

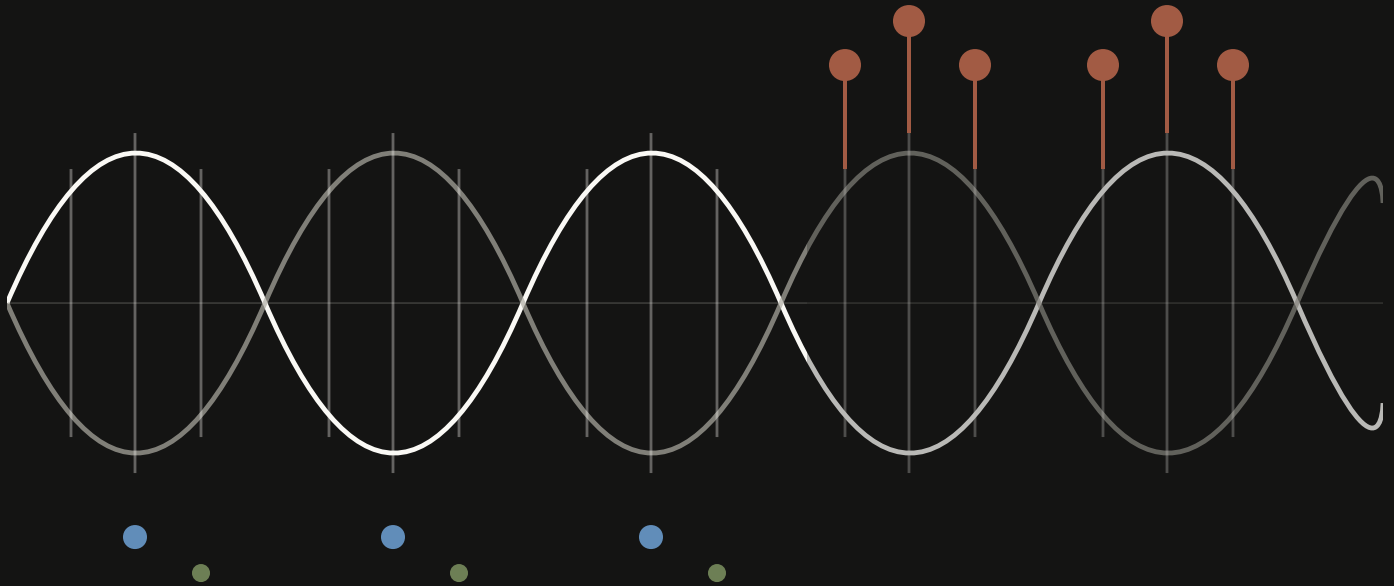
INFLECTION.

The Weekly Magazine of Innovation

ISSUE 02

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DEEP DIVE — EPIGENETIC EDITING



ACTIVE

SILENCED — SEQUENCE UNCHANGED

THE FEATURE · HEPATITIS B & THE DAWN OF EPIGENETIC MEDICINE

The best edit changes *zero* letters.

Two teams just showed they can switch off a virus hiding inside human liver DNA without cutting a single base — by laying chemical tags on it. The quiet version of gene editing may turn out to be the one that reaches hundreds of millions.

THE CONTRARIAN

Why the weaker tool may win the bigger market.

SIGNALS

37,075 clinical trials, read by AI agents in about six hours.

BY THE NUMBERS

Seventeen months of viral silence from a single infusion.

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THE FEATURE

Silence Is the New Scalpel

How epigenetic editors switch off hepatitis B without touching its sequence.

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AGAINST THE GRAIN

The Weaker Tool Wins the Bigger Market

A contrarian read on why "less permanent" may be the killer feature.

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SIGNALS

Agents, Phonons & a Telescope With Time to Spare

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BY THE NUMBERS

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THE LONG VIEW

Editing the Instructions About the Instructions

Plus every source behind this issue.

DISPATCH

Stop editing
the source.
Edit the
config.

Every engineer knows the difference between changing the source code and flipping a feature flag. One is a rebuild, a review, a risk. The other is a line in a config file that decides whether code that already exists ever runs. Biology has the same split. Your DNA is the source. The epigenome, the chemical tags that tell a cell which genes to read, is the config.

For a decade, genetic medicine has been a source-code business: cut, paste, rewrite. That is thrilling when a single broken letter causes a rare disease. It is terrifying when the "patient" is a healthy liver in one of hundreds of millions of people. This week, *Nature Biomedical Engineering* published nChroma Bio's case that you can flip the flag instead: tag a virus's DNA so the cell stops reading it. Tune Therapeutics already has human data doing the same.

