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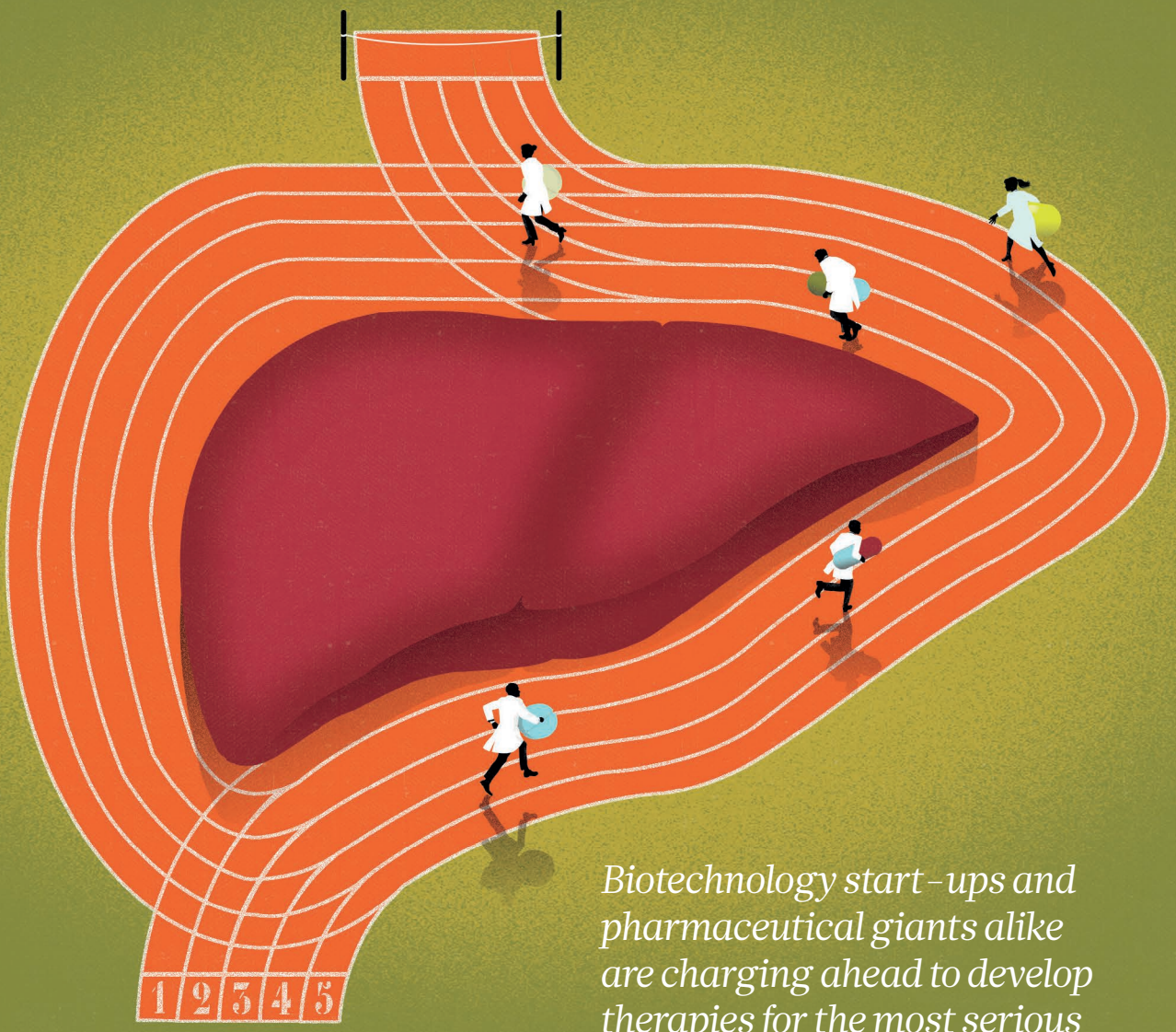


