p = 0.245$), with all complications occurring in non-cirrhotic patients. These results suggest a possible clinical relevance of shorter therapy duration in cirrhosis, warranting further investigation with a larger sample.

Discussion/Conclusion: The combination of atezolizumab and bevacizumab appears to be an effective and well-tolerated treatment option for patients with hepatocellular carcinoma in routine clinical practice. Despite the limited sample size, these findings suggest that this therapy offers a meaningful clinical benefit in terms of disease control and treatment duration. Further studies with larger patient cohorts and longer follow-up are needed to better evaluate long-term outcomes, particularly in relation to cirrhosis status.

39. Hypothermic oxygenated and normothermic machine perfusion mitigate innate systemic and hepatic inflammation after extended criteria donation liver transplantation

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Introduction: Immune-mediated injury plays a pivotal role in the pathophysiology of ischemia-reperfusion injury (IRI) in liver transplantation. While hypothermic oxygenated machine perfusion (HOPE) and normothermic machine perfusion (NMP) offer clinical benefit, their immunological effects remain unclear. This study examined hepatic and systemic immune responses associated with static cold storage (SCS), HOPE, and NMP in the peri- and post-transplant period.

Methods: We analyzed immune responses in recipients of extended criteria donor (ECD) livers from brain-dead donors preserved with SCS (n = 11), end-ischemic HOPE (n = 24), or NMP (n = 12), as part of the HOPE-NMP randomized controlled trial (NCT04644744). Liver biopsies were obtained at organ arrival and post-implantation during early IRI. Blood samples were collected preoperatively, during reperfusion, and on postoperative days (POD) 1, 2, 3, and 7. Analyses included spectral flow cytometry, spatial multiplex immunofluorescence, cytokine profiling, cellular respiration and energetics, and mass spectrometry.

Results: Machine perfusion altered the phenotype of liver-infiltrating myeloid cells, marked by downregulation of pro-inflammatory, antigen presentation and adhesion markers. Liver neutrophil infiltration during IRI was attenuated by both HOPE and NMP. Despite unchanged monocyte counts, their inflammatory phenotype was reduced. Machine perfusion did not affect the hepatic spatial distribution of leukocytes.

Peripheral lymphocyte subsets recovered more rapidly in HOPE recipients and were associated with reduced hepatocellular injury. Myeloid and innate lymphoid cells from recipients of perfused livers showed a less inflammatory phenotype

at POD1, 2, 3, and 7. Postoperative neutrophil counts were reduced only in the HOPE group. Neutrophils exhibited a postoperative phenotypic shift towards an activated, immature profile at POD1 and POD2, and matured one-week posttransplant. Leukocyte mitochondrial respiration declined during IRI but recovered postoperatively.

Discussion/Conclusion: End-ischemic HOPE and NMP both mitigate hepatic and systemic leukocyte activation and attenuate neutrophil-driven inflammation in human ECD transplantation. Our findings highlight protective hepatic and systemic immunomodulation through machine perfusion.

40. In-situ vaccination with FtIt3L elicits immune responses against hepatocellular carcinoma and improves checkpoint blockade therapy

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Introduction: Checkpoint blockade has limited efficacy in hepatocellular carcinoma (HCC). We developed an in situ vaccine (ISV) strategy to recruit and activate classical dendritic cells type 1 (cDC1), enhancing their antigen cross-presentation to cytotoxic T lymphocytes (CTLs) and improving anti-tumor immunity.

Methods: Male C57BL/6J mice received a single injection of N-nitrosodiethylamine (DEN), followed by either repeated intraperitoneal carbon tetrachloride (CCl4) injections or Western Diet to induce orthotopic HCC with chronic liver disease. The ISV combined systemic injections of the DC growth factor Flt3 ligand (Flt3L), a Fas agonist, and adjuvants (agonistic anti-CD40 or polyIC). Combination with checkpoint inhibitors was investigated. Immune responses were characterized by spectral flow cytometry, multiplex immunofluorescence and bulk RNA sequencing of sorted intratumoral leucocytes. Tumor progression was monitored by longitudinal MRI. Intratumoral cDC1-related signatures were explored in the TCGA-HCC dataset and checkpoint-treated patients with HCC. The immune microenvironment of human HCC was investigated with multiplex immunofluorescence.

Results: Flt3L injections significantly expanded systemic and intratumoral cDC1 populations. Adjuvants induced maturation of these cDC1s, marked by increased antigen cross-presentation and co-stimulatory markers. ISV-treated mice showed activated, antigen-experienced CTLs with effector memory phenotypes, delayed tumor growth, and improved survival versus controls. Depleting CD8+ T cells or cDC1 abolished ISV efficacy. Due to high PD-1 and PD-L1 expression in the immune microenvironment, ISV was combined with checkpoint blockade. While checkpoint monotherapy was ineffective, ISV plus anti-PD1 synergistically enhanced survival. In human HCC, TCGA analysis revealed that elevated cDC1 signatures

correlated with adaptive immune gene expression and better 24-month progression-free survival, independent of tumor stage or grade. Pre- cDC1 or immune cancer cell death signatures were higher in responders to immunotherapy.

Discussion/Conclusion: Flt3L-based ISV elicits anti-tumor immunity and induces response to checkpoint blockade in previously unresponsive HCC tumors.

41. Metabolic associated steatohepatitis is a risk factor for liver injury in the chemotherapy dynamic of acute leukemia and approaches to prophylaxis

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Introduction: Chemotherapy of acute leukemia (AL) is accompanied by a high risk of cytostatic-induced liver injury.

Methods: The aim – to assess the metabolic associated steatohepatitis (MASH) in an increase of risk level of hepatotoxic reactions in AL chemotherapy dynamics.

Study involved 64 pts with newly diagnosed AL (52 – acute myeloid leukemia [AML], 12 – acute lymphoblastic leukemia [ALL]), ECOG I–II, aged 20–71 years, 28 (43.7%) women, 36 (56.3%) men. The pts were divided in 2 groups: I (n = 34) – without MASH, II (n = 30) – with MASH.

The liver function was assessed by the alanine aminotransferase (ALT), aspartate (AST) aminotransferase, alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT) activity, bilirubin, protein in the blood serum. To assess the severity of hepatotoxic reactions the CTCAE scale was used.

Results: In AL pts of group I before the start of chemotherapy functional liver state was not significantly different from healthy people. In group II there was an increase of ALT activity in 1.6 times, AST – in 1.2 times, ALP and GGT in 1.3 times compared to the norm ($p < 0.05$) and reached grade I level.

On the 56th day of treatment in 5 (14.7%) pts of group I the violation of the functional liver state was revealed, which was characterized by the increased activity of ALT in 1.6 times, AST – in 1.3, ALP – in 1.5, GGT – in 1.7 times compared to normal levels, the bilirubin and protein levels remained in the normal range, that consistent with grade I.

In group II hepatotoxicity was detected in 21 (70%), which was characterized by the increased activity of ALT and AST in 2.7 and in 2.4 times, GGT and ALP in 2.8 and 3.9 times respectively, the level of bilirubin increased in 3.2 times ($p < 0.05$), of which in 7 (23.3%) pts hepatotoxic reactions were of grade I, in 14 (46.6%) – grade II.

Discussion/Conclusion: Patients with concomitant MASH are at high risk of cytostatic-induced liver injury in the dynamics of chemotherapy, which requires the development of methods for drug prevention of hepatotoxic effects.

Thus, the appointment of the ursodeoxycholic acid on the background of induction

therapy is an optimal approach to treatment and prevention options of drug-induced liver injury, especially cholestatic and mixed types, in patients with AL and concominant MASH, can reduce the grade of the functional liver state injury.

42. Modern approaches to increase efficiency of hepatotoxic reactions prevention in patients with acute myeloid leukemia

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Introduction: Chemotherapy of acute myeloid leukemia (AML) is accompanied by the risk of secondary complications of organs and body systems. The hepatotoxic reactions develop in these patients due to a combination of the tumor influence, cytostatic medications. The issue of liver injury prevention during chemotherapy remains relevant.

Methods: The aim is to study the role of Ursodeoxycholic acid (UDCA) in the prevention of hepatotoxic reactions development during AML chemotherapy.

The study involved 32 pts with newly diagnosed AML: M0–M5 according to FAB-classification. Including 13 (40.6%) women, 19 (59.4%) men, aged 19–54 years. All pts were assigned with remission induction chemotherapy "7+3" or "5+2" for M0–2, "7+3+etoposide" or "5+2+etoposide" for M4–5. The pts were divided into groups: I (n = 18) – chemotherapy; II (n = 14) – chemotherapy and UDCA 15 mg/kg 60 days. At baseline the assessed biochemical parameters in AML pts were within normal ranges.

