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SYMPOSIUM
NEXT GEN LIVER IMMUNOLOGY:
BRIDGING BASIC SCIENCE AND CLINICAL PRACTICE

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Bringing Basic Science into Clinical Practice: Advancing Everyday Care of Liver Diseases

by eickhoff kommunikation GmbH

Liver diseases are uniquely challenging and complex, largely because the liver functions as a highly specialized immunological organ. At the International Symposium of the Falk Foundation e.V., "Next Gen Liver Immunology: Bridging Basic Science and Clinical Practice," leading experts gathered in Freiburg, Germany, and addressed current challenges and recent advances in hepatic immunology, with particular focus on steatotic liver disease and hepatocellular carcinoma (HCC). By convening experts from fundamental research, translational science, and clinical practice, the symposium created a dynamic platform for cross-disciplinary dialogue at all career levels and highlighted critical gaps in the diagnosis and management of liver diseases.

Systemic inflammation: Principal mechanisms driving acute decompensated cirrhosis

Acute decompensation (AD) of liver cirrhosis describes the sudden onset of one or more of the major complications—ascites, hepatic encephalopathy, and gastrointestinal bleeding—and marks the shift from compensated to decompensated cirrhosis [1–3]. If an AD is accompanied by a rapid multi-organ failure, it is referred to as acute-on-chronic liver failure (ACLF), a distinct clinical syndrome with a high short-term mortality.

In the traditional model, acute deterioration of portal hypertension and/or hepatic function is regarded as the primary precipitating event of AD [1]. Within this framework, ascites, hepatic encephalopathy, and gastrointestinal bleeding are interpreted as separate clinical manifestations resulting from distinct mechanisms, as **Prof. Thomas Reiberger** (Vienna, Austria) recalled. In contrast, the systemic inflammation hypothesis challenges this compartmentalized view by proposing that AD represents a specific clinical entity [1–5]. According to this concept, systemic inflammation is the central and overarching driver of the progression from compensated to decompensated cirrhosis, the recurrence of AD during the clinical course of the disease, and the development of single or multiple organ system failures [1]. An abnormal gut—liver axis, causing intestinal dysbiosis, a disrupted intestinal barrier, and increased bacterial translocation, has a leading pathogenic role in systemic inflammation, as Reiberger pointed out [5].

These pathological mechanisms demonstrated in animal models have been confirmed in humans, as supported by data from the Vienna Cirrhosis Study (VICIS), a prospective observational trial conducted by Reiberger and co-workers in patients with advanced chronic liver diseases treated at the General Hospital of the Medical University of Vienna [6]. In addition to a detailed characterization of patients using epidemiologic, clinical, and laboratory data, participants are invited to optionally contribute to biobanking procedures, including collection of gastrointestinal mucosal biopsies, liver biopsies, and stool samples. Preliminary findings reported by Reiberger demonstrated an ileal barrier dysfunction that strongly correlates with the Child–Pugh score, accompanied by downregulation of tight junction proteins and antimicrobial peptides in the gut barrier, as well as increased activation of liver sinusoidal endothelial cells (LSECs).

Which diagnostic and prognostic systemic inflammation biomarkers are available for use in routine clinical practice? According to the Austrian expert, the CLIF Consortium ACLF (CLIF-C ACLF) and Acute Decompensation (CLIF-C AD) scores, developed by the European Foundation for the Study of Chronic Liver Failure (EF-CLIF), are specialized, dynamic prognostic models for patients with cirrhosis [7]. The CLIF-C AD score predicts mortality in hospitalized patients with acute decompensation (without ACLF), while the CLIF-C ACLF score focuses on patients with ACLF. Furthermore, a systematic review and meta-analysis presented by Reiberger evaluated emerging blood and urinary biomarkers for their ability to predict 90-day mortality in patients with decompensated cirrhosis [8]. The analysis demonstrated that interleukin-6 (IL-6), urinary neutrophil gelatinase-associated lipocalin (uNGAL), and copeptin may enhance risk stratification and short-term prognostic accuracy beyond the MELD (Model for End-Stage Liver Disease) score alone.