*Biotechnology start-ups and pharmaceutical giants alike are charging ahead to develop therapies for the most serious form of non-alcoholic fatty liver disease.*

BY LIAM DREW

In January 2014, Intercept Pharmaceuticals announced that it had stopped a phase II clinical trial of a potential treatment for non-alcoholic fatty liver disease (NAFLD) almost one year early. It was clear that the treatment protocol being assessed, a 72-week course of a synthetic bile acid, obeticholic acid, was working. The trial participants had an advanced form of NAFLD known as non-alcoholic steatohepatitis (NASH) and the drug had made their livers less inflamed and scarred. On the day of the announcement, New York-based Intercept's stock price almost quadrupled; and by the week's end it had nearly doubled again.

One year later, global healthcare company Merck shook hands on a US$450-million deal with NGM Biopharmaceuticals of San Francisco, California, for NGM's most interesting NAFLD therapeutic drugs. And Gilead Sciences, of Foster City, California, agreed to pay Phenex Pharmaceuticals of Ludwigshafen, Germany, up to $470 million for its NAFLD drug-development programme. In 2016, the deals continued. In April, Gilead acquired another promising NAFLD compound by purchasing a subsidiary of biotechnology company Nimbus Therapeutics, based in Cambridge, Massachusetts, for an initial $400 million, which could increase to $1.2 billion in total. A few months later, Dublin-based pharmaceutical company Allergan acquired Tobira Therapeutics of South San Francisco and its NAFLD candidate drugs for $1.69 billion. Compared with the frenetic pace of the past few years, 2017 has been quiet — but even so, Swiss pharmaceutical giant Novartis has paid Conatus Pharmaceuticals of San Diego, California, an initial $50 million to develop Conatus's lead NAFLD drug, with payments potentially increasing to a total of $650 million.

These are large sums of money, but the value of the main prize could be much greater: financial analysts predict that by 2025, the drug market for NAFLD will be worth $20 billion to $35 billion a year. And so far, no drug has been specifically approved for treating the condition.

There are currently more than 200 active trials of NAFLD treatments, and review articles that aim to provide up-to-date discussions of the drugs under development are published regularly. In 2013, such articles would have considered only a handful of potential therapies; now they include more than 30. Although some of these drugs target the same processes at a molecular level, what's most striking is not the number of compounds in the pipeline, but the diversity of their modes of action.

Asked whether the NAFLD field is exceptionally busy at present, Scott Friedman, a hepatologist at the Mount Sinai Hospital in New York, replies: "That would be an understatement." Friedman currently acts as a consultant for more than 40 companies. Apart from the potential to make vast sums of money, he and others in the field attribute the mushrooming of interest in treatments for NAFLD to a combination of factors: shifts in clinical understanding; an improved response by drug-regulatory bodies to disease trends; forward-thinking biotechnology companies; and a pharmaceutical sector that is ready for the challenge.

## THE ROAD TO NOW

At a basic level, NAFLD is now accepted as a serious condition. But, unlike the accumulation of fat in the liver caused by excessive consumption of alcohol, NAFLD was recognized as a distinct condition only in 1980. Before then, people with fatty livers who told their doctors they weren't big drinkers were generally assumed to be lying. Even when they were believed, "there was a perception that fat in the liver not due to alcohol was a fairly benign diagnosis", says Christopher Day, a hepatologist at Newcastle University in the United Kingdom. It took an array of studies, conducted by Day and others throughout the 1990s, to establish that fat accumulation not associated with excessive drinking could lead to a serious disease.

These days, NAFLD is viewed as a progressive condition that can be classified into several stages (see page S92). A fatty liver — in which 5% or more of cells contain large deposits of fat but little or no inflammation — is the mildest category and is generally considered to be benign. However, if the accumulated fat leads to inflammation, telltale cell 'ballooning' and then cell death, the person affected is said to have NASH.

