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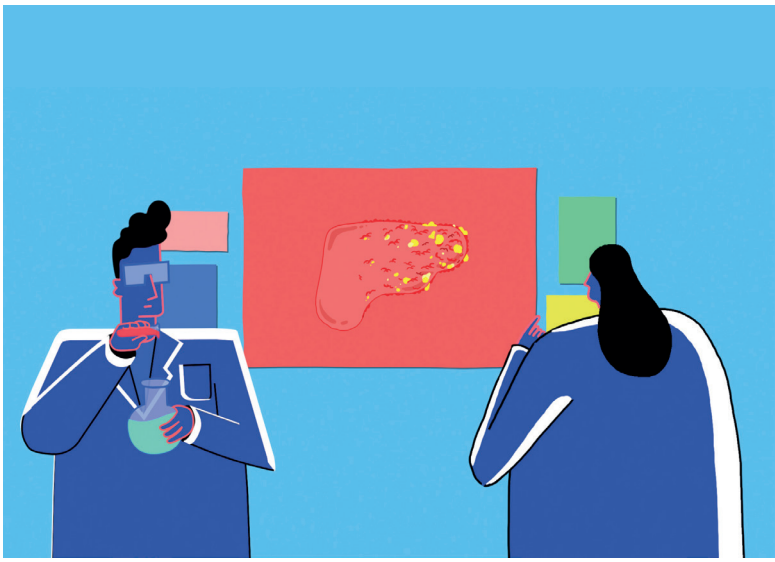
LIVER CIRRHOSIS: SCAR WARS

Once thought to be irreversible, cirrhosis of the liver now seems treatable — and drug development is proceeding apace.

BY LIAM DREW



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When people talk about scars, they often speak of indelible reminders of old wounds. For most of the twentieth century, liver cirrhosis — a condition defined by extensive scarring of the liver — was similarly thought to be irreversible.

However, researchers now know that this is not necessarily true. If the underlying disease process can be thwarted, mechanisms intrinsic to the liver can begin to resolve the scarring. Although a few studies had hinted at the liver's resilience, only after the broad introduction of effective treatments for the viral liver infections hepatitis B and hepatitis C did clinicians become widely convinced.

Scientists have also gained a deeper understanding of the biology of scar formation (fibrosis) and regression, and numerous drug companies are redoubling efforts to find interventions that can help to halt scarring or even remove existing scars.

Biologists refer to scar formation as fibrosis because scar tissue is comprised mainly of collagen fibres rather than cells. Laying down these bundles of protein — a process known as fibrogenesis — is the body's basic response to injury. But injury to the liver — induced by alcohol abuse, non-alcoholic fatty liver disease, the viruses that cause hepatitis and several other conditions — can lead to ongoing fibrogenesis.

Fibrosis is mediated by cells known as myofibroblasts. In the liver, most myofibroblasts are derived from hepatic stellate cells (HSCs) — enigmatic cells that store vitamin A. Drug companies are aiming both to prevent the activation of these HSCs, stopping them from becoming myofibroblasts, and to suppress the fibrogenic functions of activated cells.

No drug is yet approved for treating cirrhosis, but one approach involves blocking the activity of chemical messengers that initiate fibrogenesis. A drug that binds to receptors for signalling molecules called cytokines is in an advanced clinical trial. Frustratingly, however, many of the chemical messengers that instigate fibrosis have crucial functions beyond the liver — raising concerns about potential side effects. Another strategy, which involves blocking the intracellular signalling pathways that maintain HSC activation, is similarly prone to unwanted effects.

Other approaches take direct aim at the scarring process. Drugs that interfere with collagen synthesis and secretion are being targeted to activated HSCs by packaging them with vitamin A. And drugs that block enzymes that build cross-links between collagen fibres enable collagen to be broken down more easily by the liver.

Another option for promoting liver recovery comes from cell therapy. Many researchers have explored the use of stem cells in cirrhosis — so far, without clinical success. However, one group found that administering immune cells called macrophages can suppress fibrosis in mice. A trial in people is now under way.

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