Results: On the 7th day of chemotherapy, hepatic test abnormalities were detected in 6 (33.3%) pts in group I, 1 (7.1%) – group II. The administration of UDCA in group II was associated with decreased risk of hepatotoxic reactions (RR = 0.13; 95% CI: 0.018–0.95; $p < 0.05$).

In group I the hepatotoxic reactions of grade I according to CTCAE were found in 5 (83.3%), grade II – in 1 (16.7%) patiens. The hepatotoxic reactions were consistent with cytolytic type in 1 (16.7%), cholestatic – in 3 (50%), mixed type – in 2 (33.3%) pts. Gamma-glutamiltransferase activity increased 2.2-fold ($p < 0.05$), alkaline phosphatase 3.3-fold compared to the primary examination ($p < 0.05$).

In group II on the 7th day of chemotherapy, 1 patient was diagnosed with cholestatic type reaction grade I.

On the 28th day, the reversible hepatotoxic reactions were recorded. In group I hepatic test abnormalities within grade I were revealed in 3 (22.2%) pts (f whom 1 (33.3%) had mixed injury, 2 (66.7%) – cholestatic. In group II all tests were within the normal range on the 28th day.

Discussion/Conclusion: Treatment with UDCA as a supportive therapy during chemotherapy in AML patients reduces the risk of hepatotoxic reactions.

43. Multiscale structural analysis reveals ferroptosis as a key mechanism of hepatocyte injury in primary sclerosing cholangitis

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Introduction: Primary sclerosing cholangitis (PSC) is a complex, progressive liver disease involving dysregulation of the bile ducts, the immune system and the microbiome. Although hepatocyte damage is central to liver failure, its underlying mechanisms in PSC remain poorly understood. Hepatocytes are highly polarized cells with a distinct intracellular organization that is not only essential for their metabolic function but also shapes the architecture of the liver. Understanding disease progression therefore requires more than insight into molecular composition – it calls for attention to alterations in morphology and spatial organization, from tissue-level structure to subcellular complexity.

Methods: Here, we apply for the first time enhanced focused ion beam – scanning electron microscopy (eFIB-SEM) on native human liver, demonstrating a multiscale imaging approach that allows to analyse liver tissue from tissue-scale topology to intracellular organelles to subcellular structures within single imaging volumes at isotropic, nanoscale resolution.

Results: Using this approach, we uncovered extensive ultrastructural alterations in hepatocytes from PSC patients. These included pronounced mitochondrial fragmentation, peroxisomal proliferation, lysosomal dysfunction, and accumulation of lipofuscin, alongside marked depletion of glycogen and lipid droplets. Together, these features point to a bile acid-induced metabolic crisis and suggest ferroptosis as a key mode of hepatocyte death. Strikingly, we were able to directly visualize ferroptotic hepatocytes within PSC liver tissue, and confirmed ferroptosis-related stress through complementary functional assays.

Discussion/Conclusion: In summary, we demonstrate how eFIB-SEM enables comprehensive, multiscale structural analysis, offering a new framework for understanding the cellular and molecular basis of human liver tissue dysfunction.

44. Real-world insights into hepatotoxicity associated with immune checkpoint inhibitors: A retrospective single-center study

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Introduction: This analysis evaluated immune-related hepatic complications in a cohort of 14 cancer patients treated with various immune checkpoint inhibitors (ICIs), including atezolizumab, pembrolizumab, nivolumab, ipilimumab, and their combinations.

Methods: A retrospective single-center study analyzing real-world data from patients treated with immune checkpoint inhibitors was conducted in 2024,

focusing on the severity and management of hepatotoxicity in relation to the type of therapy. Clinical and laboratory data were extracted from medical records, and hepatotoxicity was defined and graded according to CTCAE v5.0.

Results: Most patients presented with elevated liver enzymes, consistent with hepatocellular injury. The average AST and ALT levels were markedly elevated (mean value 314 U/L and 427 U/L, respectively), accompanied by high GGT (mean 371 U/L) and inflammatory markers (mean CRP 84 mg/L). Severity of hepatic adverse events was notable, with 50% of patients experiencing Grade 3 toxicity and one patient experiencing Grade 4. These events typically occurred within three weeks of the most recent treatment cycle. Combination regimens, particularly nivolumab-based therapies and sequential administration (e.g., ipilimumab + nivolumab followed by nivolumab monotherapy), were associated with the highest average toxicity grades. In contrast, milder events were observed in patients treated with atezolizumab + bevacizumab or ipilimumab/nivolumab administered as a single cycle.

Discussion/Conclusion: Hepatotoxicity from immune checkpoint inhibitors is common, often severe, and typically occurs early. Higher toxicity was observed with combination and sequential nivolumab-based regimens. These findings emphasize the need for vigilant monitoring, standardized management protocols, and further research to optimize safety and outcomes in patients receiving immunotherapy.

45. Non-invasive diagnostic methods for liver cirrhosis: Comparison of the performance of APRI and FIB-4 with FibroScan

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Introduction: Mongolia has a high burden of viral hepatitis, with HCV and HBV affecting 11.1% and 8.5% of the population, respectively; however, the prevalence of liver cirrhosis among these individuals remains unclear. This gap is partly due to the limited use of gold-standard diagnostic methods such as liver biopsy and elastography. This study aims to determine the correlation between FibroScan and non-invasive methods – APRI and FIB-4 – and to assess whether these scores can be used independently or in combination for evaluating liver cirrhosis.

Methods: Data from 869 individuals (414 men, mean age 52.2; 455 women, mean age 54.3) enrolled in the DETECT-HCC study who met the inclusion criteria and had no cancer diagnosis were analyzed. Hepatitis infection status was determined using quantitative HBsAg and anti-HCV tests on the HISCL-5000 analyzer. Liver cirrhosis was evaluated using FibroScan 630 Expert (Transient Elastography) (Echosens, France), the Child–Turcotte–Pugh (CTP) classification. APRI and FIB-4 scores were calculated from routine laboratory data. Statistical analyses were performed using R software.

Results: From a total of 870 participants – including 290 with liver cirrhosis, 289 with chronic hepatitis, and 290 healthy controls – the correlation between APRI and FibroScan E score was weakly positive overall (r = 0.479), while the correlation between FIB-4 and FibroScan E score was slightly stronger (r = 0.535).

When stratified by etiology, the FIB-4 score showed the strongest correlation in the non-viral group (r = 0.664) and the weakest in the HDV group (r = 0.466). Conversely, APRI showed the highest correlation in the mono-HBV group (r = 0.803) and the lowest in the HDV group (r = 0.430).

Discussion/Conclusion: In this study, the non-invasive APRI and FIB-4 scores demonstrated a weak positive correlation with FibroScan in identifying liver cirrhosis. However, among participants with HBV/HDV co-infection, the correlation was notably lower compared to other etiological groups. These findings highlight the need for further research, particularly involving combinations with other radiological methods, to improve diagnostic accuracy in this subgroup.

Keywords: APRI, FIB-4, Elastography, Fibroscan, HDV

46. Association between inflammatory markers, ferritin and C-reactive protein, and quality of life in patients with alcohol-associated cirrhosis

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Introduction: Alcohol-associated liver disease (ALD) represents one of the deadliest yet preventable consequences of excessive alcohol use. Our study was undertaken to assess the quality of life (QoL) of patients with alcohol-associated cirrhosis and explore the association between the QoL and the level of inflammation assessed by ferritin and CRP level.

Methods: A cross-sectional survey was conducted on 57 patients with alcohol-associated cirrhosis, mean age 59 ± 8 years, 46 men (80%), Child Pugh A – 36 patients (63%), B – 15 patients (26%), C – 6 patients (11%). Clinical, demographic and laboratory data were collected.

Patients were screened for alcohol use with the Alcohol Use Disorders Identification Test (AUDIT) and QoL was measured through the Chronic Liver Disease Questionnaire (CLDQ), with 6 domains: activity (AC), fatigue (FA), emotional function (EF), abdominal symptoms (AS), systemic symptoms (SS), worry (WO).

Results: Ferritin and CRP, markers of acute and chronic inflammation, tend to be higher in decompensated cirrhosis and correlate with systemic inflammation and short-term mortality. Analysis at QoL domain level showed that the fatigue domain was the most impacted (mean score 21.63 ± 9) and abdominal symptoms was the less impacted (mean score 13.93 ± 6). The results highlight that elevated CRP levels are linked to diminished quality of life, particularly through abdominal symptoms domain ($p < 0.001$). There was no evidence of a statistically significant relationship between ferritin and any of the domains.

Discussion/Conclusion: Most patients with alcohol-associated cirrhosis experience a reduced quality of life. However, quality of life scores did not differ significantly by Child-Pugh class, which may be due to symptom denial in advanced disease or to the limited sample size. Beyond the clinical classification of disease severity, our

findings highlight the need for motivational enhancement, rehabilitation counseling, and treatment of alcohol use disorder within liver disease care settings.