Microbiome-directed interventions: An emerging therapeutic paradigm for MASLD?

In his presentation, **Prof. Kai Markus Schneider** (Dresden, Germany) provided an in-depth analysis of the gut microbiome as a critical interface between the environment and the host [9–11], and examined its pivotal role in the pathophysiology and progression of metabolic dysfunction-associated steatotic liver disease (MASLD), the world's most common liver disease with continuously rising incidence [9].

The liver receives approximately two thirds of its blood supply via the portal vein and is therefore continuously exposed to products of microbial metabolism as well as microbial components, as Schneider noted [9]. The intestine and the liver interact through tightly interconnected, bidirectional pathways involving the biliary tract, the portal vein, and the systemic circulation. The liver, in turn, signals back to the gut by releasing bile acids and other bioactive mediators into the biliary system and the bloodstream.

Based on this crosstalk, commonly referred to as the gut—liver axis, the liver plays a central protective role by shielding the host from bacterial translocation and systemic infections through the reticuloendothelial system [9]. While dietary nutrients are absorbed and metabolized, microbial components and toxins must be efficiently cleared to prevent their entry into the systemic circulation and the development of systemic infection.

Schneider explained that MASLD involves a complex interplay of diet, the gut—liver axis, and genetics [9–11]. Unfavorable dietary patterns can disrupt the gut microbiome, typically resulting in reduced microbial diversity and decreased production of protective metabolites. Collectively, these alterations can promote low-grade intestinal inflammation, compromise epithelial barrier integrity, and facilitate increased translocation of microbial components and metabolites into the liver, inducing inflammatory responses within the hepatic parenchyma. The resulting inflammation can subsequently reshape the composition and diversity of the gut microbiome. This bidirectional interplay establishes a self-perpetuating cycle in which intestinal dysbiosis further amplifies liver inflammation and metabolic imbalance, ultimately driving MASLD progression (Fig. 1).

In addition, a recent study presented by Schneider showed that the systemic loss of *Transmembrane 6 Superfamily Member 2* (TM6SF2), a gene highly expressed in both the liver and intestine, promotes severe steatohepatitis, independent of dietary fat content [12]. Furthermore, recent studies strongly suggest that periodontitis and MASLD are linked through a bidirectional relationship, with periodontitis acting as a driver of gut microbiota dysbiosis that exacerbates MASLD [13].

