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SYMPOSIUM 242
ADVANCES IN HEPATOLOGY – FROM MECHANISTIC INSIGHTS TO NOVEL THERAPEUTIC CONCEPTS

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Current Status and Progress in Understanding and Management of Liver Diseases

by Dr. Michael Bonk

Liver diseases are an increasing challenge for healthcare systems worldwide – not only in Western industrialized nations. The 242nd International Symposium of the Falk Foundation e.V., "Advances in Hepatology – From Mechanistic Insights to Novel Therapeutic Concepts", held on October 24 and 25, 2025, in Berlin, focused on the molecular and cellular mechanisms of liver diseases, novel therapeutic targets and approaches, as well as innovative research methods, and diagnostic options. It also became clear to what extent liver diseases affect other organs and vice versa, underscoring the importance of considering this interplay in diagnosis and management.

News on epidemiology, pathophysiology, and therapy

In his keynote lecture opening the event, **Prof. Vlad Ratziu** (Paris, France) highlighted recent advances in hepatology. Metabolic dysfunction-associated steatotic liver disease (MASLD) is no longer solely a problem of affluent Western societies. In North Africa, the Middle East, and Asia, the number of cases is rising significantly and is increasingly affecting younger individuals. MASLD is associated with overweight, obesity, hypertension, and diabetes. Recent data specifically indicate that hypertension increases the risk of MASLD progression [1]. Conversely, liver disease itself can contribute to the development of both diabetes and hypertension [2]. One challenge in clinical practice is that, according to a data-based cluster analysis, groups of people with similar morphology can differ significantly in their risk of developing associated diseases [3]. This underscores the urgent need for effective diagnostic and therapeutic strategies, as well as risk stratification models tailored to individual risk profiles.
For example, some MASLD patients are at increased risk for cardiometabolic complications, while others are primarily at risk for liver complications. New classes of drugs, some of which are already available in hepatology and others in clinical development, are demonstrating promising effects in studies on liver fat content, liver inflammation, metabolism, and antifibrotic outcomes. According to Prof. Ratziu, personalized therapy will play an increasingly important role in the future due to the diversity of mechanisms of action. In metabolic dysfunction-associated steatohepatitis (MASH), the most promising

drug candidates include analogues or mimetics of fibroblast growth factor 21 (FGF21). Through coordinated effects on both the central nervous system (CNS) and the liver, these agents are capable of reversing MASH [4].
Many years of research into therapies for primary biliary cholangitis (PBC) are also yielding results. Among other things, there are promising studies on agonists of the peroxisome proliferator-activated receptor (PPAR) [5,6]. Additional therapeutic options are currently in development.
Prof. Ratziu also reported on advances in liver cancer therapy and transplant medicine. A recent study demonstrated that immunotherapy prior to liver transplantation offers advantages in terms of survival and safety for patients with hepatocellular carcinoma [7]. For a recent auxiliary xenotransplantation of a genetically modified pig liver in a patient with advanced liver cancer, see the report on page 3.

Role of HSCs in fibrosis and hepatocyte regulation

Hepatic stellate cells (HSCs) play a central pathogenetic role in the development and regression of liver fibrosis. However, fibrosis-independent and homeostatic functions of HSCs remain poorly understood. **Prof. Robert F. Schwabe** (New York, USA) presented a study in which genetic HSC depletion in mice was combined with conditional knockout of candidate genes to analyze fibrosis-independent functions of HSCs [8]. This study identified hepatocyte-regulating functions of HSCs that control hepatic zoning, metabolism, injury, and regeneration via R-spondin 3 (Rspo3) and subsequent activation of WNT signaling, a major regulator of liver zonation and function. It has been shown that genetic depletion of HSCs affects WNT activity and hepatocyte zonation, leading to significant changes in liver regeneration, cytochrome P450 metabolism, and liver injury. Rspo3 is an HSC-enriched modulator of WNT signaling and has been identified as responsible for these hepatocyte-regulating effects of HSCs. HSC-selective deletion of Rspo3 mimics the effects of HSC depletion on hepatocyte gene expression, zonation, liver size, regeneration, and cytochrome P450-mediated detoxification, and exacerbates alcohol-related liver disease (ALD) and MASLD. Rspo3 expression decreases with HSC activation and is inversely related to outcomes in patients with these two disease entities. Since the protective and hepatocyte-regulating functions of HSCs via Rspo3 are similar to those of the R-spondin-expressing stromal niche in other organs, Prof. Schwabe believes that these mechanisms should be integrated into current therapeutic concepts.

