Interviews

EMJ is delighted to welcome Scott Friedman and Massimo Colombo in two insightful interviews that explore the latest advancements in liver disease research. Friedman discusses the evolution of liver disease treatment, focusing on early diagnosis, personalised approaches, and the promising roles of genomics, the microbiome, and weight-loss medications. Meanwhile, Colombo shares his expertise on groundbreaking treatments, including the potential of CAR-T cell therapies for hepatocellular carcinoma and emerging breakthroughs in hepatitis B therapies.

Featuring: Scott Friedman and Massimo Colombo

Scott Friedman

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Q1 What specifically sparked your initial interest in investigating the underlying causes of scarring or fibrosis associated with chronic liver disease?

My interest started when I was a medical student at Mount Sinai, New York, USA. There were lectures by leading experts at the time, the late Hans Popper and Fenton Schaffner, who made the liver seem extremely interesting, complex, and mysterious; that mystery attracted me. A med school rotation at the Royal Free in London, UK, where I worked for a few months with the team under Dame Sheila Sherlock, solidified my interest.

Then, when I got to residency and fellowship, particularly at the University of California San Francisco (UCSF), USA, I chose a lab that was attacking a problem that seemed very relevant to my patients. I was mostly a clinical doctor, and that was a lab run by Monty Bissell, UCSF Liver Center, who was beginning to study scarring or fibrosis, and I thought this was something that, as a clinician, made sense to me.

It wasn't esoteric, yet in the end, it could impact the lives of patients. That turned out to be a good choice because, firstly, my mentor was outstanding and supportive, and secondly, because the question we were tackling needed answers. We have made some progress since then, and the ongoing challenge has kept me interested for the last 40 years.

It just so happens, though it didn't influence my decision, that liver disease is widespread across the globe, not just in the USA or Western Europe. As a result, I've had the privilege of travelling to incredible places where people speak the universal language of

liver disease, giving us much to share and learn from one another.

Q2 Given the significant impact of metabolic dysfunction-associated steatotic liver disease (MASLD) and its progression to metabolic dysfunction-associated steatohepatitis (MASH) and cirrhosis, what are the most critical unmet needs in this field?

The biggest unmet need is that the problem is vast, with somewhere on the order of 30–40% of the world's population having fat in the liver. The number one unmet need is that we don't have a good handle on who's at risk, because patients generally don't have too many symptoms. Therefore, systematic screening efforts are very nascent and need a lot of attention to uncover silent disease that could end up being very serious.

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Another related problem is that we are still required to do biopsies as we test drugs for FDA approval. Fortunately, with the availability of a new therapy in the USA, resmetirom, the FDA has not required that patients undergo a liver biopsy to justify the use of the drug. Instead, they have to demonstrate non-invasive evidence of moderate-to-advanced scarring. However, for Phase III clinical trials, we're still obligated to do liver biopsies, which are invasive; we are moving away from them as quickly as possible.

I would say the next unmet need, even for resmetirom and the drugs that are likely to be approved in the next couple of years, is they don't benefit every patient. In fact, on average they benefit less than half of patients. So, we need more potent and more personalised drugs that can ensure that every patient responds and benefits, and that we can find a way to monitor that response without having to do biopsies.

The final unmet need is for patients who have very, very advanced scarring or advanced cirrhosis, who, as we are discovering, have a much lower likelihood of responding to many of the drugs that work in patients at earlier stages. We're going to need a new class of drugs that helps degrade the scar that's already there.

Q3 As a pioneer in understanding the role of hepatic stellate cells in liver fibrosis, how has our understanding of these cells evolved in recent years, and what are the most promising therapeutic targets within this pathway?

We were instrumental in getting the field accelerated many years ago when we developed a method to isolate, grow, and characterise the cells in culture and then *in vivo*. That led to a series of observations, both by us and now many labs in the world, that defined the cells in one of two and then three states. In a healthy liver, they remained quiescent; in an injured liver, they became activated; and as the disease regressed they were either deactivated or underwent senescence.

What we've learned now with the development of fantastic new technologies, particularly single cell and single nuclear sequencing, where we can obtain

the transcriptomic sequence of every individual cell, is that there are many 'flavours' of stellate cells. It's not just three types, but probably six or even more. We're still trying to figure out what those different subtypes of stellate cells do, how important they are to fibrosis, and how we can target them for therapeutic benefit, both in fibrosis and liver cancer, as fibrosis is an important contributor to both. Single-cell sequencing has been, in my experience, the most transformative advance in the fibrosis field for some time in terms of therapeutic targets.

Most of the therapies that are currently under development, or the one now approved for MASH, target the hepatocyte, which is the source of almost all the fat, injury, and damage signals. The resulting benefits of these agents to fibrosis are likely indirect, achieved by reducing the injury and inflammation that drive fibrosis. But there is a new class of drugs emerging that targets the fibrogenic stellate cells themselves by zeroing in on different receptors that drive fibrosis on the cell surface; in particular, integrins, a class of cell surface receptors that we've known about for more than 25 years.