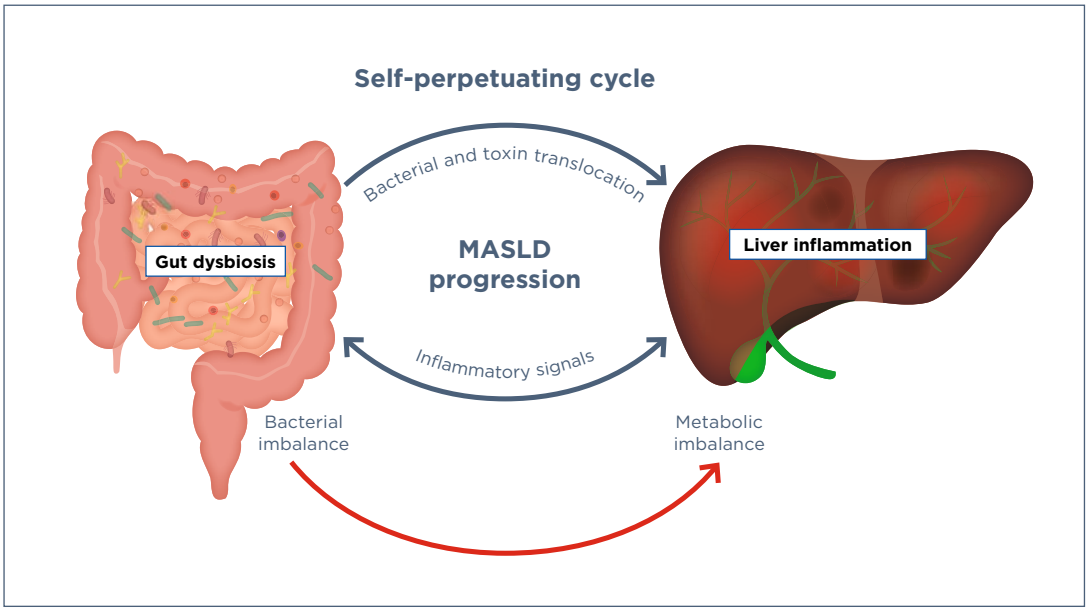

Fig. 1: Bidirectional interaction between the gut microbiome and the liver in the pathophysiology of MASLD [adapted from 9–11]

This deeper mechanistic understanding of gut–liver crosstalk may pave the way for innovative therapies to restore systemic metabolic homeostasis. Schneider emphasized that a substantial proportion of effective therapies for steatotic liver disease appear to act, at least partially, through alterations of the gut microbiome. He highlighted metformin as a representative example, explaining that in treatment-naive patients with type 2 diabetes, the drug induces measurable shifts in microbial composition, which may contribute to its clinical benefits [14].

Broad, non-specific strategies designed to correct microbial imbalance such as prebiotics, probiotics, and fecal microbiota transplantation (FMT) have been explored as therapeutic options. Nevertheless, accumulating data reveal substantial interindividual differences in response to prebiotic interventions, explaining why one-stop-shop microbiome strategies often fail. As Schneider emphasized in conclusion, these findings underscore the need for microbiome-based precision medicine approaches tailored to patients with MASLD [15].

Immunotherapy for HCC: Present strategies and emerging perspectives

Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer and ranks as the sixth most frequently diagnosed malignancy worldwide [16]. Over the past several years, growing insight into the immunogenic nature of HCC has fundamentally transformed the treatment landscape for advanced disease. According to **Prof. Matthias Pinter** (Vienna, Austria), combination regimens containing immune checkpoint inhibitors (ICIs), specifically atezolizumab plus bevacizumab and tremelimumab plus durvalumab, supported by the positive data of the IMbrave 150 and HIMALAYA studies [17, 18], are currently endorsed by guidelines as the standard first-line treatment for patients with advanced HCC [19, 20].

The favorable outcomes achieved with ICIs in advanced HCC prompted their investigation in earlier disease stages, including patients with potentially resectable early- and intermediate-stage tumors. However, as outlined by Pinter, several randomized phase 3 trials evaluating adjuvant ICI strategies such as KEYNOTE-937 and IMbrave050 have not shown a meaningful clinical benefit [21, 22]. Consequently, current guidelines do not endorse systemic therapy in the adjuvant setting, even for individuals considered to be at elevated risk of recurrence [19, 20].

As Pinter further explained, a rational next step would be to investigate neoadjuvant strategies that introduce immunotherapy while the tumor and its associated antigens are still present [23] (Fig. 2). This approach may induce a stronger immune response than adjuvant treatment, where the tumor and its antigens have already been removed. This concept has previously been shown to be more effective than adjuvant treatment alone in melanoma [24], and its validity in HCC is further supported by recently published data from the CARES-009 study presented by Pinter [25].