NASH is associated with a doubling of the risk of dying from cardiovascular disease, and a tenfold increase in the chance of developing cirrhosis (extensive scarring) or cancer of the liver. But NASH can also be subdivided into stages, and the risk of developing further complications from the condition is not evenly spread. In particular, people with inflammation accompanied by some degree of scarring — termed fibrosis — are most at risk of the disease progressing, as well as being the most likely to experience adverse clinical outcomes. And it is these people who liver specialists think would benefit the most from the forthcoming drugs.

Another reason that the medical and pharmaceutical communities are taking NAFLD more seriously is that its prevalence has soared since 1980. Although age, ethnicity, sex and genetics all play a part, the main risk factors are obesity and diabetes, as well as other aspects of metabolic syndrome such as hypertension, high levels of fat in the blood and insulin resistance. These factors combine, says Arun Sanyal, a gastroenterologist at Virginia Commonwealth University in Richmond, to "start driving metabolic substrate — carbohydrate and fat — into the liver at rates that the metabolic machinery was not designed to handle."

> "FAT IN THE LIVER NOT DUE TO ALCOHOL WAS A FAIRLY BENIGN DIAGNOSIS."

The worldwide spike in obesity in the past few decades has driven "a huge epidemiological surge" in NAFLD, says Friedman. The number of liver transplants given because of NASH has soared in the United States since 2004, and the condition is projected to be the leading cause of transplants within 5–15 years.

In fact, it has been estimated that 1 in 4 people worldwide have some form of NAFLD. In the United States, up to 100 million people may have fatty livers and, of them, 20 million–30 million could have NASH. The medical advice, for most individuals, is to exercise and to lose weight because mild to moderate NAFLD can be reversed through lifestyle change. However, 1 million–3 million people in the United States probably have a type of NASH that is serious enough to warrant treatment with drugs — a figure that has spurred the pharmaceutical sector into action to capitalize on the large and growing unmet medical need.

The surge in prevalence and interest from the drug sector has made the regulators pay attention. Both the US Food and Drug Administration (FDA) and the European Medicines Agency have been praised by doctors for creating viable pathways for getting NASH therapies to market rapidly — and in time frames that are attractive to drug developers.

The crucial change in the process was to decree that trials need only to show that new treatments reduce the severity of liver inflammation and fibrosis — as indicated by liver biopsy — instead of having to demonstrate directly that fewer participants progress to cirrhosis, or die of liver failure or other outcomes. Because this type of tissue change can be measured over 6–24 months, as opposed to the decades sometimes needed to observe the outcome of accumulated liver damage, the potential time to market was slashed. And thanks to the current paucity of treatments for NASH, there are no established drugs to beat — therapies being tested need only to perform better than placebos.

Other factors behind the surge in NAFLD drug development are more subtle, but still important. Both Day and Friedman describe how the hepatitis C epidemic of the 1990s drew the pharmaceutical sector to the liver, which meant that drug makers developed relevant expertise in hepatology, and that their presence was ensured at conferences where researchers and physicians were charting the alarming rise of

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NAFLD. When hepatitis C was effectively cured — antiviral therapies now resolve at least 95% of cases — liver disease seemed tractable and, for pharmaceutical companies, it was a sensible and straightforward choice to move resources to another, increasingly common form of chronic liver disease.

However, it isn't just research into hepatitis C that is relevant to NAFLD. Because it is a multifaceted and progressive condition, investigations into NAFLD span several areas, including metabolic issues linked to obesity and insulin resistance; chronic inflammation; and fibrosis. Contributing to the diversity of drugs in trials, the pathological processes underpinning each of these may represent a valid target for halting NASH. But because each area has also been an independent focus of research for decades, many drugs that are under investigation for use in NASH have been repurposed from other conditions. "People who've been working in inflammation for the last 20 years, people who've been working in metabolism for the last 20 years, people who've been trying to reduce pulmonary fibrosis and other fibrogenic diseases — everybody is throwing whatever they have at NASH hoping that something is going to stick," says Sanyal.

