



Interviews

EMJ spoke with three leading voices in hepatology, exploring the evolution of liver disease research and care. Frank Tacke discusses advances in immune-mediated liver disease and personalised therapies, while Nancy Reau reflects on progress from antiviral treatments to expanding transplant frontiers. Massimo Pinzani highlights the impact of translational science, from liver fibrosis research to regenerative medicine. Together, the interviews showcase major advances in hepatology and the continuing importance of collaboration and patient-centred research in driving the field forward.

Featuring: Frank Tacke, Nancy Reau, and Massimo Pinzani



Frank Tacke

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“**CAR-T cells targeting activated hepatic stellate cells, the principal matrix-producing cells in liver fibrosis, have shown very promising results in preclinical models**”

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Q1 Your research has consistently focused on immune-mediated mechanisms in liver disease. How has our understanding of hepatic inflammation evolved in recent years, and what implications does this have for clinical management?

The field of liver research has benefited enormously from technological breakthroughs. We now have access to single-cell sequencing technologies, spatial transcriptomics at single-cell resolution, and advanced proteomic analyses. These tools have allowed us to understand inflammatory processes in the liver in far greater detail.

We can now identify the different cell types involved, how they communicate with one another and with parenchymal liver cells, and how distinct ‘flavours’ of inflammation emerge. Importantly, we have come to appreciate that while inflammation drives fibrosis

and hepatocyte injury, it also plays a crucial role in orchestrating tissue repair. Once the injurious stimulus ceases, inflammatory cells such as macrophages can promote regeneration and coordinate repair mechanisms.

So, inflammation has become a much more complex concept. We now better understand the balance between pro- and anti-inflammatory mechanisms in the injured liver, and how these pathways interact dynamically rather than acting in a purely detrimental way.

In terms of clinical management, the biggest therapeutic breakthroughs so far, particularly in steatotic liver disease, have focused more on modulating hepatic metabolism and metabolic injury rather than directly targeting inflammation. Many of the drugs currently entering clinical practice primarily influence metabolic pathways in hepatocytes and

their crosstalk with inflammatory cells, rather than suppressing inflammation per se.

However, with the growing body of knowledge around inflammatory pathways, I believe we are in a strong position to develop therapies that more directly modulate inflammation and fibrosis. We are not quite there yet, but the data and technologies are in place to help close this translational gap.

Q2 You work at the interface between basic science and clinical hepatology. Where do you see the biggest challenges in translating mechanistic discoveries into effective treatments for patients?

One of the major challenges is patient heterogeneity. In clinical practice, patients are affected by numerous factors: comorbidities, concomitant medications, genetic background, and environmental influences. These variables shape disease trajectory in complex ways.

In contrast, experimental models often rely on a limited number of animals or highly controlled cellular systems, where pathways are more clearly defined. In real life, however, we see overlapping conditions and far greater biological variability. The idea that a single treatment will

markedly reduce fibrosis or liver inflammation across a broad patient population is probably unrealistic.

We observe this in clinical trials, where efficacy often does not exceed placebo by large margins. Many confounding factors influence disease progression, and some clinical trial endpoints, such as histological improvement over a relatively short timeframe, are very demanding. It is possible that we have promising drug candidates, but they may not demonstrate sufficient efficacy across a heterogeneous patient population under current trial designs.

Q3 Liver fibrosis remains a key determinant of prognosis across chronic liver diseases. Which fibrotic or immunofibrotic pathways currently appear most promising as therapeutic targets?

From an experimental perspective, cell-based therapies are particularly exciting. For example, CAR-T cells targeting activated hepatic stellate cells, the principal matrix-producing cells in liver fibrosis, have shown very promising results in preclinical models. There have also been impressive data on genetically modified or autologous macrophages that are conditioned to maintain

a more anti-inflammatory, immunomodulatory phenotype.

However, given the global burden and scale of chronic liver disease, including fibrosis and cirrhosis, I do not expect these highly sophisticated approaches to enter routine clinical practice in the near future.

A more realistic strategy may be to modulate the inflammatory microenvironment. Macrophage activation, for instance, is strongly shaped by the surrounding signals. If we can shift this environment towards a reparative rather than injurious phenotype, we could harness the liver's intrinsic capacity for repair, suppress fibrogenesis, and promote fibrosis resolution. Modulating the inflammatory milieu towards less injury and more repair may ultimately prove the most feasible and impactful approach.