Notably, the negative correlations observed with CRP suggest that this biomarker may reflect not only physical illness, but also aspects of subjective well-being and mood-related symptoms, underscoring the importance of integrated psychosocial approaches in patient assessment.

47. Plectin loss disrupts mechanotransduction and attenuates hepatic stellate cell activation

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Introduction: Fibroproliferative disorders contribute to nearly 45% of all deaths and are often driven by chronic inflammation that predisposes to liver cancer and metastasis. In liver pathology, hepatic stellate cells (HSCs) are the principal effectors of fibrosis. In their quiescent state, HSCs exhibit a characteristic star-like morphology. Upon liver injury, increased tissue stiffness activates mechanosensitive signaling pathways in HSCs, promoting their transdifferentiation into myofibroblasts. These activated HSCs deposit excessive extracellular matrix (ECM), further enhancing tissue rigidity and reinforcing a pathological feedback loop.

Methods: To interfere with HSC mechanotransduction and halt fibrotic progression, we targeted plectin, a cytolinker protein essential for integrin-mediated mechanical signaling. We generated an HSC-specific plectin knockout (KO) mouse model using Cre-negative littermates as wild-type (WT) controls. Fibrotic responses were assessed in vivo using two clinically relevant models of liver injury: carbon tetrachloride (CCl_4) and thioacetamide (TAA). ECM deposition was quantified to compare fibrosis severity between genotypes. Additionally, primary HSCs from WT and KO mice were isolated at quiescent and activated stages for in vitro phenotypic analysis. To uncover affected molecular pathways, single-cell transcriptomic profiling was performed on primary HSCs.

Results: Plectin-deficient mice exhibited significantly reduced ECM deposition in both CCl_4- and TAA-induced liver injury models, alongside accelerated fibrosis resolution following toxicant withdrawal. In vitro, KO HSCs displayed impaired migration and proliferation, indicating a diminished activation phenotype. Furthermore, plectin-deficient HSCs showed fewer focal adhesions, suggesting attenuated mechanosignaling as a likely mechanism underlying their reduced activation. Single-cell transcriptomic analysis identified distinct unactivated and activated HSC clusters in UMAP space. Differential gene expression analysis revealed that KO HSCs downregulated myofibroblast-associated genes while upregulating markers of quiescence, corroborating the in vivo and in vitro findings.

Discussion/Conclusion: Our study reveals a central role for plectin in HSC mechanotransduction and fibrogenic activation. Using a preclinical model, we demonstrate that disrupting plectin function dampens fibrotic signaling and ECM accumulation, highlighting plectin as a promising therapeutic target to combat liver fibrosis and its pathological sequelae.

48. LLM-based high throughput integration of multi-source healthcare data in liver transplant recipients

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Introduction: Hepatocellular carcinoma (HCC) frequently develops in patients with chronic liver disease (CLD), yet most cases are still diagnosed at advanced stages with poor prognosis. Patients with CLD undergo regular surveillance, generating large volumes of unstructured clinical reports, potentially holding latent indications of disease progression. We evaluated the potential of large language models (LLMs) to extract structured variables from this data and apply this approach at scale in a real-world cohort of liver transplant (LT) recipients.

Methods: We conducted a multi-stage evaluation of LLM-based extraction from pre-LT records using a calibration set of radiology, pathology, and LT assessment (LTA) reports from 30 patients, evaluating four open-source LLMs. The best-performing model was applied to data from 835 patients (with > 22,000 reports) transplanted in our centre over the past decade and used to construct a per-patient longitudinal dataset summarising disease and treatment timelines.

Results: Llama 3.3 70B consistently outperformed other LLMs, achieving ≥ 90% accuracy on the majority of data extraction tasks. Timeline reconstruction demonstrated LLMs' ability to capture longitudinal information, with Llama 3.3 70B identifying 139/143 known LR lesions across the calibration set. Applied to the full LT cohort, the model automatically generated structured per-patient datasets, allowing for analysis of HCC risk factors at scale. Patients with HCC were more likely to be older, male, diabetic, smokers, and of viral aetiology (all $p < 0.05$); recurrence was linked to larger lesions and poorer differentiation, emerging as the only factor significantly associated with post-LT mortality ($p = 0.001$). Assessment of LIRADS grading revealed that LR-5 labels predicted pathology-confirmed HCC with 99% specificity and 85% sensitivity.

Discussion/Conclusion: Open-source LLMs can reliably extract prognostically-relevant data from heterogeneous clinical records, with utility for risk stratification and outcome prediction. These results support the deployment of LLM-driven pipelines for large-scale research in chronic disease populations.

49. From retina to liver: A cohort study on opportunistic screening for fibrosis in individuals with type 2 diabetes mellitus

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Introduction: Steatotic liver disease (SLD) is a global health burden, particularly among individuals with cardiometabolic risk factors, especially those with type 2 diabetes mellitus. Yet it often remains undiagnosed until complications of advanced liver disease arise. Although current recommendations advise screening

high-risk groups using non-invasive tests (NITs), these tools remain underutilised, partly due to limited awareness among healthcare providers.

Methods: We evaluated an opportunistic SLD screening strategy by incorporating vibration-controlled transient elastography (VCTE) into routine annual diabetic retinopathy assessments. The protocol included clinical examination, history-taking, and calculation of non-proprietary blood-based NITs. Individuals with liver stiffness measurement (LSM) ≥ 8.0 kPa were referred for hepatology consultation, including repeat VCTE, liver ultrasound and aetiological workup screening for viral hepatitis, autoimmune liver disease, and hemochromatosis. We analysed baseline characteristics, fibrosis predictors, and the performance of blood-based NITs.

Results: In this ongoing prospective cohort, 267 individuals have been enrolled. Among participants with valid LSM (261, 97.8%), 49 (18.8%) had LSM ≥ 8.0 kPa, including 27 (10.3%) who had LSM ≥ 12.0 kPa, suggestive of significant and advanced fibrosis, respectively. CAP ≥ 280 dB/m was observed in 147 cases (56.3%). Of the 29 who presented for hepatology consultation, 24 (82.8%) had persistently elevated LSM and among them, 6 (25.0%) demonstrated ultrasound features of cirrhosis. SLD was diagnosed in 156 individuals (59.8%) and classified as MASLD (125, 80.1%), MetALD (25, 16.0%), ALD (5, 3.2%), or miscellaneous (1, 0.6%). Of the 44 participants with LSM ≥ 8.0 kPa, 40 had available FIB-4 index values and based on current recommendations, 22 (55.0%) of them would have met referral criteria for liver elastography.

Conclusion: Integrating VCTE into diabetic retinopathy screening is feasible and can enhance detection of SLD while utilising existing workflows. This strategy identified more cases of liver fibrosis than a FIB-4 index-based algorithm, without requiring additional referrals. Further research should assess the health economic impact and integrability of this strategy.

50. Correlations between hepatic steatosis and associated comorbidities in patients with occult hepatitis B virus infection

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Introduction: Occult Hepatitis B Virus Infection (OBI) is characterized by the presence of replication-competent HBV DNA in the liver, with or without detectable levels in the blood, in the absence of hepatitis B surface antigen (HBsAg) in the serum. The relationship between OBI and metabolic liver changes, particularly hepatic steatosis (HS), remains an area of interest. Aims: This study aims to investigate the correlation between HS and OBI in patients with different comorbidities.

Methods: A total of 87 patients, assessed between 2023–2024, with HBsAg-negative, HBcAb-positive and/or HBsAb-positive, were retrospectively enrolled. Hepatic steatosis was quantified using the Controlled Attenuation Parameter

(CAP) via FibroScan, with no steatosis defined as S0 < 248 dB/m and the presence of steatosis defined as S1–S3 ≥ 248 dB/m.

Results: Patients were divided into three groups: Group A (n = 28; 32.2%) included individuals without additional pathologies; Group B (n = 39; 44.8%) included patients with immune-mediated diseases, namely rheumatoid arthritis (n = 17), psoriatic arthritis (n = 6), Crohn's disease (n = 7), and ulcerative colitis (n = 9); Group C (n = 20; 23.0%) comprised patients co-infected with hepatitis C virus (HCV). Across the study population, hepatic steatosis was identified in 51 (58.6%) patients while 36 (41.4%) had S0. The distribution of steatosis was as follows: group A – 10 (35.7%) patients, group B – 25 (64.1%) patients and group C – 16 (80%) patients. A significant association was observed between patient groups and the presence of steatosis (p = 0.006), with higher proportions in Groups B and C compared to Group A.