Our lens for this issue: **the most scalable intervention is often the one that changes the least.** Keep it in mind as you read the Signals, too. The pattern shows up in agents, in qubits, even in rocket fuel.

— THE EDITORS

DEEP DIVE · EPIGENETIC EDITING

Silence Is the New *Scalpel*

Hepatitis B hides a copy of itself inside liver cells that no pill can reach. The newest answer doesn't cut it out. It puts it to sleep.

BY THE INFLECTION DESK · 9 MIN READ

Picture a piano with one string that plays a sour note every time the hammer falls. You could saw the string out, but a saw near a soundboard is a risky tool. Or you could lay a strip of felt on the string. The piano is intact. The note never sounds. That, in one image, is epigenetic editing, and this month it stopped being a thought experiment.

The enemy is an archive. Chronic hepatitis B affects more than 250 million people worldwide, according to *Nature*. When the virus infects a liver cell, it repairs its genome into a tight loop called cccDNA, a free-floating mini-chromosome that sits in the nucleus and keeps printing viral RNA. One Lyon hepatologist calls it "a genomic archive of the virus." It is the reason the disease is chronic.

Today's standard drugs, nucleos(t)ide analogues, stop the virus from copying itself, but they do not touch the archive. Stop the pills and the virus comes back. Fewer than 10% of people treated for at least ten years can safely stop, *Nature* reports. Tune Therapeutics puts the rate of functional cure on current therapy at roughly 1% per year.

A second hiding place. HBV also stitches fragments of itself into the host's own chromosomes. That integrated DNA keeps making viral proteins that confuse the immune system, and the molecular damage it causes is linked to liver cancer.

Why not just cut? CRISPR-style nucleases can chop viral DNA, and several programs are trying. But cutting DNA in a liver already studded with integrated viral fragments means making many breaks at once, and breaks are exactly what cancer biology feeds on. *Nature* notes that cutting therapies "can increase cancer risks for people with hepatitis B." The scalpel is sharp in the wrong direction.

The felt, not the saw. Epigenetic editing leaves the sequence alone. It uses a CRISPR protein whose cutting blades have been deliberately disabled ("dead" Cas9), guided by RNA to a chosen stretch of DNA and bolted to enzymes that attach methyl groups. Methylated DNA gets packed away and goes quiet. The idea borrows from nature: a rare few chronic HBV patients silence the virus on their own through exactly these repressive marks.

CONTINUED OVERLEAF →

THE BREAKTHROUGHS

01 • Tune: seventeen months of quiet

The first human proof arrived at the European liver congress (EASL) in May. Tune Therapeutics' TUNE-401 is an mRNA-plus-guide payload in a lipid nanoparticle that the liver translates into an HBV-targeting silencer. It methylates both the cccDNA archive and the integrated viral DNA.

In a Phase 1b/2a study across New Zealand, Hong Kong and Moldova, doses ran from 0.2 to 0.85 mg/kg, with a multi-dose arm of up to three infusions. Every participant at dose levels 2 through 4 showed repression of HBV biomarkers. Among HBeAg-negative patients at the two highest doses, 4 of 7 lost detectable pregenomic RNA, the direct readout of an active archive. Among HBeAg-positive patients, 3 of 5 lost HBeAg. After a single dose, repression has held for up to 17 months.

"Rarely seen a clinical signal this clear."

JOHN MCHUTCHISON, CEO, TUNE THERAPEUTICS,
ON 30 YEARS IN HEPATOLOGY

That CEO spent years running R&D at Gilead, where, he told *The Scientist*, his team screened millions of small molecules looking for one that could silence cccDNA safely. None could. The safety profile so far is mild to moderate infusion reactions and brief liver-

enzyme bumps that resolve within days. Tune says Phase 2 could start as early as late 2026.

02 • nChroma: a two-front war, now peer-reviewed

On 21 September, nChroma Bio and collaborators at Milan's San Raffaele Telethon Institute published the preclinical case for CRMA-1001 in *Nature Biomedical Engineering*. The design is the same: dead Cas9, guide RNA, methylating effectors, lipid nanoparticle. It attacks both hiding places at once.