Q4 Are there therapies in development that move in this direction of modulating the inflammatory environment?

Yes, some of the newer drugs may exert such effects, even if they were not originally designed as purely anti-inflammatory agents.

For example, peroxisome proliferator-activated receptor



agonists, transcription factor modulators with different isoforms expressed across tissues, appear to improve metabolism and also influence inflammatory cell polarisation towards a more reparative phenotype. Pan-peroxisome proliferator-activated receptor agonists are a good example of agents that may act through both metabolic and inflammatory pathways.

“**Fibroblast growth factor 21, a hormone produced in the liver and adipose tissue, also shows strong antifibrotic potential**”

Fibroblast growth factor 21, a hormone produced in the liver and adipose tissue, also shows strong antifibrotic potential. We do not yet fully understand whether its effects are entirely indirect or whether there are direct antifibrotic mechanisms involved.

Similarly, acetyl-CoA carboxylase inhibitors, targeting *de novo* lipogenesis and developed primarily as metabolic therapies for metabolic dysfunction-associated steatohepatitis (MASH), may also reduce hepatic stellate cell activation and fibrosis. So, while these drugs are not exclusively anti-inflammatory or antifibrotic, they may exert meaningful effects on these pathways.

Q5 In MASH, how do you view the role of immune dysregulation and inflammation in disease progression beyond metabolic risk factors alone?

If we consider disease progression, simple steatosis is not yet true liver disease. It represents a risk state associated with cardiometabolic burden and visible hepatic response to metabolic stress. The liver disease begins when inflammation develops, when steatosis transitions to steatohepatitis.

It is this inflammatory stage that confers risk for fibrosis, cirrhosis, and hepatocellular carcinoma. If we could decouple steatosis from steatohepatitis, preventing inflammation from being triggered, this would significantly reduce progression to clinically meaningful liver disease. The transition from steatosis to steatohepatitis is therefore critical.

Q6 Liver biopsy remains a key diagnostic tool. How close are we to replacing it with non-invasive biomarkers?

We have already made significant progress in reducing the need for liver biopsy in clinical practice. What we still cannot reliably diagnose without biopsy is steatohepatitis itself. Current routine biomarkers lack sufficient sensitivity and specificity for diagnosing MASH.

However, for staging liver disease, particularly identifying advanced fibrosis, non-invasive tools are extremely valuable. Serum-based tests and especially imaging biomarkers, such as elastography measuring liver stiffness, are widely used and very effective in identifying patients with advanced fibrosis.

Blood-based tests can also capture advanced fibrosis and cirrhosis reasonably well.

In hepatocellular carcinoma detection, progress has also been substantial. α -fetoprotein (AFP) alone is insufficient, as many cancers are AFP-negative. When combined with additional markers into composite scores, such as the Gender, Age, AFP-L3, AFP, and Des-carboxy-prothrombin (GALAD) score, diagnostic performance improves significantly. While these tools cannot yet replace imaging modalities such as ultrasound or MRI, the advances are encouraging.

There are also promising approaches using cell-free DNA to detect tumour-specific signatures, a form of liquid biopsy. These strategies aim at early cancer detection rather than advanced disease. Although not yet definitive, progress in this area is rapid.

Q7 Looking ahead, what developments in hepatology research are most likely to meaningfully change patient outcomes over the next decade?

One particularly exciting area is the concept of disease clusters and heterogeneity. For many patients, liver disease is only one component of a broader cardiometabolic risk profile. In MASH, for example, patients may face competing risks, progression to liver cancer, or death from myocardial infarction or stroke.

Understanding these risk clusters and tailoring management accordingly will be crucial. Hepatology should be integrated into a broader, multidisciplinary, multimodal risk management framework.

Personalised strategies for therapy, diagnostics, surveillance, and long-term monitoring will likely incorporate factors such as the microbiota, the gut–liver axis, and even the gut–brain axis. We already have therapeutic options from hepatology, diabetology, and cardiology. The challenge is to combine them appropriately for the individual patient.

Integrating hepatology more closely with other disciplines, and tailoring management according to individual risk, will likely represent one of the most meaningful advances for patient outcomes in the coming decade.

