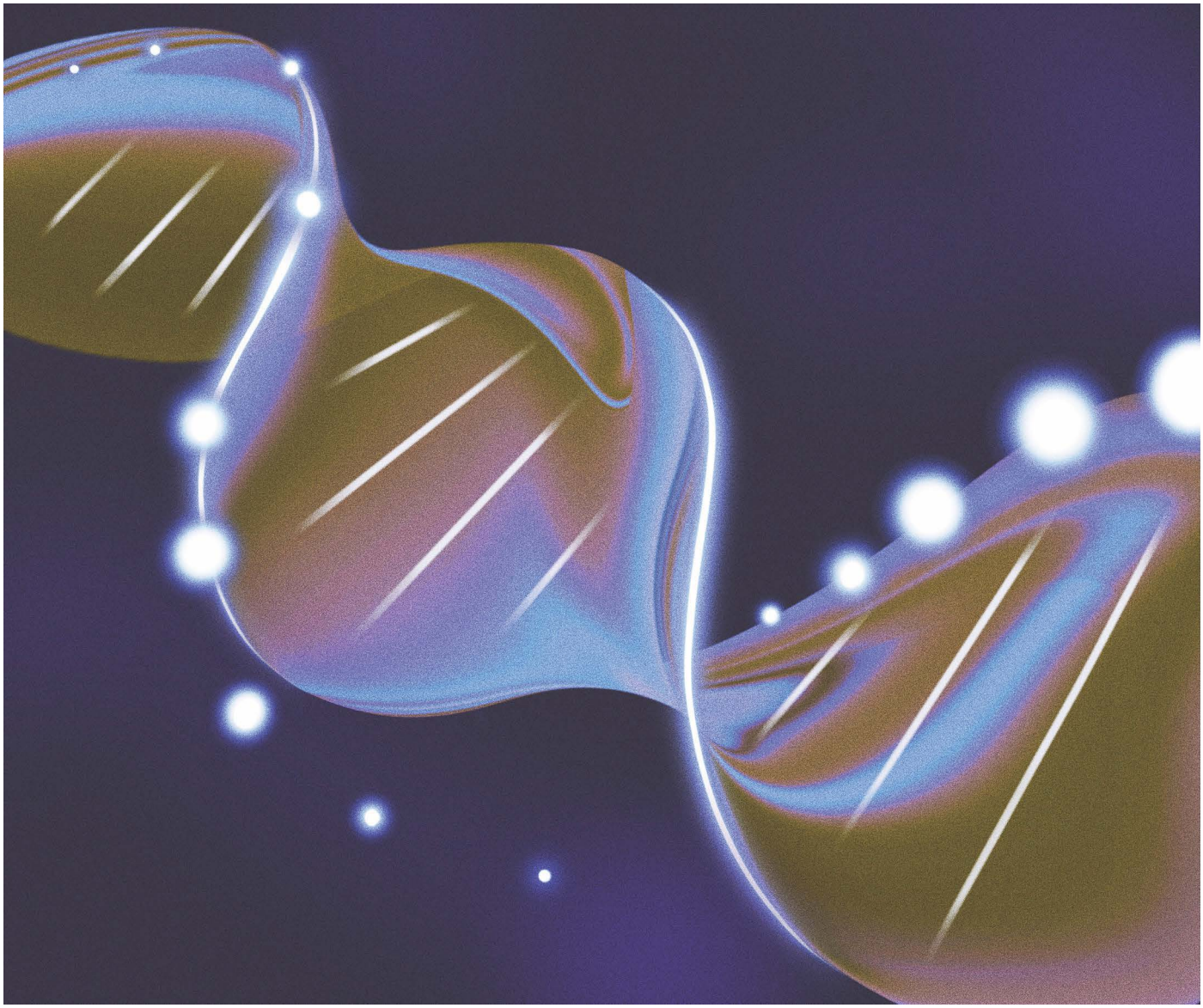

ILLUSTRATION: AGNES JONAS

CRISPR'S NEXT ACT: EPIGENETIC EDITING

A handful of start-up firms are testing therapies that target specific epigenetic markers to treat everything from high cholesterol to a rare muscular disorder. **By Roxanne Khamsi**

In late 2021, Amber Salzman interviewed for a job that she had no intention of taking. A relatively new start-up company, called Epicrispr Biotechnologies, was looking for a chief executive, and it was keen on vetting Salzman — who had decades of experience in the pharmaceutical industry — for the role. She had said yes to the meeting only as a favour to a recruiter, who had helped her to fill a key position at another company she had worked with. Joining the start-up wasn't something she was enthusiastic about.