**"THE FIELD IS RAPIDLY EVOLVING TOWARDS COMBINATION THERAPIES."**

But it is not simply a matter of big pharma shifting its resources from one liver disease to another. Vlad Ratziu, a hepatologist at the Université Pierre et Marie Curie in Paris, thinks that the NAFLD field owes much to "the very strong will and dedication of two brand-new biotechs with no other compounds in development — Genfit and Intercept". These companies established programmes for NASH long before the FDA updated the regulatory pathway, and led the way in instigating large clinical trials. The results of these trials, especially the one conducted by Intercept, "all of a sudden changed the landscape and showed people that improvement is possible in this disease", Ratziu says.

## THERAPY, PILLS AND NASH

To make sense of the scores of drugs being tested across hundreds of trials, Sanyal likes to place potential therapies into one of four categories, each composed of drugs with a common goal but varied mechanisms of action. One group includes those that target the initial metabolic stress that is triggered by excess fat. Another contains drugs that aim to quell inflammation and prevent cell death. Then there are antifibrotic drugs. And finally, there are drugs that act in the gut to block the absorption of fat or to reduce inflammation, which may be triggered by issues related to the intestinal microbiome. Sometimes the categories blur — for example, certain drugs straddle the anti-inflammatory and antifibrotic classes.

The compounds being developed by Intercept and by Genfit, based in Loos, France, target metabolic stress. Both activate receptors in the cell nucleus that regulate gene expression. Intercept's obeticholic acid switches on a receptor known as FXR, whereas Genfit's drug, called elafibranor, activates two types of a related receptor known as PPAR.

Because they can alter the expression of many genes, these drugs act — at least, in animal models — on a variety of cell injury pathways, Ratziu explains. For example, drugs that activate FXR reduce insulin resistance and levels of lipid synthesis, and also have anti-inflammatory and antifibrotic effects. "It just seems to push all the right pathways in the right direction," says Friedman.

Other drugs that aim to reduce metabolic stress do so by mimicking endogenous hormones. The drug that Merck bought from NGM in 2015, an engineered version of the hormone FGF19 that is involved in FXR signalling in humans, has several effects. There's also considerable interest in analogues of the hormone GLP-1 — such drugs are used to treat type 2 diabetes and are now undergoing trials for NASH.

Another drug that is licensed for treating diabetes — evogliptin — was part of Allergan's deal with Tobira for NAFLD therapies. By inhibiting the enzyme DPP-4, evogliptin exerts several effects, including an increase in insulin secretion, which may ease the pathology of NASH. Meanwhile, the thinking behind inhibitors of enzymes that synthesize fatty acids — Gilead's purchase from Nimbus — is that NASH may be halted if the build-up of toxic fat products can be prevented.

On the anti-inflammatory front, Allergan has high hopes for the other drug it acquired from Tobira, a blocker of receptors for molecules called chemokines, which are instrumental in mediating persistent inflammation. The drug that Novartis purchased from Conatus this year dampens inflammation by inhibiting an enzyme called a caspase. And Gilead has reported that a drug in its pipeline blocks ASK1, an enzyme involved in programmed cell death; by inhibiting this process, the drug reduces liver fibrosis in people with NASH in just six months.

Further therapies that aim to halt liver-scarring pathways are also under trial, as are a number of intestinally targeted drugs, including probiotic supplements.

## WINNER TAKES ALL

The multiplicity of approaches to the treatment of NASH reflects its complex nature and the uncertainty about its essential drivers. "This is a disease that has many convergent abnormalities and we don't have a hierarchy yet of which are important," says Friedman. "Does it start with fat? Does it start with an altered microbiome? Does it start with insulin resistance, or oxidative stress?"

With the answers still hazy, drug developers view each quirk of NASH as a potential therapeutic target. But Friedman stresses that the contribution that each process makes to the overall disease phenotype is still unclear. "We could get to a point where we have an implicated drug target, and the targeting is engaged completely," he says. "But ultimately that target contributes only 5–10% of the overall phenotype."