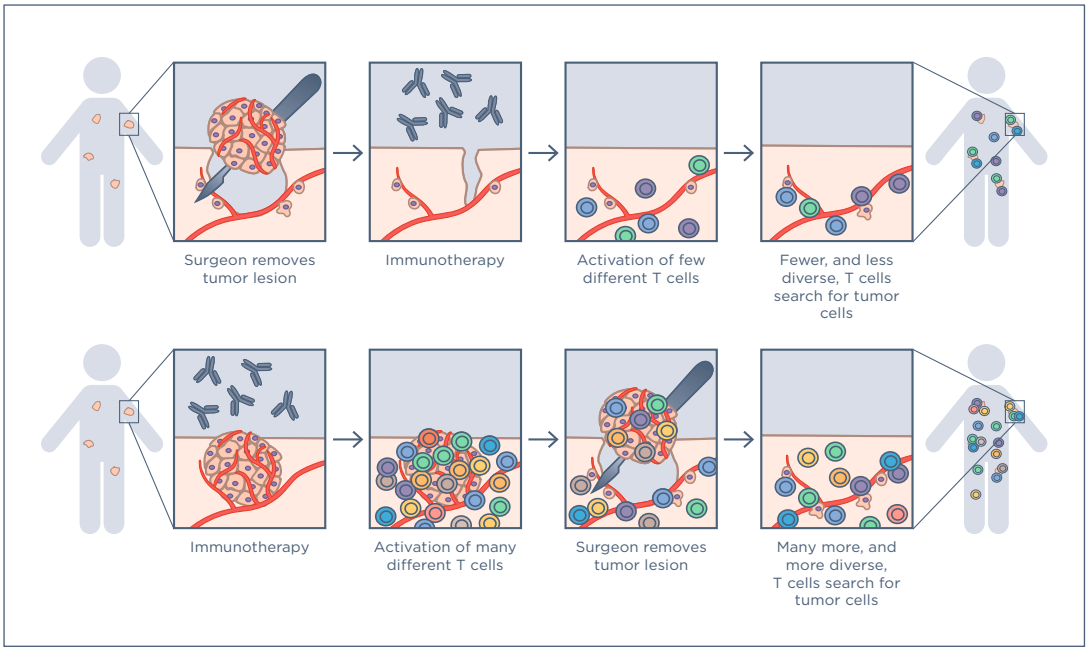

Fig. 2: Neoadjuvant versus adjuvant immunotherapy [adapted from 23]

Finally, the expert turned to emerging treatment options for patients with intermediate-stage HCC where locoregional therapies, in particular transarterial chemoembolization (TACE), represent the standard of care. With the advent of effective cancer immunotherapy, it has also been investigated whether combining ICIs with TACE could enhance the immune reaction and be a more effective therapeutic approach [26]. Among dual-combination strategies, TACE plus ICIs have been widely studied and have shown encouraging efficacy and an acceptable safety profile. For instance, the phase 3 EMERALD-1 study (TACE + durvalumab + bevacizumab) demonstrated a significant improvement in progression-free survival (PFS; primary endpoint) compared with TACE alone (p=0.032) [27]. Similarly, the LEAP-012 study showed a significant PFS benefit with TACE + lenvatinib + pembrolizumab compared to TACE alone (p=0.0002) [28]. However, as no significant improvement in overall survival (OS) was observed—the endpoint, which Pinter regarded as most critical—he concluded that this strategy is unlikely to become the standard of care for patients with intermediate-stage HCC in the foreseeable future.

Spatial immunotypes strongly correlate with ICI response

While ICIs have significantly advanced the treatment of HCC and outperform tyrosine kinase inhibitors (TKI), objective response rates are still limited to 20%–30% [29]. As a result, most patients derive little or no benefit from currently available ICI-based therapies, and determinants of the response to ICI in HCC remain poorly understood, as emphasized by **Prof. Bertram Bengsch** (Freiburg, Germany).

Accordingly, it continues to be unclear which patients are most likely to respond to immunotherapy and how ICI treatment outcomes are influenced by cellular interactions within the tumor immune microenvironment (TME), particularly in highly heterogeneous cancers such as HCC [29–31]. A more detailed characterization of the HCC immune architecture is anticipated to facilitate the development of clinically useful biomarkers that can guide and refine immunotherapy. Recent studies have identified different subsets of PD-1 (programmed death-1)-expressing $CD8^+$ T cells within the HCC TME that vary in their functional characteristics and are associated with distinct clinical outcomes [29–31]. These findings suggest that PD-1–positive $CD8^+$ tissue-resident memory T cells (TRM), rather than exhausted $CD8^+$ T cells (TEX), may play a central role in mediating favorable responses to therapy.