The development of therapies for PSC is a challenge

The cause of primary sclerosing cholangitis (PSC) remains unknown. However, PSC frequently occurs in conjunction with inflammatory bowel disease (IBD), and other autoimmune and inflammatory diseases are also more common, as **Prof. Tom Hemming Karlsen** (Oslo, Norway) explained. Elevated serum levels of alkaline phosphatase (ALP) may indicate PSC and, according to the guidelines of the European Association for the Study of the Liver (EASL), warrant further investigation [9]. According to the guidelines of the American Association for the Study of Liver Diseases (AASLD), the cholangiographic features of PSC, together with the exclusion of secondary sclerosing cholangitis, are sufficient for diagnosis, as a significant proportion of PSC patients may have normal ALP levels [10]. The course of PSC is highly variable, and critical processes often cannot be reliably tracked. While inflammation progresses to cholestasis and fibrotic processes lead to cirrhosis, disease activity as assessed by blood tests, including ALP determination, fluctuates. This affects their usefulness as surrogate endpoints in clinical trials. The severity of IBD also fluctuates during the course of PSC. Blood-based fibrosis markers show less spontaneous fluctuation than ALP and generally increase during the course of the disease, as does elastographically measured liver stiffness. Various microbial biomarkers in the intestine often remain stable over the course of the disease, and some may remain elevated after liver transplantation and influence the risk of PSC recurrence [11]. Cholestasis, bacterial cholangitis, and malignancies are common clinical events. Regular screening of PSC patients for malignancies is essential [9,10]. The limited understanding and difficult monitoring of critical disease processes make it challenging to identify relevant mechanisms of action for potential drugs.
For ursodeoxycholic acid, the study data for PSC are inconsistent, and guidelines therefore offer only limited recommendations [9,10]. Agonists of the peroxisome proliferator-activated receptor (PPAR) show efficacy at least for some endpoints [12,13]. Various immunosuppressive therapies and antibiotics have not yet led to a breakthrough and are not clearly recommended in guidelines. IBD with PSC should be treated like IBD without PSC, with the goal of mucosal healing [9-11]. Prof. Karlsen concluded by noting that various drugs are currently being investigated in studies to address the urgent need for effective treatment options.

First xenotransplantation of a pig liver into a living patient

Dr. Beicheng Sun (Hefei, China) reported on the world's first xenotransplantation of a genetically modified pig liver in a patient with advanced liver cancer [14]. Previously, only hearts and kidneys from pigs had been transplanted. Due to additional physiological incompatibilities, much more extensive genetic modifications are necessary in the liver to avoid rejection. Ten targeted genetic modifications were made to the pig liver before it was transplanted as an auxiliary organ into the patient's right liver lobe. In the first 31 days after transplantation, no hyperacute or acute rejection reactions, infections, or significant complications were observed, and the patient's liver and kidney functions remained stable. The xenotransplant produced bile acids, albumin, and coagulation factors. An early postoperative coagulation disorder, manifested by elevated D-dimer and fibrin degradation products, was treated with anticoagulants. On the 38th postoperative day, the xenotransplant had to be removed due to associated thrombotic microangiopathy (xTMA). Subsequent treatment with eculizumab and plasma exchange led to successful healing of xTMA. Repeated bleeding in the upper gastrointestinal tract ultimately led to the patient's death on day 171. Nevertheless, this case demonstrates that auxiliary xenotransplantation of a pig liver can help bridge the time until a human liver becomes available [14].

Targeted case finding in risk groups instead of mass screenings

Personalized treatment concepts first require the earliest possible identification of affected individuals, especially those with fibrosis or compensated cirrhosis. Early identification can improve treatment outcomes, delay progression, and enhance quality of life. However, **Prof. Maja Thiele** (Odense, Denmark) emphasized that there is currently no evidence supporting general, population-wide liver screening. Mass screening carries risks such as overdiagnosis, overtreatment, and psychological and somatic distress. Furthermore, there is no evidence that it can reduce liver-related morbidity and mortality [15,16]. Prof. Thiele proposed that expectations for general population screening should be scaled back. Instead, she advocated for targeted case finding in risk groups, particularly in individuals with high alcohol consumption and/or cardiometabolic risk factors such as obesity and diabetes. Her assessment was based on a study showing that 70% of individuals with these risks had steatotic liver disease, 10% had increased liver stiffness, and 2% had advanced liver fibrosis confirmed by biopsy [17]. The tests used to identify at-risk individuals should be practical, widely available, and scalable. These include, in particular, blood-based scoring systems and ultrasound-based liver elastography, a non-invasive imaging technique. National and international guidelines already recommend the appropriate use of these diagnostic tools [18–20].