Discussion/Conclusion: Steatosis is common in patients with OBI, particularly in those with immune-mediated diseases or HCV co-infection. These results highlight the importance of assessing metabolic liver involvement in OBI, especially in the presence of comorbid conditions.

51. Stage-specific drivers of clinical progression in advanced chronic liver disease

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Introduction: Advanced chronic liver disease (ACLD) encompasses diverse pathophysiological mechanisms that evolve during disease progression. We analyzed the clinical course of ACLD using a multistate framework and evaluated the stage-specific prognostic relevance of biomarkers representing key pathogenic mechanisms.

Methods: In a prospective cohort of 464 ACLD patients undergoing hepatic venous pressure gradient (HVPG) measurement (2017–2021), clinical stages were categorized as compensated ACLD (cACLD), first decompensation, further decompensation/acute-on-chronic liver failure (ACLF), liver-related death (LRD), and recompensation. Stage transitions over a median follow-up of 29 months were modeled. Baseline biomarkers included markers of portal hypertension (HVPG), endothelial dysfunction (VWF), fibrogenesis (ELF), liver function (MELD, albumin, bile acids), systemic inflammation (CRP, IL-6, procalcitonin), and circulatory dysfunction (proBNP, copeptin).

Results: At 24 months, 12% of cACLD patients progressed to first decompensation. Among those with decompensated cirrhosis, 19% developed further decompensation/ACLF at 12 months, and of those with further decompensation, 33% experienced LRD. Biomarker relevance varied by stage: in cACLD, portal hypertension (HVPG), fibrogenesis (ELF), and liver function (albumin) were indicative of disease progression, shifting towards systemic inflammation (CRP) and liver function (albumin) in decompensated cirrhosis, with the additional contribution of circulatory dysfunction (copeptin) in further decompensation. Network analyses confirmed a stage-dependent shift in biomarker interconnectivity, from portal hypertension and fibrogenesis in early stages to inflammatory and circulatory drivers in advanced disease.

Discussion/Conclusion: The prognostic landscape of ACLD is dynamic, with distinct biomarker profiles dominating at different disease stages. Strategies targeting portal hypertension and liver fibrosis are most relevant in cACLD, while inflammation and circulatory dysfunction gain importance after decompensation. These insights support stage-tailored interventions and biomarker-guided personalization of care in ACLD.

52. Patient-led digital health assessment to capture key care metrics is accepted by patients with primary biliary cholangitis translating into high levels of pruritus and fatigue assessment independent of clinician input

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Introduction: Primary biliary cholangitis (PBC) is a progressive, lifelong autoimmune condition, affecting 35 per 100,000 in the UK, characterised by intrahepatic bile duct cholangitis causing chronic cholestasis and progressive fibrosis. There is no cure, with current therapies attempting to improve quality-of-life (QoL) and slow progression. International guidance is clear on targets to optimise care. A recent UK audit highlighted PBC care to be suboptimal against all guideline metrics nationally. PBC disrupts QoL by intrusive symptoms, including pruritus and fatigue, however a lack of regular assessment of these is a major deficiency of care. Validated QoL tools are useful to identify these challenges and are accepted by patients, however, are not embedded in care due to the onus being on clinicians. Empowering people with chronic conditions is important to deliver holistic care which caters to the needs of each individual and enriches clinician-patient interactions. To support this ethos, the PBC Everyday Assessment (PBC-EA) was developed to capture aspects of care important to patients. The purpose of this digital patient-led PBC assessment is to support individualised evaluation against international care standards, QoL metrics and encourage patient-centred conversations.

Methods: Adults (> 18 years) with PBC were identified retrospectively at a UK tertiary care centre (Nottingham University Hospitals NHS Trust) using clinical coding, existing specialist care databases and hospital pharmacy dispensing records between 01-May-2022 to 30-April-2024. Patients referred to the PBC second-line therapy MDT were included (n = 44). A combination of guidelines and QoL metrics informed development of a digital PBC-EA. Using a digital patient interface, PBC-EA was linked to patient appointments and delivered to a mobile device. PBC-EA was sent to patients prior to an appointment. Once completed, results from PBC-EA were immediately available in the patient's digital health record.

Results: Over the study period, a total of 129 (89%) PBC-EA requests were sent to 39 (89%) patients at an average of 3 requests per patient; 5 (11%) patients did not have access to an electronic device at home. Of these requests, PBC-EA was completed on 110 (85%) occasions (104 (95%) female, 6 (5%) male) by 35 (90%) patients with an average age of 60. PBC-EA was generally completed 12 days prior to an appointment on 106 (82%) occasions; 4 (3%) were completed during the appointment. This translated to symptomatic assessment (fatigue and pruritus) and accurate ursodeoxycholic acid dosing information for 106 (84%) appointments independent of clinician input and in a 100% of those completing PBC-EA.

Discussion/Conclusion: Patient-led digital health assessment is acceptable to PBC patients with high uptake independent of clinician input. PBC-EA empowered patients to direct the discussion of their care whilst supporting clinicians to easily review relevant individualised information to raise the standard of PBC care.

53. Effectiveness of the ursodeoxycholic acid in liver injury prevention during multiple myeloma chemotherapy

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Introduction: Modern chemotherapy of multiple myeloma (MM) can increase the remission rate, extend the relapse-free survival. Chemotherapy is accompanied by a risk of liver injury developing due to plasma cells infiltration of the liver tissue, intoxication, microcirculatory disorders, the influence of cytostatics.

Methods: Aim – to assess ursodeoxycholic acid (UDCA) role in the prevention of hepatotoxic reactions in patients with MM during chemotherapy.

The study involved 48 patients with newly diagnosed MM (IgG/κ – 17 (35.4%) pts, IgG/λ – 5 (10.4%), IgA/κ – 15 (31.2%), IgA/λ – 9 (18.8%), non-secretory MM – 2 (4.2%), of which 21 (43.7%) men, 27 (56.3%) women, mean age 64.1 ± 7.71 years. According to ISS classification, 24 (50%) pts had stage I, 18 (37.5%) – stage II, 6 (12.5%) – stage III; ECOG 0–1. Assessment was performed twice: at baseline, after 6 CT courses. The biochemical parameters were evaluated: alanine (ALT), aspartate (AST) aminotransferases, gamma-glutamyltranspeptidase (GGTP) activity, total protein level, bilirubin, urea in the blood serum. Patients received

6 bortezomib-containing chemotherapy courses randomly were divided into two groups: I (n = 22) – chemotherapy; II (n = 26) – additionally treated with UDCA 15 mg/kg within 6 chemotherapy courses. The group of practically healthy (PH) consisted of 24 persons.

Results: At baseline in patients of groups I and II, total protein was increased in 1.4 and 1.3 times ($p < 0.05$), urea – in 1.7 and 1.8 times respectively ($p < 0.05$) compared to PH.

After 6 chemotherapy courses the total protein decreased in 1.4 times in pts of group I ($p < 0.05$) and in 1.3 times in pts of group II ($p < 0.05$). Serum urea in pts of group I decreased in 1.3 times ($p > 0.05$), which was accompanied by an increased GGTP activity in 1.8 times compared with baseline ($p < 0.05$). In pts of group II liver tests were within the normal ranges. Serum urea level in pts of group II decreased in 1.8 times ($p < 0.05$) compared with baseline.

Discussion/Conclusion: UDCA during chemotherapy of MM reduces the risk of cytostatic-induced liver injury.

54. S-ademethionine potentiates hypolipidemic effect of statins in patients with metabolic dysfunction-associated steatotic liver disease with concomitant ischemic heart disease

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Introduction: Hypolipidemic therapy in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) with concomitant ischemic heart disease (IHD) continues to be a complicated problem.

Methods: The aim - to investigate the effectiveness of S-ademetionine (S-Ame) additional prescription together with the standard statin therapy in MASLD patients combined with IHD.

40 MASLD patients and concomitant IHD were examined, 23 (57.5%) men and 17 (42.5%) women, mean age 56.18 ± 7.18 years. Patients with minimal activity of MASLD were included in the clinical study and divided into two groups according to the treatment: I (n = 20) – rosuvastatin 20 mg daily 3 months; II (n = 20) – rosuvastatin 20 mg and S-AMe 1000 mg daily 3 months. The lipid profile of all patients was assessed 3 times: at baseline before treatment, after 1 month and after 3 months of treatment. The content of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) in the patients' blood serum was determined.

Results: At the initial examination, patients of groups I and II had impaired lipid metabolism: increased serum levels of TC ($p < 0.0001$), HDL-C ($p < 0.001$), LDL-C ($p < 0.0001$) and TG ($p < 0.0001$).