Increasingly, we know that some integrins are important in activating fibrogenic signals, especially TGF-β. So, the principle is to turn off the integrin's ability to activate TGF-β as an anti-fibrotic strategy. There's been some progress there, so far primarily in animal models, except for one company that already has clinical trials going on for fibrosis to antagonise integrin αvβ6. There are a lot of targets for stellate cells, but none have reached the point of approval yet. However, I'm highly confident that their success is only a matter of time. In my lab we have some of our own new targets that we think are very promising and can be blocked by antibodies or small molecule inhibitors.

Q4 Can you discuss the interplay between the gut microbiome, the liver, and the immune system in the pathogenesis of liver disease, and how this knowledge can inform novel therapeutic strategies?

That's a complex question. The microbiome, more generally, is emerging as one of the unsung regulators of health and disease in many different diseases, including cancer. Of course, because the gut communicates directly with the liver through the portal blood, it's not surprising that the products and the composition of the microbiome can influence normal and diseased liver.

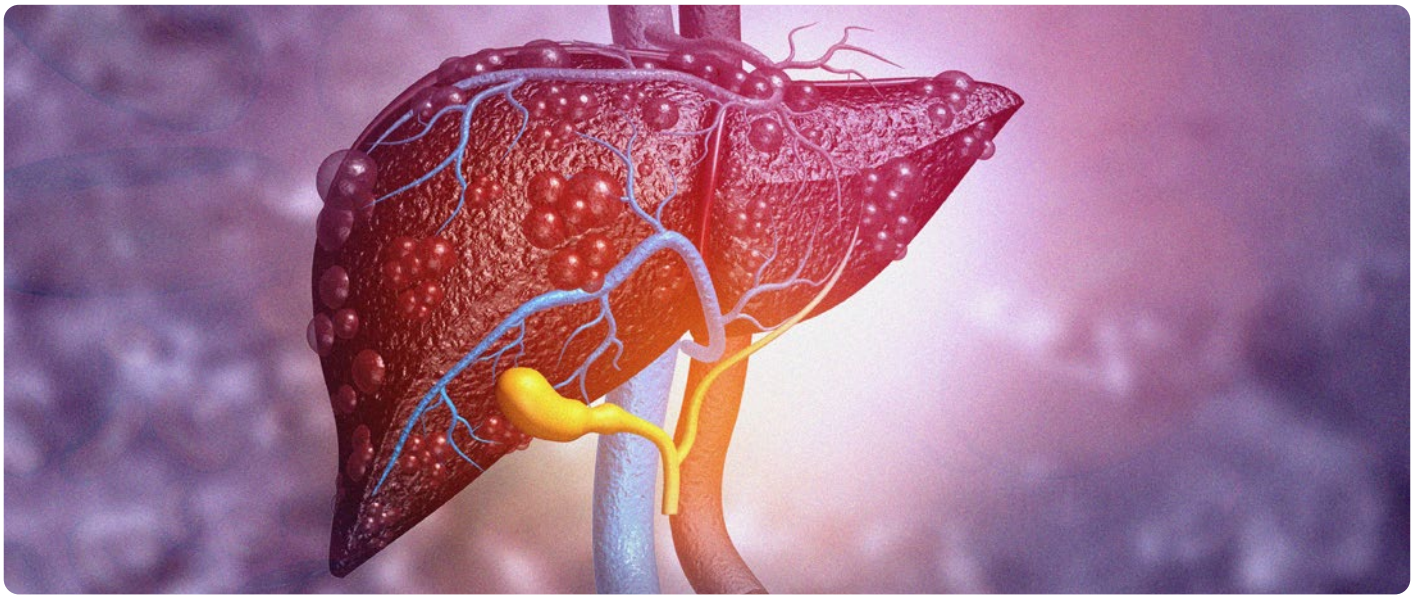
There are examples in animal models where one can collect the microbiome of an obese mouse and transplant it into a skinny mouse, making them obese. There's a school of thought that argues that the reason that we have a MASH epidemic now, and not 50 years ago, is because our microbiome as a population is evolving to promote fat in the liver as a result of exposure to antibiotics in our world, both in what we eat and antibiotics that we take therapeutically. Lessons from the microbiome have not translated into new treatments yet, but I think there are a lot of mysteries yet to unfold in terms of how the microbiome contributes not only to liver disease but to cancer, where it may influence responsiveness to chemotherapy. Gastrointestinal diseases and many other systemic conditions are likely also influenced by microbiome composition.