## ON THE LIVER
### TREATMENT TRAIL

*After decades of development, drugs for treating non-alcoholic fatty liver disease are almost ready for use in the clinic.*

**1980**

Jurgen Ludwig and colleagues at Mayo Clinic in Minnesota describe fatty liver disease in 20 people who are not heavy drinkers[1]. The researchers name the condition non-alcoholic steatohepatitis (NASH).

**1990**

A team of researchers in Australia presents the first description of NASH's advance[2]. By following 42 people over several years, the researchers show that, as well as having a variable progression, NASH can lead to cirrhosis.

**1999**

Using liver biopsies, a team led by Elizabeth Brunt at Saint Louis University in Missouri devises a way to quantify the severity of NASH[3]. The scheme scores fat accumulation, cell ballooning, inflammation and fibrosis.

**2004**

Fledgling biotechnology company Intercept Pharmaceuticals shows that obeticholic acid, which it is developing to treat non-viral liver diseases such as NASH, can halt liver fibrosis in animal models[4].

**2004**

Ingrid Hickman and Elizabeth Powell at the University of Queensland in Australia show that modest weight loss and increased physical activity improve liver health in overweight patients with chronic liver disease[5].

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**Hepatologist Scott Friedman is investigating non-alcoholic fatty liver disease.**

Only by running clinical trials will this become clear. Indeed, Day notes that, despite there being many drugs that "look great in a mouse model" and that have had early, limited success in people, "the number of drugs that have gone through a proper randomized control study, with two-years' follow-up and biopsy at the start and at the end is virtually none".

This is why the successes of obeticholic acid and elafibranor in similar trials, involving hundreds of people, were so newsworthy. However, even in those studies, the proportion of participants whose livers showed improvement was a sobering 20–45% compared with 10–20% for those who received a placebo.

Obeticholic acid and elafibranor, although acting on the correct targets, might therefore not be particularly effective. A number of companies are developing second-generation FXR activators and other PPAR activators, with the hope of improving the response rates to such drugs. Futhermore, the side-effects of obeticholic acid have caused concern: some people taking it had slightly elevated levels of low-density lipoproteins (also known as 'bad' cholesterol), and almost 1 in 4 developed persistent itchiness. More pressingly, in September 2017, the FDA issued a safety warning after obeticholic acid was linked to the deaths of 19 people who had been taking it for another serious liver condition — causing Intercept's share price to drop to a value similar to that before its spike in 2014.

Alternatively, these underwhelming results could reflect a basic heterogeneity in the root causes of NASH or, as Friedman suggests, that NASH is a condition in which several processes contribute varying amounts to the overall presentation. The former scenario suggests that different people may benefit from different drugs, whereas the latter proposes that full resolution of NASH may require the prescription of a combination of drugs that simultaneously target distinct aspects of the condition.

Sanyal suggests that disease activity, as indicated by the ongoing level of metabolic stress and inflammation, and disease stage, as reflected in the degree of fibrosis, are parameters that can be separated. Assessing them independently might reveal the types of drug from which a patient would benefit most. "It's not going to be one size fits all," he says. A higher level of disease activity would favour the provision of inhibitors of metabolic stress or anti-inflammatory drugs, whereas more-advanced scarring would point to the use of antifibrotics.

Friedman says that "the field is rapidly evolving towards combination therapies". He cites, as evidence, an April 2017 deal between Novartis and Allergan to test a combination therapy consisting of Allergan's anti-inflammatory, antifibrotic chemokine-receptor blocker and an FXR activator that Novartis has developed.

When it comes to establishing the specific causes of individual cases of NASH, the consensus is that more research is needed — after all, the field is still in its infancy. "Somebody may have a very fibrogenic microbiome; someone else may be prone to insulin resistance; others may have more sensitivity to the toxic effects of lipid accumulation," Friedman says, and what's needed is better diagnostic techniques to assess the diversity and to monitor how well people respond to treatment.