Consequently, Bengsch and colleagues proposed that examining the spatial distribution of immune cells within the TME may uncover mechanisms of immune evasion and aid in predicting response to ICI therapy. These analyses have been made possible by novel methodological approaches, such as highly multiplexed imaging mass cytometry (IMC), which enables precise characterization of tumor and immune cell populations using single-

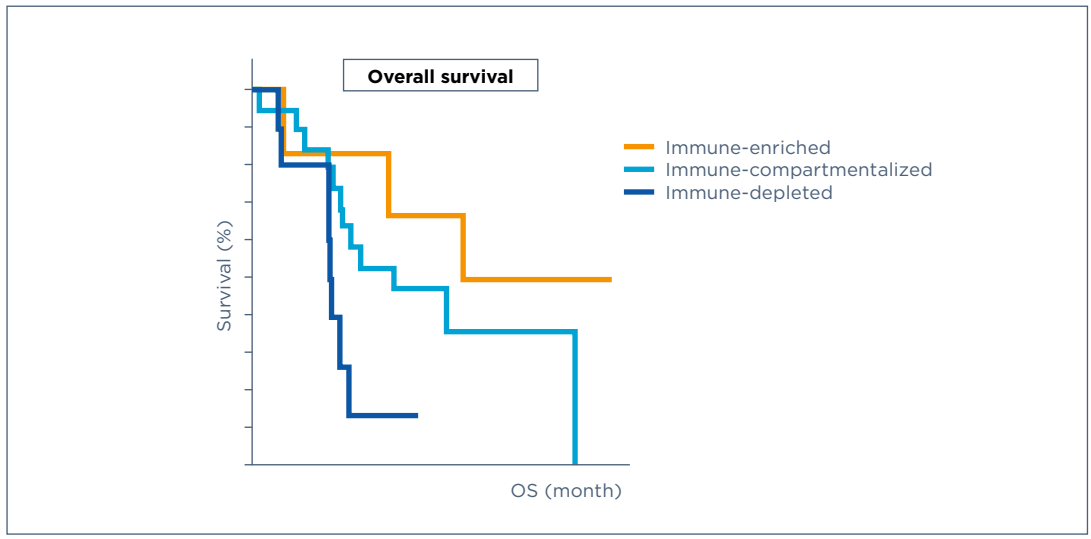

Fig. 3: Spatial immunotypes of HCC and their association with ICI response [adapted from 29, 31]

cell proteomics while preserving spatial information to dissect tumor–immune ecosystems. Using the IMC technology, three major HCC immunotypes (immune-depleted, immune-compartmentalized, and immune-enriched) were defined and validated as prognostic in an independent cohort with the enriched immunotype associated with the longest survival after ICI therapy (Fig. 3) [29–30].

Because stratifying patients based on detailed tumor–immune architecture requires high-dimensional single-cell analyses and complex immune cell network profiling, this approach may not be feasible in resource-limited settings. To address this limitation, Bengsch and colleagues developed a simplified classification based on $CD8^+$ T-cell infiltration into the tumor and stromal versus parenchymal distribution, facilitating broader clinical implementation by identifying patients that could be prioritized for ICI therapies [31].

Is this strategy potentially practice-changing and ready for routine clinical use? Bengsch answered both questions with a clear “yes”. He explained that a recent evaluation of the Freiburg cohort demonstrated that the simplified analysis of $CD8^+$ T-cell infiltration can be easily integrated into routine pathological workflows for HCC, and the classification can typically be issued within approximately one week of the biopsy, making it available in time for tumor board discussions. However, the predictive role of such biomarkers requires further evaluation in prospective studies and the main challenge to broader adoption continues to be the limited availability of sufficient tissue specimens.