Baveno VIII aims to provide answers to questions from the research agenda

To improve the management of portal hypertension, experts have been meeting every five years since 1990 in Baveno (Lake Maggiore, Italy) to discuss the available evidence, adopt definitions and consensus statements, and answer questions raised by new evidence in the years leading up to the next meeting. In patients with compensated cirrhosis or compensated advanced chronic liver disease (cACLD), clinically significant portal hypertension (CSPH) can play an important role in the progression to decompensation. As **Prof. Annalisa Berzigotti** (Bern, Switzerland) explained, the Baveno VII consensus on portal hypertension no longer focused on the management of bleeding episodes. Instead, the therapeutic goal was defined as preventing any decompensation. Ideally, simple, non-invasive tools should be used to rule out or confirm CSPH and treat patients at risk of decompensation as early as possible [21].

Prof. Berzigotti presented some of the results achieved in recent years from the Baveno VII consensus research agenda, which should lead to corresponding statements and recommendations at the Baveno VIII workshop in March 2026: Important improvements in the non-invasive risk stratification of CSPH and decompensation include non-invasive tests for CSPH in obese MASLD patients, the measurement of spleen stiffness for stratification and prognosis, alternative blood tests, reduction of ambiguous cases with unclear CSPH (liver stiffness 15–25 kPa), and assessment of CSPH in hepatocellular carcinoma (HCC). In addition, the concept of recompensation is to be validated and refined. Recommendations on non-pharmacological and pharmacological therapies that act on portal hypertension and liver fibrosis prevent (further) decompensation and promote recompensation will be updated. New findings on the optimal use of intrahepatic portosystemic shunts (e.g., risk stratification) are also expected.

Influence of the immunological environment on the development and treatment of HCC

Prof. Mathias Heikenwälder (Heidelberg, Germany) emphasized the importance of the immunological environment in liver cancer. Chronic hepatitis promotes the development of HCC through necroinflammation, i.e., the inflammatory response to necrotic cell death. Inflammation is also promoted by lifestyle factors, especially alcohol abuse and metabolic risk factors, partly due to the Western diet. Systemic factors of the gut microbiome and the immune system may also be involved.

Kinase inhibitors, VEGF receptor blockers, and immune checkpoint inhibitors are part of the standard therapy for advanced HCC. However, the effectiveness of the therapies may depend on the etiology (viral or non-viral) [22]. There are now approaches to using metformin in combination with other tumor therapies [23].

Using MASH-HCC mouse models, Prof. Heikenwälder's research group demonstrated that the combination of metformin and immune checkpoint inhibitors can control tumor growth. This occurs through the infiltration of CD8 T cells into the tumor and indirectly through the reduction of fatty acid accumulation in MASH-HCC. As yet unpublished data confirm the effectiveness of the combination, with prolonged survival in diabetic HCC patients.

Antiplatelet therapy is also established for MASH and HCC. Since glycoprotein Ibα (GPIbα) plays an important role in platelet activation, Prof. Heikenwälder's research group engineered a GPIbα antibody that has already proven effective in preclinical trials. Platelet enrichment in HCC may be associated with resistance to immunotherapy. Mouse models have shown that blocking GPIbα and thus platelet activation can improve the effectiveness of immuno-therapy.

Current and future therapies for MASH

MASLD is associated with increased cardio-renal-metabolic outcomes. According to **Dr. Arun J. Sanyal** (Richmond, USA), understanding its pathogenesis provides a rationale for targeting common disease processes and is important for developing multi-organ therapies based on mechanisms of action. The liver is a fat-accumulating organ whose fat can be broken down again if weight and visceral fat are reduced, e.g., through treatment with glucagon-like peptide-1 (GLP-1) receptor antagonists [24]. GLP-1 receptor antagonists can also promote the regression of MASH and fibrosis [25]. A new approach is the use of a selective agonist of the thyroxine β-receptor in patients with MASH and fibrosis [26]. MASH and fibrosis can also be improved by sodium-glucose-linked transporter 2 (SGLT-2) inhibitors [27].

According to Dr. Sanyal, combination therapies with new approaches that build on the benefits of currently available drugs such as GLP-1 receptor antagonists or SGLT-2 inhibitors will be important in the future. One example of this is the combination of a fibroblast growth factor-2 (FGF-2) analogue with a GLP-1 receptor antagonist, which has been shown to reduce hepatic fat fraction and fibrosis markers in patients with MASH and type 2 diabetes [28].