After 1 month of treatment, the serum TC level of group I patients 1.9-fold decreased ($p = 0.008$), HDL-C –1.2-fold ($p = 0.003$), LDL-C – 1.8-fold decreased ($p = 0.0001$) without significant changes in the TG index. The blood serum content

of TC was 1.2-fold lower (p = 0.03), HDL-C – 1.1-fold (p = 0.01), LDL-C – 1.1-fold (p = 0.04), TG – 1.3-fold (p = 0.04) lower in group II patients after 1 month of treatment.

During the examination after 3 months of treatment, the content of TG in patients of group II was 1.3-fold (p = 0.0009) lower compared to patients of group I, without a significant difference in the indicators of TC, LDL-C, HDL-C.

Discussion/Conclusion: The use of S-AMe on the background of rosuvastatin in MASLD patients with concomitant IHD potentiates the reduction of the TG level in the blood serum.

55. Transient elastography in the prediction and diagnosis of pediatric acute graft versus host disease

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Introduction: Acute Graft-versus-Host Disease (GVHD) remains a primary cause of morbidity and mortality following bone marrow transplantation. While FibroScan® has emerged as a valuable non-invasive tool for monitoring liver health, its application in the pediatric population, particularly for assessing GVHD, is not well-established. Data on its predictive and diagnostic utility in children undergoing bone marrow transplant is scarce.

This study aimed to explore the role of FibroScan as a non-invasive method for the prediction and diagnosis of acute GVHD in pediatric patients undergoing bone marrow transplantation.

Methods: We conducted a prospective cohort study involving pediatric patients undergoing bone marrow transplantation. All participants underwent pre-scheduled FibroScan measurements at baseline and at specified intervals post-transplant. These measurements, including liver stiffness (LSM) in kPa and Controlled Attenuation Parameter (CAP), were collected alongside standard liver function tests, APRI, FIB-4 and AST/ALT ratio scores and clinical outcomes. Additional data on patient background, indication for transplant, conditioning protocol, donor type, and engraftment status were also collected. Statistical analysis was performed to identify associations between these parameters and the incidence of acute GVHD.

Results: Results: Ten pediatric patients have been enrolled in the study to date. Our analysis revealed significant correlations between several non-invasive markers and the diagnosis of acute GVHD. Higher levels of gamma-glutamyl transferase (GGT) (r = 0.46), baseline (pre-transplant) CAP (r = 0.44), and total bilirubin (r = 0.35) were positively correlated with the development of acute GVHD. Conversely, higher post-transplant liver stiffness (kPa number 2, r = -0.43), lactate dehydrogenase (LDH, r = -0.43), and albumin (r = -0.42) were negatively correlated, suggesting a protective association.

Discussion/Conclusion: While post transplant FibroScan measurements do not

predict acute GVHD, as well as other non-invasive fibrosis scores, some standard biochemical markers, show considerable promise as a non-invasive tool for monitoring and risk stratification in pediatric bone marrow transplant recipients. The finding that pre-transplant CAP, representing liver steatosis, is a risk factor for GVHD ignites new insights into the role of the liver's metabolic status in GVHD pathogenesis, the relationship between metabolic and immune liver diseases, and the potential for modifying GVHD risk through pre-transplant metabolic interventions. These findings suggest that FibroScan could aid in risk stratification of acute GVHD, though further prospective studies are warranted to confirm these findings and explore the role of other metabolic parameters.

56. Metabolic dysfunction-associated steatotic liver disease, mesenteric circulation, intestinal dysbiosis and their pathogenetic linkages via angiotensin-converting enzyme and angiotensin II receptor type genes

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common liver disorder in developed countries with about 20–30% prevalence during the last decade as shown in the study using the National Health and Nutrition Examination Survey. MASLD frequently combines with other systemic and metabolic disorders (comorbidities) like obesity, diabetes (DM), arterial hypertension (AH), and others due to multiple similar pathogenesis mechanisms. Moreover, pathogenetic linkage of liver conditions and intestinal changes while having strong clinical evidence lacks genetic background explanations. Angiotensin converting enzyme (ACE) and angiotensin ii receptor type 1 (AGTR1) genes attracted our attention following recent data of these structures involvement into the coronavirus-related multiorgan injury, especially liver failure, especially keeping in mind presence of ACE. The aim of this study is to find possible connections between MASLD, intestinal dysbiosis, changes in the system of portal/mesenteric circulation, and ACE (I/D) and AGTR1 (A1166c) genes' polymorphisms.

Methods: 104 MASLD patients participated in the study: 50 (48.1%) women, and 54 (51.9%) men. Mean age – 53.2 ± 8.7. MASLD and comorbidities (AH and DM) diagnosis and management according to AASLD/ACG/AGA, ASC/ESH and ASD Guidelines, respectively. Intestinal microbiology examination included taxonomic group identification and population levels determination with 33.3% variation as dysbiosis single step deviation (dysbiosis severity grades I–III). Visceral blood circulation status evaluated by Doppler-sonography. ACE (I/D) and AGTR1 (A1166c) genes' single nucleotide polymorphisms were studied in RT-PCR.

Results: Abdominal ultrasonography showed that ischemic changes in mesenteric blood vessels were characterized by decrease of time average velocity (reliable

in D-allele carriers of ACE gene and C-allele of AGTR1 gene by 1.4–1.94 times, $p < 0.05$), increase of peak systolic and end diastolic velocity (not depending on genotypes of analysed genes by 1.5–3.05 times, $p < 0.05$) and peripheral resistance by Gosling index (2–2.35 times, $p < 0.05$). Severity of dysbiosis moderately or strongly ($r = 0.61–0.83$, $p \leq 0.04–0.001$) but positively correlated with MASLD, AH and DM severity/grade in D (ACE) and A (AGTR1) allele's carriers while changes in mesenteric blood vessels correlated with dysbiosis severity with weaker dependence on genotypes. AGTR1 gene's CC-genotype carriers had the highest risk of abdominal vessels changes.

Discussion/Conclusion: Pathogenetic linkage of liver conditions and intestinal changes has strong clinical and pathogenetic evidence. However, while genetic predisposition to MASLD is considered to be a well-established fact, the role of genetic background explaining systemic changes in MASLD patients is somehow controversial. Both ACE and AGTR1 genes' polymorphisms may have both direct influence on liver but surely determine changes of blood vessels and intestinal microbiota, influencing liver function via gut-liver axis. Following this concept, it causes respective influence on metabolic profile and intestinal metabolism with reliable correlation of dysbiosis and liver disease severity.

57.Liver injury in COVID-19: Gut-liver axis mechanisms over direct infestation

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Introduction: An exponential growth of evidences confirms that patients with coronavirus disease 2019 (COVID-19) experience multiple hepatobiliary disorders varying from acute cholecystitis to diverse degrees of liver injury. Whereas, the exact features and mechanisms of liver injury associated with COVID-19 are not fully understood, it has been also shown that the ACE 2 receptor, specific to SARS-CoV-2 virus is highly expressed in bile duct cells except alveolar epithelial cells, supporting the hypothesis of direct bile duct cells infestation via ACE 2 receptor, leading to liver biochemical parameters abnormality. Significantly smaller attention is attracted to another possible mechanism involving gut-liver axis, which is important in many other liver conditions like MASLD and MASH. The stability of the colonic microbiome is maintained by specific mechanisms of symbiosis with the host, which was formed in the process of long-term adaptation of coexistence in the form of a single ecological system. Gut microbiota changes during and after a long-term infectious process can potentially affect the hepatobiliary system, as well as liver conditions can affect the colonic microbiome. Therefore, we hypothesized that gut-liver axis universal mechanisms may be responsible for hepatic changes in COVID-19 and aimed on investigating liver-gut axis interaction in moderate and severe COVID-19 clinical course.

Methods: 197 patients with SARS-CoV2 infection and COVID-associated community-acquired pneumonia participated in the observational study. Among them 50.76% (100) were women, 49.24% (97) were men, the average age – 55.93 ± 8.75 years; 27.92% (n = 55) subjects were with moderate severity of COVID-19, 72.08% (n = 142) patients – with severe COVID-19. The control group included 48 practically healthy individuals. Biochemical examination included total bilirubin and its fractions, total protein, albumin, activity of alanine-, aspartate aminotransferases (ALT, AST), urea, creatinine with following glomerular filtration rate (GFRcr) calculation. Microbiological (bacteriological and mycological) examination of colonic content was performed for 44 patients: 20/24 patients with moderate/severe COVID-19, respectively. Keeping in mind systemic nature of COVID-19 infection, and the fact that SARS-CoV-2 uses the ACE2 receptor for entry and the transmembrane protease, serine 2 (TMPRSS2) for S protein priming, TMPRSS2, fibrinogen, D-dimer, and IL-6 were studied in ELISA.