Halfway through the meeting, she changed her mind. Salzman had watched as Stanley Qi, the founder of Epicrispr, drew diagrams on a whiteboard explaining that the company wanted to make a genetic therapy — not by editing the code itself, but by changing the chemical markers attached to DNA, which can switch genes on or off. Then Salzman asked another team member: "'What disease are we going after?' And she said, 'FSHD'."

Salzman knew the condition all too well. FSHD, short for facioscapulohumeral muscular dystrophy, is an inherited disorder in which muscle problems first begin in the face and upper body and can spread to other parts, sometimes requiring wheelchair use. Salzman's husband of more than 35 years had several cousins and a grandmother with the disease, although he had not inherited it himself.

Her family's experience of this disorder had always been on her mind, but Salzman had never seen a way to make a difference in her previous positions: "At the time, nobody really understood what caused it." But the

conversation with Epicrispr gave her a chance to address the disease.

She took up the company's offer to become its chief executive. In doing so, Salzman joined a niche group of drug developers trying to advance a technique called targeted epigenetic editing. The idea is to remove or add epigenetic markers — essentially chemical groups that sit on DNA (and the proteins that it is wound around). Depending on which chemical group is present or absent, genes can be activated or switched off.

Some existing medications influence epigenetic markers, but these drugs act broadly and lack specificity. This new cadre of scientists has found ways to precisely alter the epigenetic markers influencing specific genes. Epicrispr, based in South San Franscisco, California, is one of several companies working on such therapies. At the International Research Congress on FSHD, held in late June in Chicago, Illinois, it became one of the first to announce data from an epigenetic-editing trial.

Epigenetic markers have a huge impact on how our cells interpret DNA. Changing the epigenetic tags on a genome is akin to using an audio mixing board to alter a piece of music to sound like the works of composer Franz Schubert or pop star Taylor Swift, says biologist Fyodor Urnov at the University of California, Berkeley. Urnov helped to pioneer the use of various gene-editing technologies and co-founded an epigenetic-editing company called Tune Therapeutics in Seattle, Washington.

The tools being deployed in this new era of epigenetic editing put a twist on standard gene editing, which involves using the CRISPR system to cut DNA. That system is precise, but even so, it can lead to cuts in the wrong place, which can disrupt or damage genes. "Epigenetic editing is a truly exciting concept for therapeutics because there is no chance of off-target DNA mutations being made, as is the case with gene editing," explains Jessica Tyler, a molecular biologist at Weill Cornell Medicine in New York City.

Most epigenetic-editing platforms, rather than making changes to the DNA itself, modify the markers attached to DNA. That is thought to be safer for two reasons: first, the system can't mistakenly cut in the wrong place, and second, it reduces the possibility that the DNA could rearrange itself — which is a risk whenever DNA breaks. In addition, preclinical experiments in human cells show that epigenetic modifications are reversible.

But epigenetic forces are potent, and researchers should proceed with caution, says Yann Joly, a bioethicist who heads McGill University's Centre of Genomics and Policy in Montreal, Canada. "Epigenetic regulation plays a central role in development and reproduction," he says. The community needs to ensure that epigenetic therapies are delivered safely and without unintended consequences, he says.

Dead right

In 2012 and 2013, several independent groups published a series of papers describing the original CRISPR–Cas9 editing system and its application[1–3]. In conventional CRISPR, a guide RNA finds the target sequence in the genome, and a Cas9 enzyme then cuts the DNA. The discoveries garnered huge attention for their potential to rewrite DNA. But at the time, most people might not have appreciated that biologists were already contemplating how to adapt CRISPR editing to modulate gene expression, rather than break or rewrite the genetic code.

One such biologist was Qi, who had worked in the lab of CRISPR pioneer Jennifer Doudna at the University of California, Berkeley. He wanted to know how to control a cell's programming, rather than altering its code.