Interview with Prof. Frank Tacke

Bringing Innovations into Clinical Practice

Prof. Dr. Frank Tacke, Director of the Department of Hepatology and Gastroenterology at Charité, Berlin (Germany), co-organized the symposium "Advances in Hepatology". The event focused on the molecular and cellular mechanisms of liver diseases, novel therapeutic approaches, innovative research methods, and diagnostic options. We spoke with Prof. Tacke during the symposium.

What were your main objectives for the symposium "Advances in Hepatology", and what impact did it have?

Our goal was to take stock of the current landscape in hepatology: What has changed, what are the most pressing unresolved issues, and what new solutions have emerged? This includes the detection and management of liver diseases, especially in cases where there were no therapeutic options a decade ago. Today, new treatment possibilities are emerging, for example, for fatty liver diseases, now called MASLD, or for rare diseases like primary sclerosing cholangitis.

Which topics and areas of research do you currently consider particularly important?

Thanks to technological advances, we've seen an enormous increase in knowledge in basic science. Today, we can partially characterize what happens in a diseased liver at the single-cell level. The challenge lies in translation; using these findings to better understand disease mechanisms and develop new interventions. This is the beginning of a new wave of truly personalized, tailored therapy options.

How are fatty liver diseases, hepatocellular carcinoma, and liver immunology interconnected?

Any type of liver damage triggers an inflammatory response that can lead to fibrosis or cirrhosis, and it increases the risk of liver cancer. These processes are closely linked and represent different stages of disease progression. Fatty liver disease is the biggest challenge because it affects so many people.

What progress has been made in diagnostics and therapy?

Non-invasive diagnostic procedures have led to significant advances. Liver biopsies used to be essential, but today we can accurately determine the severity of liver diseases using tests like elastography or magnetic resonance imaging. In terms of therapy, the approval of the first medication for fatty liver diseases was a milestone. There have also been advances in cancer therapy, such as immunotherapies. For diseases like primary biliary cholangitis, new second-line medications are available.

How important is interdisciplinary collaboration?

It is essential. Progress in research requires collaboration among cell biologists, immunologists, data scientists, and computer scientists. In clinical practice, interdisciplinarity means close cooperation between radiologists, pathologists, surgeons, and hepatologists. Other specialties—such as nephrology, cardiology, and diabetology, where the liver isn't the primary focus—should also be more involved, as they can often contribute to diagnosing liver diseases.

What role does a symposium like this play in that context?

It's important to open up to other disciplines and, for example, consider the cardiometabolic consequences of liver diseases within hepatology, and vice versa. We also need to raise awareness in other fields that the liver is often affected, such as in cases of long-term diabetes. When it comes to liver diseases, you always have to consider their impact on the entire organism. For example, interventions that influence the microbiome can affect—or even improve—the gut-liver or gut-liver-brain axis.

Precision medicine: The presentations covered organoids, single-cell omics, multi-omics, and AI. How do you assess the potential of these technologies, especially for personalized medicine?

The potential is enormous, but we're currently using only a small part of it. Technologies like organoids, which are produced from stem cells, could allow us to analyze signaling pathways and test potential therapies. Single-cell and multi-omics, as well as AI, help us develop personalized therapies. These approaches aren't fully explored yet, but they offer great promise. They help us determine who should receive which therapy in a personalized way to achieve the best outcomes.

What would you recommend to colleagues who didn't attend the symposium?

Stay informed about the latest developments, for example, by visiting the symposium website, and try not to miss the next Falk Symposium. It was a fantastic event with leading experts who showed us where we stand, what questions remain unanswered, and how we can implement innovations in clinical practice.

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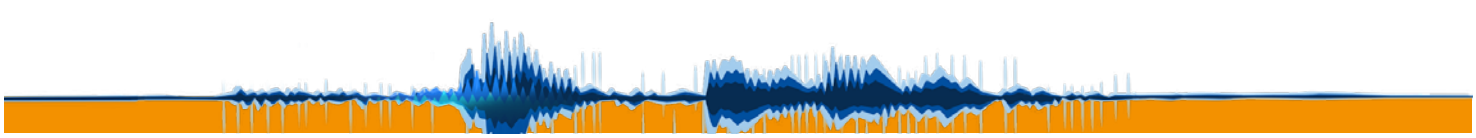

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