Results: In patients with COVID-19, the cytolytic and to lesser extent mesenchymal-inflammatory syndrome development is clearly observed with a decrease in detoxification and protein-synthetic liver functions, and with following evolution of chronic kidney disease (hepato-renal syndrome), which statistically significantly depends on the COVID-19 severity (moderate vs. severe), This processes are characterized by a significant elevation of AST – 1.46–2.69 times ($p < 0.001$), a slightly lower ALT – 1.43–2.53 times ($p < 0.001$), which caused the AST/ALT growth; total protein and albumin serum level abate by 15.4–28.9% ($p < 0.05$); urea and creatinine blood concentration grew 1.67–2.2 times ($p < 0.001$) and by 18.54–29.88% ($p < 0.001$), against the background of GFRcr reduction by 29.16-36.42% ($p < 0.001$), respectively, more significant in women and in patients with severe disease course. The inflammation and liver cytolysis markers in unvaccinated COVID-19 patients were "worse" than in vaccinated patients with higher ALT and AST values in venous blood by 23.79% ($p = 0.012$) and 18.64% ($p = 0.032$), respectively.

In moderate COVID-19 patient's colonic microbiota the highest level of dominance among taxons was observed for E. coli (129.06 u.), descending levels – Bifidobacterium (19.34% less) > Lactobacillus (75.97%) > Staphylococcus (2.07 times) > E. coli Lac- (2.26 times), genus Candida (2.54 times) > E. coli with altered properties (2.67 times) > bacteria of the genus Proteus, Enterobacter, Acinobacter (7.04 times) > Klebsiella, Citrobacter (7.62 times).

In severe COVID-19, compared to patients with moderate disease, the population level of conditionally pathogenic Enterobacter and Citrobacter did not change, but the population level of Bifidobacter genus bacteria decreases by 20.67% ($p < 0.001$), Lactobacillus by 5.69% ($p < 0.05$), E. coli (with typical properties) – by 1.44%, E. coli with altered properties increases by 3.37%, E. coli Lac- by 2.85%, Proteus – by 2.69%, Klebsiella – by 5.50% ($p < 0.05$), Acinobacter – by 18.18% ($p < 0.001$) and Staphylococci – by 10% ($p < 0.01$).

In control, moderate, and severe course patients – TMPRSS2 (ng/ml) was 1.81 ± 0.12, 2.87 ± 0.18 ($p < 0.001$), 2.30 ± 0.19 ($p = 0.003$; $p1 < 0.001$); fibrinogen (g/l) was

3.52 ± 0.22, 4.84 ± 0.50 ($p < 0.001$), 5.20 ± 0.37 ($p < 0.001$); D-dimer (mg/l FEU) was 0.34 ± 0.05, 0.91 ± 0.13 ($p < 0.001$), 0.86 ± 0.10 ($p < 0.001$); IL-6 (pg/ml) 7.79 ± 1.26, 42.86 ± 7.48 ($p < 0.001$), 100.79 ± 4.96 ($p,p1 < 0.001$), respectively.

Discussion/Conclusion: Severe COVID-19 and moderate COVID-19 are accompanied by the development of hepatic cytolytic and mesenchymal inflammatory syndrome with a decrease in detoxification and protein-synthetic functions of the liver (more severe in women), which is associated with a worsening of colonic dysbiosis: an increase of conditionally pathogenic Enterobacteria population level, with a decrease of the genus Bifidobacterium and Lactobacillus bacteria, uncovering additional pathogemetic mechanism of liver injury. Vaccination against SARS-CoV2 infection is associated with less pronounced cytolytic and mesenchymal inflammatory syndromes in COVID-19.

58. Gut-liver axis in metabolic dysfunction-associated steatotic liver disease and alcoholic liver disease

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Introduction: While having multiple common pathogenetic mechanisms, as well as morphology and clinical presentations, alcoholic liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease are principally different in various terms, emphasizing not only etiology, which is obvious, but clinical course and management strategy. ALD, a disorder caused by excessive alcohol intake represents a global health care burden and is a leading cause of morbidity and mortality worldwide. ALD encompasses a broad spectrum of hepatic injuries including asymptomatic steatosis, alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Naturally, this raises questions of finding similarities and peculiarities of both conditions that may assist in their management. The human gastrointestinal lumen is the physiological habitat for a variety of microorganisms, and is the largest reservoir of microorganisms in the body. The gut microbiota is a vital component of homeostasis through not only direct involvement in nutrients and energy from ingested food, but also production of numerous metabolites that can regulate host metabolism and immunity. While the exact mechanisms of gut microbiota remain largely unexplored, it participates in vitamins and amino acid synthesis, energy providing, macromolecule catabolism, immune hemostasis, drug and toxin metabolism, and intestinal barrier preservation. It looks like chronic alcohol consumption induces both enteral malabsorption and modification of colonic microbiota, altering gut microbiota metabolism. Multiple studies showed that intestinal dysbiosis is associated with endotoxemia and propagates liver injury in both MASLD and ALD, supporting well established concept of gut-liver axis. Therefore, the objective of the study is to analyze gut microbiota changes in MASLD and ALD and find their common and distinguishing features.

Methods: 87 individuals participated in the study, with 23 ALD and 31 MASLD patients, and 33 control. Male patients prevailed in all groups (49 males, 39 females, mean age 53.12 ± 7.09). MASLD and ALD diagnoses and management according to respective EASL and AGA/ACG/AASLD Clinical Practice Guidelines. Colonic lumen and mucosal microflora studied microbiologically.

Results: Colonic flora changes significantly in all MASLD patients: substantial decrease ($P < 0.05$) or elimination of autochthonic anaerobic microorganisms and hyperproliferation of conditionally pathogenic Enterobacteriacea: E. coli, including Hly+ – 9.31 ± 0.62 lg CFU/g against 7.39 ± 0.56 lg CFU/g in control; Klebsiellae – 5.17 ± 0.40 lg CFU/g against 3.48 ± 0.49 lg CFU/g in control, Proteus – 6.23 ± 0.35 lg CFU/g, and Serratia – 5.49 ± 0.74 lg CFU/g (not found in control). Similarly, in ALD patients significant ($p < 0.01–0.05$) decrease or elimination of autochthonic anaerobic microorganisms Bifidobacteriaceae and Lactobacillus species. and a higher abundance of Proteobacteriaceae and Fusobacteriaceae was found. However, in distinction to MASLD, ALD patients also had over-representation of Gram-negative endotoxin-producing Proteobacteriaceae and a particular increase in the Clostridia, and Firmicutes genus. Furthermore, both conditions were characterized by significant growth of both frequency and population levels of Candida yeasts.

Discussion/Conclusion: Through different pathways, gut microbiota is strongly entangled in the pathogenesis and the progression of liver injury in both MASLD and ALD patients. The results of this research is supported by many other studies. However, few studies showed different data when decreased levels of Parabacteroides genus, Prevotella, and Clostridium, with higher values of Lactobacillus and Bifidobacterium were observed in ALD. Anyway, current clinical guidelines indicate alcohol abstinence, corticosteroids, or pentoxifylline, or surgical interventions as a gold standard in the management of ALD. Taking into account presented data and possible pathogenetic mechanisms involved, there is a need to identify novel therapeutic strategies focused on gut microbiota to tailor ALD management.

59. Environmental volatile organic compound exposure and MASLD-related disease: Insights from the general population and liver organoids

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Introduction: Volatile organic compound (VOC) exposure is an environmental health concern and could be considered part of the liver exposome. The associations with MASLD-related disease have not yet been explored.

Methods: This study was embedded in NHANES 2017–2020, a United States population-based cohort with data on controlled attenuation parameter (CAP), liver stiffness measurements (LSM) and urinary VOC metabolites. Participants

with viral hepatitis, excessive alcohol consumption or missing urine creatinine data were excluded. MASLD was defined as CAP ≥ 275 dB/m together with metabolic dysfunction, at-risk MASH as FAST ≥ 0.35 and increased LSM as ≥ 8 kPa. Weighted quantile sum (WQS) regression was performed to quantify and weigh the associations of the urine metabolites. Analyses were adjusted for age, sex, smoking and alcohol consumption. Additional assessment of phenylglyoxylic acid (PGA) and mandelic acid (MA) included logistic regression for the MA/PGA ratio and human liver organoid experiments.

Results: The cohort comprised 2004 participants (41.4% MASLD, 5.4% at-risk MASH, 9.7% LSM ≥ 8 kPa). Higher VOC metabolite levels were associated with increased risk of MASLD (aOR = 1.47 per quartile, 95% CI: 1.06–2.04) and at-risk MASH (aOR = 2.69 per quartile, 95% CI: 1.23–5.87), primarily driven by CEMA and HMPMA, with inverse associations driven by PGA. No significant associations were found for increased LSM. A higher MA/(MA+PGA) ratio was associated with increased risk for at-risk MASH and LSM ≥ 8 kPa. In liver organoids, PGA exposure increased lipid droplet number and size, whereas MA modestly increased droplet size only under steatotic conditions.