Interview with Prof. Robert Thimme

Next-generation liver immunology: From bench to bedside

Prof. Robert Thimme, Head of the Department of Gastroenterology, Hepatology, Endocrinology, and Infectious Diseases (Medicine II) at the University of Freiburg Medical Center, Germany, was the scientific organizer of the symposium "Next-Generation Liver Immunology: Bridging Basic Science and Clinical Practice." We spoke with Prof. Thimme during the event.

Prof. Thimme, why is the understanding of liver immunology so crucial for the pathology of liver diseases and their treatment and what distinguishes liver diseases from other conditions?

A symposium about liver immunology is important and highly relevant for several reasons. First, the liver itself is an organ with a highly specialized immunology. A similarly clear immunotolerant and immunosuppressive role, as observed in the liver, has not been described for other organs. Second, many liver diseases are fundamentally driven by immune mechanisms. Third, current and emerging therapies are specifically designed to modulate immune responses. Taken together, these aspects clearly illustrate why organizing a scientific meeting like this is so important.

In which of the indications addressed during the symposium—hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, or HCC—do you currently see the greatest progress or the most promising developments?

That's difficult to say as we are currently seeing major advances in several areas of hepatology. For example, in autoimmune hepatitis we now have more options for immunosuppressive therapy. The clinical problem of hepatitis C has essentially been resolved with the advent of direct-acting antiviral therapies; however, we need to diagnose those unaware of their infection. In hepatitis B and hepatitis D, we are currently testing new antiviral therapies. Also, new disease-specific therapies for primary sclerosing cholangitis (PSC) are approaching regulatory approval, and for MASLD, the first specific therapy to prevent fibrosis progression has recently been approved.

Are there any specific developments your team in Freiburg is involved in?

Our work focuses extensively on the immunobiology and immune responses in viral hepatitis and HCC, particularly on the mechanisms underlying T cell dysfunction. A major emphasis is on the fundamental question of why the immune response fails in these diseases. We have also developed a novel spatial immune classification that may facilitate the prediction of immunotherapy outcomes and guide the development of immunotype-directed treatment strategies in patients with HCC.

In the area of liver cirrhosis, we have achieved significant advances, for example through work on the transjugular intrahepatic portosystemic shunt (TIPS) which was developed here in Freiburg, and the Freiburg index of post-TIPS survival (FIPS) score. In addition, we are actively involved in numerous clinical trials, including studies in PSC and MASLD.

How important is interdisciplinary collaboration for the development of new therapies?

This is of central importance. As was evident from the presentations at this symposium, it is crucial that basic scientists and clinicians jointly develop research questions such as those discussed today. Immunologists, in this context, are uncovering entirely new aspects of the liver and its role in immunobiology and disease pathogenesis.

Addressing these questions requires a broad range of disciplines coming together around the liver as an organ. This is precisely the strength of this meeting and of the German Association for the Study of the Liver (GASL): We actively foster collaboration across different scientific and clinical disciplines.

What do you hope participants will take away from the symposium?

The key message is that the liver remains one of the most remarkable and fascinating organs in the human body. Few fields in medicine have witnessed such rapid and far-reaching progress, with major breakthroughs extending from basic mechanistic research to innovative therapies that are already transforming patient care. If I were a young physician embarking on a career today, hepatology would undoubtedly still be my first choice.

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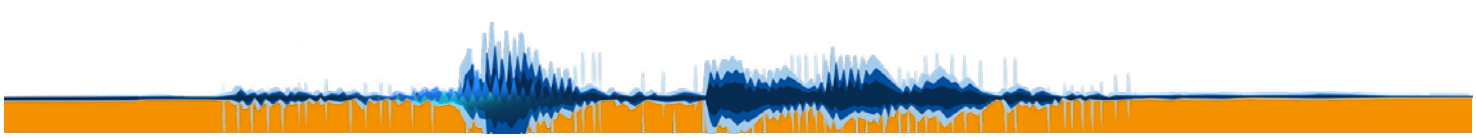
Robert Thimme (Freiburg, Germany)



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