He launched his lab at the University of California, San Francisco (UCSF), and started working out how to modify the CRISPR–Cas9 system so that it would still grab on to the targeted DNA but wouldn't snip the sequence after reaching it. In 2013, Qi and his colleagues, including biochemist Jonathan Weissman, also at UCSF at the time, and Doudna, landed on modifications that achieved just that[4]. They called the repurposed Cas9 'dead' because it lacked its normal enzymatic cutting activity.

"Epigenetic editing is a truly exciting concept for therapeutics because there is no chance of off-target DNA mutations."

Next, the team deployed a guide RNA to lead the dead Cas9 to the right place, along with a protein that could turn gene expression on and off. The tests showed that the system worked in human cells and was highly precise[5]. "That's when we knew this was a transformational tool," says Weissman, who is now based at the Massachusetts Institute of Technology in Cambridge.

Not long after the publication of these key papers, Qi moved his lab to Stanford University in California. There, he continued to improve on the dead-Cas9 system and found a smaller version — called Cas12F — that could more easily be delivered to cells (the typical Cas9 protein, from bacteria, is relatively large).

Qi and his teammates found Cas12F in archaea, organisms that resemble bacteria in some ways but are evolutionarily distinct and have different cell walls. Whereas Cas9 is made up of around 1,300 amino acids, Cas12F consists of around 500. To deliver the payload to cells, the recipe for dead Cas12F is coded into a virus, known as adeno-associated virus, which is considered harmless to the body. The virus is infused into the body, and cells then produce the Cas12F construct themselves. The protein then gets to work on the target epigenetic markers.

Meanwhile, the company that Weissman co-founded, nChroma in Boston, Massachusetts, has made improvements to another component of the system: the methyltransferase element, which modifies the epigenetic markers. The firm hasn't disclosed which one it is using but says that it is efficient and small. "I think that's part of our secret sauce, frankly," says Jenny Marlowe, chief development officer at nChroma.

Treatment try-outs

In 2025, a team including scientists at nChroma published a study in mice and monkeys showing that their approach worked[6]. The team's epigenetic-editing system, encapsulated in lipid nanoparticles and delivered intravenously, could quash the production of a protein called PCSK9, which promotes 'bad' cholesterol. A single injection lowered monkeys' levels of this type of cholesterol by around 70%.

Other epigenetic-editing therapies are moving into clinical testing. In January, nChroma began administering the first doses of an experimental epigenetic silencer against the hepatitis B virus to people with chronic infection. According to the World Health Organization, an estimated 240 million people worldwide have chronic hepatitis B — which can cause liver failure and cancer. A vaccine exists, but data from 2019 suggest that 15% of children around the world do not receive the full immunization regimen, and an increasing number of parents in countries such as the United States are refusing it for their children because of health misinformation.

To make matters worse, existing drugs cannot fully clear hepatitis B from the body because the pathogen has a nasty trick up its sleeve: bits of its genome integrate into a person's DNA and from there, generate proteins that alter the immune response against it.

The nChroma silencer aims to help the body rid itself of hepatitis B by muting both the free-ranging virus and the parts of the virus that have integrated into a person's own DNA, especially in the liver. According to nChroma, that will stop hepatitis B from tricking the body and allow the immune system to go after it. "The bar is very high in terms of the number of cells that you actually have to silence in the liver," notes Melissa Bonner, chief science officer of nChroma Bio. "We believe it has to be the vast majority of cells."

nChroma is now exploring the use of gene-editing systems besides CRISPR, such as zinc-finger nucleases — which can be modified to alter gene expression without cutting DNA.

Tune Therapeutics is also among the companies targeting hepatitis B with epigenetic editing. In late May, it presented data at the

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Epicrispr Biotechnologies chief executive Amber Salzman in the company's laboratory.

European Association for the Study of the Liver Congress in Barcelona, Spain, showing that its epigenetic-silencing therapy caused levels of hepatitis B markers — such as its RNA intermediate and one of its viral proteins — to plummet to undetectable levels in some recipients.

After Salzman started work at Epicrispr, she encouraged the company to move towards real-world testing of its FSHD treatment, called EPI-321. By spring 2025, the company had clearance from the US Food and Drug Administration to begin trials of the therapy. Over the summer, the first participant received a dose. Since then, more than half a dozen adults with FSHD have received the starting dose. The company plans to enrol 12 participants in total.