Discussion/Conclusion: Urinary metabolites of VOCs have distinct associations with MASLD, at-risk MASH and increased LSM in the general population. In particular CEMA and HMPMA were associated with increased risk of MASLD and at-risk MASH and have previously been associated with metabolic dysfunction traits. PGA was the primary factor associated with inverse associations with MASLD, at-risk MASH and increased LSM. Contrastingly, PGA induced steatosis in human liver organoids and the beneficial association might be contributed to poor metabolizing (e.g. by CYP2E1 variants) of styrene and ethylbenzene and intracellular PGA accumulation.

60. A novel orally bioavailable small-molecule inhibitor of the sodium taurocholate co-transporting polypeptide (NTCP) prevents HBV infection and ameliorates cholestasis in humanized mice models

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Introduction: The sodium taurocholate co-transporting polypeptide (NTCP, SLC10A1) is the main transporter of conjugated bile acids at the basolateral membrane of hepatocytes and serves as the entry receptor for the hepatitis B virus (HBV) and hepatitis delta virus (HDV). Daily injection with a peptide inhibitor of NTCP, called bulevirtide (previously Myrcludex-B), is approved in the EU for treatment of patients co-infected with HBV and HDV. Pre-clinical studies suggest

that pharmacological inhibition of hepatic bile salt uptake using bulevirtide ameliorates cholestatic liver injury. Both treatment of viral hepatitis and cholestatic liver diseases require chronic treatment, thus indicating the necessity of orally available small molecule inhibitors for this liver-specific transporter/receptor.

Methods: Based on a high-throughput screen, a comprehensive drug discovery effort was deployed to optimize small-molecule inhibitors of NTCP-mediated bile acid uptake and HBV/HDV entry, with DMPK characteristics suitable for oral dosing. Urokinase-type plasminogen activator-severe combined immunodeficiency (uPA-SCID) mice engrafted with human hepatocytes were used to determine in vivo impact on bile acid kinetics and HBV infection. Finally, in vivo effects of the lead candidate were assessed in DDC-induced cholestasis mouse models transgenic for human NTCP.

Results: We identified a novel chemical series of NTCP inhibitors with multiple compounds having single-digit nM potency for NTCP and high selectivity (> 100x) against ASBT and BSEP mediated bile salt transport. Consistently, these compounds dose-dependently reduced intracellular bile acid levels in sandwich-cultured human hepatocytes. In vitro infection studies demonstrated low nM HBV and HDV entry inhibition, similar to bulevirtide. We prioritized a lead molecule, CIM212930, with good oral bioavailability and excellent liver distribution. PK/PD experiments with CIM212930 in uPA/SCID mice with humanized livers illustrated dose-dependent and prolonged elevation of serum bile acid levels demonstrating clear target engagement and supporting a once-daily oral dosing regimen. Finally, CIM212930 completely blocked HBV infection in a humanized liver mouse model and largely reduced liver damage in DDC-induced cholestasis models.

Discussion/Conclusion: We describe novel and specific small-molecule orally bioavailable NTCP inhibitors that have the potential to treat HBV/HDV and cholestatic liver disease.

61. Therapeutic potential of CLM-022, an inhibitor of NLRP3 inflammasome-mediated pyroptosis, for acute and chronic inflammatory liver diseases

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Introduction: Inflammation and hepatocyte cell death are central elements in the pathogenesis of most chronic liver diseases ultimately leading to cirrhosis and liver failure. Inflammation involves innate immune cell activation, pro-inflammatory cytokines release and pyroptosis, a form of lytic and inflammatory regulated cell death. Pyroptosis is regulated by inflammasomes which are intracellular multiprotein complexes. These complexes respond to danger signals such as pathogen-associated molecular patterns (PAMPs), by activating caspase-1 and releasing IL-1β and IL-18. The aim of this work was to characterize the activity

of CLM-022, a small-molecule inhibitor of inflammasome priming and activation, focusing on its effect on NLRP3 signaling both in vitro and in vivo.

Methods: Human peripheral blood mononuclear cells (PBMCs) were stimulated with LPS, and NLRP3 priming was assessed by RTqPCR analysis of gene expression. To evaluate CLM-022 activity on inflammasome activation, LPS-primed THP1 macrophages were stimulated with nigericin. Cleaved-gasdermin D (GSDMD) and IL-1β release were assessed by JESS (automated Western-Blot) and HTRF. For in vivo efficacy, CLM-022 was administrated to different induced liver injury and inflammation rodent models. Systemic inflammation, liver injury and inflammasome activity were assessed by measuring circulating cytokines, ASAT, ALAT, and hepatic expression of inflammasome-related protein.

Results: CLM-022 inhibited IL-1β and NLRP3 gene expression induced by LPS in PBMCs. It also reduced cleaved-GSDMD levels and significantly inhibited IL-1β release, whether added before or after nigericin stimulation (IC50 ≈200nM). In vivo, CLM-022 alleviated systemic inflammation and improved liver injury in an endotoxemia rat model. In an acetaminophen (APAP)-induced liver injury model, CLM-022 administration conferred hepatic protection, as evidenced by reduced ASAT levels and decreased hepatic NLRP3 protein expression.

Discussion/Conclusion: In preclinical models, the investigational drug CLM-022 disrupts both the priming and activation of the NLRP3 inflammasome and thus demonstrates its therapeutic potential for the treatment of acute and chronic inflammatory liver diseases, including acute-on-chronic liver failure (ACLF).

62. Inflammation-educated macrophages drive exacerbated re-injury patterns via innate immune memory

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Introduction: Chronic liver injury results in significant immune alterations; however, the durability of these changes and their influence on the liver's response to subsequent injury remain unclear. Patients with chronic liver diseases suffer from phases of high disease activity followed by months of injury regression. Consequently, elucidating the effects of a history of liver injury on the reprogramming of hepatic immune cells and their susceptibility to subsequent insults is critically important for advancing the prevention and treatment of liver diseases.

Methods: Here we used a mouse model of chronic toxicity (CCl4) and regression of liver injury and simulated re-injury by administering a single dose of CCl4 after regression. Through the utilization of fate-mapping tools, intravital imaging, multiplex flow cytometry and multiplex immunofluorescence staining, we tracked macrophages from different origins and analyzed the alternations in their phenotype and function.

Results: We found that while liver architecture and damage completely normalized after regression, rechallenge injury resulted in significantly more

severe liver damage compared to long-term chronic injury and acute injury on an otherwise healthy liver. Moreover, we showed that chronic injury resulted in a significant influx of monocytes into the liver, with infiltration of monocyte-derived macrophages, which persisted into the regression phase. These monocyte-derived macrophages displayed a proinflammatory profile and engaged in frequent and prolonged interactions with circulating neutrophils. Furthermore, they were able to rapidly secrete cytokines such as TNF-α and IL-1β upon re-stimulation, indicating an increased pro-inflammatory potential. Depletion of all hepatic macrophages and monocyte-derived macrophages, instead of embryonic Kupffer cells, alleviated liver damage upon re-injury.

Discussion/Conclusion: Our study reveals that the history of inflammatory injury leads to a lasting alteration on the liver macrophage compartment. Inflammation-educated macrophages drive exacerbated re-injury via TNF-α. Targeting TNF-α or these memory macrophages may prevent severe liver damage upon re-injury.

63. Gallstones associated with non-alcoholic steatohepatitis (NASH) and metabolic syndrome

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Backgound: We aimed to evaluate the prevalence of non-alcoholic steatohepatitis and metabolic syndrome in patients with symptomatic gallstones undergoing laparoscopic or open cholecystectomy.

Methods: A study of 95 patients was performed. Simultaneous liver biopsies were taken during cholecystectomy between 2020 and 2022. There were no postoperative complications. Patients with significant alcohol intake, hepatitis B or C (virus-positive), autoimmune diseases, and Wilson's disease were excluded. Demographics, liver function tests, lipid profile, and ultrasound findings of patients with and without non-alcoholic steatohepatitis were compared.

Results: A total of 95 patients completed the study. The mean age was 52.15 years, and 29 patients were male and 66 female. Fifty-two patients (55%) had biopsies compatible with non-alcoholic steatohepatitis.

Discussion/Conclusion: Fifty-five percent of patients with gallbladder stones had associated non-alcoholic steatohepatitis. Awareness of this association may result in an earlier diagnosis. The high prevalence of non-alcoholic steatohepatitis in patients with gallbladder stone may justify routine liver biopsy during cholecystectomy to establish the diagnosis and stage and possibly direct therapy.