It's not so easy to harness the complex information from the microbiome to turn it into a treatment, but I believe we'll get there as well, and the possibilities are fascinating and very expansive in terms of the immune system. That's an even more complicated question because we're still developing the tools to characterise, which is the different components of the immune system in healthy and injured liver. We do know that there are certainly more inflammatory cells and their composition evolves, especially macrophages and the T cells, during the course of disease progression and regression.

> **"I think there are a lot of mysteries yet to unfold in terms of how the microbiome contributes not only to liver disease but to cancer"**

There is likely to be a whole class of therapeutic approaches targeting immune cells that we have not been fully able to exploit, with the exception of some very exciting work. Some of this is being done by Stuart Forbes, University of Edinburgh, UK, where he's using macrophages as a new kind of modality, infusing specialised types of macrophages to treat liver disease.

As we develop new technologies, there's yet another approach that involves either T cells, called CAR-T cells, which is an exciting method to programme a T cell into becoming a guided missile that attacks very specific target cells one would like to eliminate. The target can be a tumour cell, which is where CAR-T cells have largely been developed for liquid tumours (e.g., leukaemias), but increasingly non-cancerous cell types as well.



We're really excited about their prospects in liver.

Q5 Given the rising prevalence of MASLD worldwide, what are the most effective strategies to improve early diagnosis and intervention?

That's an important question, and as I mentioned earlier, most people with MASLD or MASH don't know they have it. We need to have a high index of suspicion in patients who are at risk. For example, anybody with Type 2 diabetes has around a 70% risk of having fat in their liver. So, one recommendation is to screen every Type 2 diabetic to determine if they have an underlying liver disease associated not only with diabetes, but also with hyperlipidaemia, hypertension, and obesity, because MASH and MASLD are part of a systemic condition called metabolic syndrome. Therefore, the first step is to suspect the disease in high-risk patients.

I don't think we're at the point yet where we should go around just screening every patient who is obese or overweight, but there are increasingly sophisticated blood tests that could eventually be part of a normal blood panel, and certainly, the standard liver tests like alanine transaminase (ALT) and aspartate transaminase (AST) can be a subtle but important sign that the liver is not 100% healthy. Therefore, it's crucial to raise awareness among high-risk patients and their immediate family members about this issue, as well as to recognise that any abnormal liver tests, such as the AST, ALT, bilirubin, international normalised ratio (INR), or platelet count, should be taken seriously. In particular, first-degree relatives of patients with MASLD and MASH are at higher risk of these conditions as well. Persistent abnormalities in these blood tests warrant further investigation and follow-up.

Overall, I think right now, the best strategy is to screen all high-risk patients, (e.g., those with Type 2 diabetes), and be suspicious of the disease in patients who have elevated liver tests and don't have any other explanation, since we want to exclude viral liver disease and alcohol-associated liver disease. Moreover, we increasingly recognise that many patients with metabolic liver disease or MASLD also drink alcohol. In fact, one of the rationales behind developing a new nomenclature for steatotic liver disease has been to allow for patients who have both metabolic liver disease or MASLD as well as alcohol-induced liver disease. So, those patients are kind of a hybrid, with a condition called MetALD, as they may require different strategies for screening, diagnosis, and treatment. Things are moving very quickly, and awareness is the first step.

Most patients with MASLD and MASH are not being seen by liver specialists, they're being seen by primary care doctors, GPs, endocrinologists who manage their diabetes, and sometimes cardiologists as well. So now, particularly because we have an approved therapy, we are trying to heighten awareness among those physician groups to think about the possibility of steatotic liver disease when they see patients with Type 2 diabetes, hypertension, and/or hyperlipidaemia, especially if liver tests are abnormal.

Q6 Your research has emphasised the importance of precision medicine in liver disease. How do you think we can leverage genomics, metabolomics, and other 'omics' technologies to personalise treatment for patients with liver fibrosis and cirrhosis?

There's been a revolution in the ability to sequence our genome and identify genes that put patients at risk. The most obvious way that's played out in MASLD and MASH is a growing list of so-called gene polymorphisms, or sequence variants, that correlate with a higher or lower risk of disease.

One of the newer approaches is to screen patients who have identified MASLD or MASH, to see if they have those at-risk polymorphisms. If they do, there are emerging specific gene therapies that can correct the defect that the gene variant imposes, to reduce risk or treat disease. Two that are now being developed as potential treatment targets are gene variants are in *PNPLA3*, which was discovered several years ago in Dallas Heart Study by Helen Hobbs, University of Texas Southwestern Medical Center, USA, and more recently, *HSD17B13*, which was reported around 7 years ago by the scientists at Regeneron Pharmaceuticals (Tarrytown, New York, USA) who identified a variant that protects patients. Gene therapy is trying to mimic the protective function of this gene variant. So that's one way that genomics is mainstream in liver disease and particularly MASH.