The question for the future, says Day, is: "Can you identify in a particular patient what it is that triggers the cascade in them, and then come up with a treatment that targets their particular disease mechanism?" In other words, the effective treatment of NASH awaits a more personalized diagnosis — a medicine-wide goal that is only slowly making its mark in the clinic.

## THE NEXT FIVE YEARS

It's widely anticipated that drugs for NASH — most probably obeticholic acid and elafibranor — will enter the market in 2020 or 2021, and that others will soon follow. The present surge of optimism could simply reflect the huge influx of funding that the field has received. But Friedman thinks that there's more to it. "There is already pretty solid evidence that you can move the needle in terms of histology," he says. "And this is at a pretty early stage of the history of drug development in this field."

A caveat that follows on from drugs being approved for sale on the basis of only their ability to resolve liver inflammation and fibrosis is that the long-term effects, in terms of both disease progression and the overall health of recipients, will need to be tracked. Most people with NASH have several related conditions, and a NASH drug must not worsen such comorbidities. Sanyal notes that although the association of NASH with an increased risk of cardiovascular illness is well established, only after NASH can be treated effectively will it be known whether having a healthier liver actually reduces that risk. A treatment for NASH might instead reveal that the liver disease and heart problems arise from a shared risk factor.

It's clear that this nuanced condition will require astute management, a process that will benefit from the availability of a number of medicines. "There is a race," says Ratziu, "and everybody wants to finish first." But it's important, he says, not to become fixated on the near term. "It will be only the first chapter that is written once these drugs reach the market," he says. "By no means will it be the end of the race." ■

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**2010**

The PIVENS trial reports that vitamin E and diabetes drug pioglitazone reduce fat accumulation and inflammation in NASH, but not in fibrosis[6]. It is the first large systematic study of treatments for NASH, but raises concern about potential side-effects.

**2014**

The Forum for Collaborative Research — an influential US public–private partnership that evolved from an effort to develop drugs to tackle HIV — establishes the Liver Forum to accelerate the development of treatments for NAFLD.

**2015**

The FLINT study — a phase IIb clinical trial of obeticholic acid, Intercept's potential treatment for NAFLD — shows that the drug improves the condition of liver tissue affected by NASH[7].

**2016**

In a phase IIb trial, elafibranor[8], Genfit's potential drug for NASH, is shown to improve the pathology of the condition and to halt the progression of liver fibrosis.

**2017**

Cenicriviroc, Allergan's chemokine-receptor-blocking drug, is the latest compound for which a phase IIb trial produces positive data[9] — fibrosis is improved in people with NASH, who also show no worsening of fat accumulation or other NAFLD hallmarks.

**2019**

Meaningful results from phase III trials of NASH treatments are expected. By 2021, the first drugs designed specifically for treating NASH are anticipated to get US Food and Drug Administration approval to be sold.

Sources: 1. Ludwig, J. *et al. Mayo Clin. Proc.* **55,** 434–438 (1980). 2. Powell, E. E. *et al. Hepatology* **11,** 74–80 (1990). 3. Brunt, E.M. *et al. Am. J. Gastroenterol.* **94,** 2467–2474 (1999). 4. Hickman, I. J. *et al. Gut* **53,** 413–419 (2004). 5. Kleiner, D. E. *et al. Hepatology* **41,** 1313–1321 (2005). 6. Sanyal, A. J. *et al. N. Engl. J. Med.* **362,** 1675–1685 (2010). 7. Neuschwander-Tetri, B. A. *et al. Lancet* **385,** 956–965 (2015). 8. Ratziu, V. *et al. Gastroenterology* **150,** 1147–1159 (2016). 9. Friedman, S. L. *et al. Hepatology* http://dx.doi.org/10.1002/hep.29477 (2017).