64. Setting-up a biliary niche-on-a-chip for the study of liver disease associated ductular reaction

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Introduction: Ductular reaction (DR), characterized by cholangiocyte proliferation associated with inflammation and liver fibrosis, is a common hallmark of virtually all chronic liver diseases (e.g., MASLD, PSC). Yet, DR implications in disease progression remain poorly understood. Diverse cells are involved in DR and, therefore, we aimed at developing a versatile in vitro system for cellular crosstalk investigation. We previously reported on a microfluidics-based, multicellular and primary cell-based liver-on-a-chip model mimicking the liver sinusoid microenvironment. This project now aims at refining the model and exploring its physiological relevance for DR studies.

Methods: Intrahepatic cholangiocytes were isolated from wild-type (WT) and Mdr2-deficient (KO) mice by positive selection and expanded to generate 3-dimensional organoids. Bulk RNA sequencing and immunostaining confirmed cell identity and evidenced differences associated with DR between the two lines. Mouse primary hepatocytes, cholangiocytes, hepatic stellate cells, macrophages and endothelial cells were seeded to generate a biliary niche-on-a-chip (BoC). Freshly isolated blood circulating immune cells were perfused. Protein and gene expression were assessed by multiplex immunocytochemistry and RT-qPCR, and immune cells were characterized by multispectral flow cytometry. Biliatresone was evaluated as a trigger for cholangiocyte injury and gene interference was used on macrophages.

Results: Primary liver and blood cells were successfully isolated and seeded into the BoC. Biliatresone increased inflammation-related gene expression and increased immune cell recruitment to the BoC. Transient gene expression interference in mICOs or macrophages modulated the BoC inflammatory response.

Discussion/Conclusion: The multicellular BoC is a first-of-its-kind, versatile primary cell-based model that may be used to study DR, allowing to dissect the relevance of cell-type specific molecular pathways for liver biology and pathogenesis ex vivo. Ongoing efforts aim at developing a similar BoC using primary human liver and blood cells.

65. Dynamic remodeling of the hepatic immune landscape during MASH regression

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Introduction: Liver fibrosis is the most relevant prognostic determinant in metabolic dysfunction-associated steatohepatitis (MASH) and is associated with the progression to liver cirrhosis, liver failure and hepatocellular carcinoma. While the role of immune cells, particularly liver macrophages, in the progression of MASH is increasingly well understood, their role in tissue regeneration, scar tissue remodeling and ultimately disease resolution remains less clear. To explore mechanisms underlying MASH regression, we assessed the dynamic changes and spatial organization linking immune cell organization and activation in the context of ongoing fatty liver disease and early regression.

Methods: Mice were fed either a high fat Western Diet (WD) or a choline-deficient L-amino acid-defined high fat diet (CDAA-HFD) for 16 or 8 weeks, respectively, to induce MASH. Resolution of MASH was induced by switching to standard chow diet for a minimum period of 2 weeks. Spatial and phenotypic remodeling of hepatic immune cells was assessed by multiplex immunofluorescence imaging and flow cytometry.

Results: Induction of disease regression for two weeks led to a marked improvement of liver injury, indicated by reduced liver transaminases, steatosis, and fibrosis. Both by flow cytometry and multiplex imaging, hepatic Kupffer cell (KC) numbers, which were reduced during MASH, partially recovered in regression, whereas monocytes and monocytic macrophages (MoMF) showed opposite trends. Regression-induced changes in macrophage composition were accompanied by a phenotypic switch with upregulation of scavenger receptors such as MSR1 and CD206 on MoMF. Spatial analyses using multiplex immunofluorescence revealed that these changes localized to distinct cellular neighborhoods characterized by TREM2+ macrophages in hepatic crown-like structures (i.e. hepatic lipogranuloma) and were accompanied by a spatial reorganization of CD4 and CD8 T cells, neutrophils, and activated hepatic stellate cells, as well as a partial restoration of the sinusoidal architecture.

Discussion/Conclusion: Early regression of MASH fibrosis is a highly dynamic process characterized by a phenotypic switch of macrophages with upregulation of scavenging receptors as well as spatiotemporal and phenotypic reorganization of the hepatic immune compartment.

66. In vivo CRISPR/Cas9 screens identify cell death inducing DFFA-like effector B as a therapeutic target of MASH

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH), represent a growing global health burden with increasing incidence in both Western and developing countries. MASH is a major contributor to liver fibrosis, cirrhosis, and hepatocellular carcinoma, often progressing despite lifestyle interventions. While the recent FDA approval of Resmetirom marks a significant milestone, its efficacy in advanced stages remains limited. Therefore, there is an urgent need to identify novel, effective therapeutic targets capable of halting or reversing disease progression.

To identify and functionally validate novel therapeutic regulators of MASH using an unbiased, genome-wide in vivo CRISPR/Cas9 screening approach, with a focus on the gene Cell death-inducing DFFA-like effector B (CIDEB), and to evaluate its therapeutic potential via genetic modulation in mouse and human 3D liver models.

Methods: A genome-wide CRISPR/Cas9 screen was performed in mouse models of MASH under both prophylactic and therapeutic conditions using an mTKO sgRNA library. Hits were identified based on enrichment or depletion in hepatic cell populations. Among several identified candidates, CIDEB was prioritized for downstream validation.

CIDEB was inhibited using:

- AAV8-shRNA vectors for gene knockdown in vivo.
- Lipid nanoparticle (LNP)-delivered cytosine base editors targeting CIDEB in hepatocytes via mRNA transfection.

Therapeutic efficacy was assessed in two murine MASH models. In parallel, human liver bud models (3D co-cultures of PHHs, Kupffer cells, endothelial, and stellate cells) were established and subjected to MASH-inducing conditions (FFA + LPS + TGF-β), with CIDEB targeted via LNP-CBE delivery.

Liver tissues and organoids were evaluated for steatosis, inflammation, fibrosis, hepatocyte editing efficiency, and safety.

Results: The in vivo CRISPR screen identified 12 reproducible regulators of MASH, including known genes (e.g., Xbp1, Nr1i3, Dgat2) and novel candidates such as CIDEB. CIDEB expression was significantly downregulated in livers from MASH mouse models and human patients.

- CIDEB knockdown via AAV-shRNA and base-editing via LNP significantly attenuated liver steatosis, inflammation, and fibrosis in vivo.
- In healthy mice, hepatocyte editing efficiency reached ~72.9% without toxicity; in MASH models, editing was ~31.3% but remained therapeutically effective.
- In human 3D liver buds, CIDEB editing reached ~72.5%, leading to marked reductions in lipid accumulation, inflammatory cytokines, and activation of hepatic stellate cells.

Discussion/Conclusion: This study presents the first genome-wide in vivo CRISPR screen for MASH, revealing CIDEB as a critical regulator of disease progression. Targeted inhibition of CIDEB – via either AAV-delivered shRNA or LNP-mediated base editing – effectively ameliorated MASH phenotypes in both mouse models and human 3D liver constructs. These findings support further preclinical and translational development of CIDEB-targeting therapies as a novel treatment strategy for patients with MASH.

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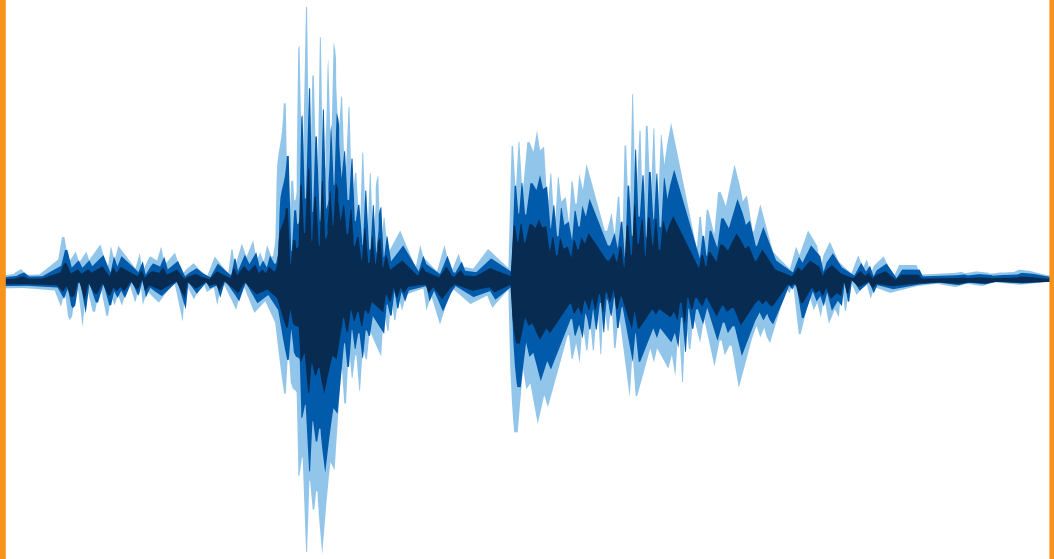

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