At the June meeting, the company announced it has evaluable data from the first three clinical-trial participants and that, by the six-month mark, a single dose of its therapy caused a statistically significant increase in whole-body lean muscle in all three people. The volunteers had an average estimated increase of around 0.4 kilograms of muscle mass. "We were startled to see at the six-month visit — because that's the first time we do an MRI [magnetic resonance imaging] — the patients were actually gaining muscle mass," Salzman says. This stands in contrast to previous data collected from around 100 people with FSHD, which predicted that, without any intervention, the participants would typically have lost muscle by that point.

FSHD is suited to treatment with epigenetic editing, because it is thought to be caused in part by abnormal epigenetic markings. People with FSHD typically have a shorter-than-normal version of a particular piece of DNA on chromosome 4 — a truncation that also strips off epigenetic markers. Usually, there are ten or more repeats of this region, known as D4Z4, and they are heavily tagged with methyl groups. These marks tell D4Z4 to silence a gene called *DUX4*, which would otherwise produce a protein that is toxic to muscles. So when these markers aren't present, the D4Z4 region can't do its usual job, and the toxic protein causes muscle deterioration. EPI-321 orchestrates the addition of missing methyl groups to the D4Z4 region.

Around 870,000 people worldwide are thought to have some form of FSHD, but it is not always caused by the same mutation. That gives epigenetic editing a crucial advantage, according to Salzman. Regular gene editing, which modifies DNA directly, must be tailored to the precise sequence error in the affected gene in a given person. The EPI-321 epigenetic editor, by contrast, binds to a portion of DNA slightly upstream of the mutated D4Z4 region. This makes it a more universal treatment for FSHD because everyone with the condition has an identical sequence in this upstream portion, says Salzman.

FSHD is not the only disease involving irregular epigenetic patterns. Epigenetic dysregulation is also associated with worsened symptoms in Huntington's disease and Parkinson's disease[7]. And beyond that, Salzman says that Epicrispr is looking to treat conditions that are not known to involve epigenetic abnormalities at all. The strategy is to bind an epigenetic editor to regulatory regions upstream of mutated genes, toggling them on or off, while delivering a functional version of the gene in the same package. For instance, the firm is developing a therapy for a progressive eye disease called autosomal dominant retinitis pigmentosa 4, in which it plans to suppress a mutated gene encoding rhodopsin, a protein that helps the eyes to see in dim lighting, and give cells a working copy — all without altering DNA directly. The company's treatment for Duchenne muscular dystrophy, meanwhile, is designed to increase the activity of a gene to restore muscle stability and protect such tissue from further damage.

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Several other biotech firms are pursuing epigenetic editing. Scribe Therapeutics in Alameda, California, co-founded by Doudna, who won a Nobel Prize in Chemistry for her gene editing discoveries[1], has an epigenetic-silencing platform called ELXR. It is a treatment for high cholesterol, targeting the *PCSK9* gene, which nChroma's therapy also goes after. Epigenic Therapeutics in Shanghai, China, is also pursuing cholesterol-lowering epigenetic editing treatments, as well as one for hepatitis B. General Control, a start-up in San Francisco, has set its sights on treating widespread age-related diseases (although it has not disclosed much about which ones). The rationale, says Lada Nuzhna, General Control's chief executive, is that the hallmarks of growing old are often associated with gene expression gone awry, rather than a mutation in a single gene.

Epigenetic editing tools seem to create durable changes to DNA markers. "Once the epigenetic editing of DNA methylation has been achieved, the cells' own machinery should maintain the edited DNA methylation pattern through subsequent cell divisions," Tyler says. Certain enzymes help to copy over the existing methylation patterns from the original DNA strands to new ones in daughter cells.

But the powerful nature of epigenetic editing is also a reason to monitor its safety closely, according to Joly. "Epigenetic editing may appear safer than genome editing because it does not involve cutting DNA, but 'non-cutting' should not be equated with 'risk-free'," Joly says. He adds that shutting off the wrong gene could have important consequences — and that this is especially true if the mistakenly silenced gene is a tumour suppressor or involved in immunity or development. Tyler similarly warns that researchers should be vigilant to make sure unintended effects don't occur. "Off-target epigenetic editing would have the potential to aberrantly alter gene expression," she notes.

Salzman knows from her extended family's history how high the stakes are. "If everything goes in our favour," she says, Epicrispr could file for a licence to sell its FSHD therapy in a few years. "It could be on the market before 2030," she adds. "That's the best-case scenario, but that's not that far away."

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