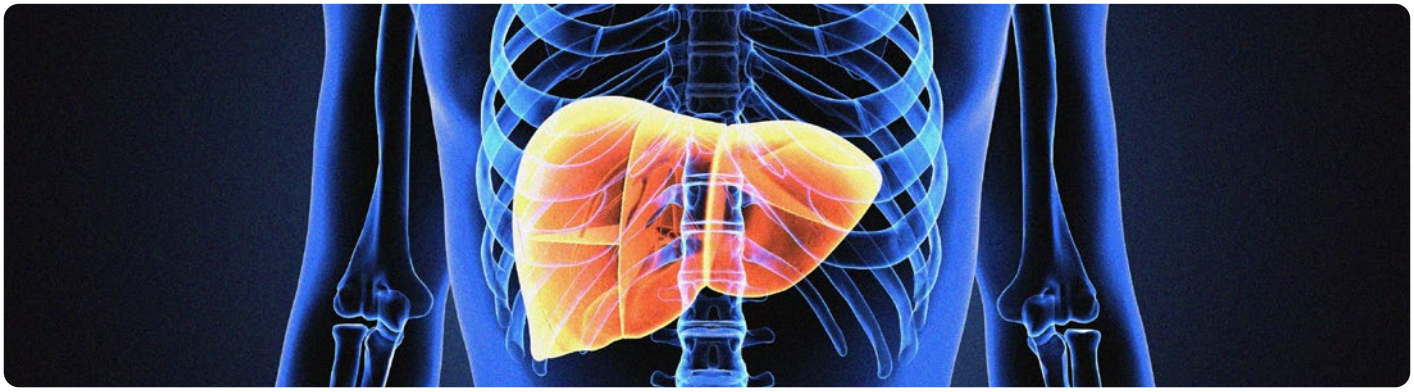
Also, as we learn more, the prospects for targeting different components of the microbiome become more likely. For example, there's fantastic work being done by Bernd Schnabl at University of California San Diego (UCSD), USA, in which he identified certain types of bacteria that may predispose to alcohol-related liver disease in animals exposed to alcohol. If they use highly specialised viruses known as bacteriophages to clear just those disease-causing bacteria, this ameliorates the disease. It's possible in humans that targeting specific bacteria could help reduce the risk or disrupt the liver-related signalling that drives fibrosis and injury.

These are two clear ways genomics is transforming medicine and increasing awareness. Genomics has significant implications for treatment personalisation; for example, patients with certain genetic profiles may be more likely to respond to one drug over another. This approach aligns with the core principle of precision medicine: identifying unique patient or disease characteristics to match individuals with the most effective therapies. That will also be increasingly available to us as part of our armamentarium.

Particular ethnic backgrounds may also influence disease risk. For example, the *PNPLA3* polymorphism is particularly prevalent in certain populations. Individuals descended from native Mesoamericans (e.g, Southern USA, and Central and South America) have a higher prevalence of the risk *PNPLA3* polymorphism, and therefore have higher rates of MASLD and MASH. Interestingly, this polymorphism only exacerbates the disease in individuals who are also obese. Lean patients with the variant do not appear to have the same risk of MASLD and MASH. However, once they become obese, likely due to other factors, their risk significantly increases. Similarly, this gene variant also heightens the risk in individuals who consume alcohol, suggesting that the pathogenesis of metabolic-associated liver disease and alcohol-associated liver disease may share overlapping mechanisms.

Q7 What do you think are the most promising areas of research that are just over the horizon in the field of liver fibrosis and MASH, and how do you anticipate these advancements will impact patient care?

I believe the most immediate benefit won't come solely from



liver-directed drugs, but rather from the wave of weight-loss medications that are transforming healthcare. GLP-1 agonists, as well as combination therapies involving GLP-1, glucagon, and GIP, are driving remarkable weight loss while also addressing many aspects of metabolic syndrome, including liver-related effects. As these so-called weight-loss drugs become more widely used and closely monitored, I expect we'll see a meaningful reduction in liver disease across a substantial portion of patients.

Beyond that, the emergence of liver-specific therapies, particularly FGF21 drugs, looks very promising. There are currently four different FGF21 drugs in development, and alongside the already beneficial GLP-1s and resmetirom, they represent the next major wave of novel treatments. With multiple FGF21 drugs expected to become available, I believe we will see significant improvements in outcomes for patients with liver disease. Many of these therapies are either already approved or are likely to receive approval within the next 2–3 years.

I think we will then turn to some of the precision medicine ideas, including gene therapy to correct those with high-risk polymorphisms, as well as potential strategies to manipulate the microbiome. Certainly, the work that we're doing in my laboratory is directed towards developing direct antifibrotic therapies, but they're a stage or two behind since we are still performing those studies in animal models.

Overall, between the imminent successes, the intermediate prospects, and the long-term successes, the future for treating steatotic liver disease and fibrosis is going to be very bright.