In mouse models the company reported more than a 3-log (1,000-fold) drop in surface antigen, with undetectable antigen and viral DNA in 90% of mice at the top dose. In monkeys, the same effector and delivery system silenced a stand-in liver gene, PCSK9, for more than a year after one dose, with only minimal, temporary side effects. The first human received CRMA-1001 in January, in a trial in Hong Kong and New Zealand.

03 • The machinery is now a platform

Look at that monkey experiment again. nChroma proved safety with a *cholesterol* gene, using the same silencer and the same nanoparticle. Only the guide changed. For an engineer, that is the headline: one chassis, many addresses. The virus is the first customer, not the last.

FROM LAB TO MARKET · WHAT IT MEANS

A dimmer switch for the *genome*.

The timeline. Closer than it looks.

Two companies now have epigenetic silencers in patients, and both are running their trials in hepatitis B hot spots in Asia-Pacific. Tune's Phase 2 will also test the real prize: whether patients can safely stop their daily pills. If silenced cccDNA stays silent, pregenomic RNA should stay undetectable, and without that RNA the virus cannot rebuild its DNA.

The capital. Built to go the distance.

Tune closed more than \$175 million in Series B financing in January 2025. nChroma was formed in December 2024 when Chroma Medicine (the epigenetic cargo) merged with Nvelop Therapeutics (the delivery tech), with \$75 million behind it. The merger thesis is the lesson: in genetic medicine, cargo is only half the product. Delivery is the other half.

The business model. From subscription to settlement.

Hepatitis B today is a lifelong subscription to a daily pill. A one-to-three-infusion silencer turns that into a single transaction. That is a hard sell to payers used to cheap generics, and a very easy sell to patients who fear liver cancer. Whoever wins will have to price the cure against decades of pills avoided.

For the CTO. Think in addresses, not molecules.

Classic drug discovery searches for a new molecule for each target. Programmable silencers keep the molecule and change the address, like swapping a routing key instead of rewriting a service. Expect the first wave in liver disease, where lipid nanoparticles already go naturally. The limit is delivery, not design.

FIELD NOTES

How a silencer works

- 1 Deliver.** A lipid nanoparticle carries mRNA and a guide RNA into liver cells, which read the mRNA and build the silencer protein.
- 2 Dock & tag.** The guide steers a bladeless Cas9 to the viral control sequence. Attached enzymes stick methyl groups onto the DNA there.
- 3 Silence.** Methylated DNA gets packed tight and stops being read. The sequence never changes. Only whether the cell reads it does.

GLOSSARY

cccDNA — the virus's circular mini-chromosome in the liver-cell nucleus; the reservoir pills can't reach.

dCas9 — "dead" Cas9: CRISPR's homing system with its cutting ability switched off.

DNA methylation — small chemical tags on DNA that tell the cell to stop reading a gene.

Functional cure — virus controlled with no treatment and surface antigen gone, even if traces remain.

THE CONTRARIAN

The weaker tool wins the *bigger* market.

The industry prizes permanence. The opening may belong to the medicine that commits to less.

The move that looks wrong

The consensus ranks genetic medicines by power. Base editing beats silencing; a permanent rewrite beats a mark that might fade. By that ranking, epigenetic editing is the junior tool, a bit like a pencil next to a pen.

Our read runs the other way. **Addressable market in genetic medicine is set by risk tolerance, not by power.** Permanent DNA surgery gets approved where the disease is dire and rare, because only there does the benefit justify an irreversible risk. That is why editing's first wins sit in rare disorders.

Hepatitis B is different. Hundreds of millions of patients are managing, not dying, on a daily pill. For them, regulators and patients will set a very low bar for risk. A therapy that makes no DNA breaks, leaves the sequence intact and borrows a mechanism some patients already use naturally clears that bar far more easily. Weaker in the lab, it becomes stronger in the market. The pencil sells more than the pen because people will actually use it.

A second-order bet follows. If the silencer chassis is reused and only the guide changes, the moat is

not any single molecule. It is the safety record of the chassis across many patients. The first company to build that record with a common disease could own the category for every liver target after it.

Why the consensus disagrees

Durability is unproven. Seventeen months is encouraging, not lifelong. Methylation can erode, and liver cells turn over. Nobody yet knows whether a mark laid in 2026 will hold in 2036.

The trials are small. Early cohorts, few patients and no placebo arm. Biomarker loss is not the same as functional cure, and patients are still on their pills.

Off-target marks are real risks. Stray methylation elsewhere in the genome could silence a gene that matters. Long-term tracking is essential.

Delivery is the ceiling. Lipid nanoparticles go to the liver naturally. Brain, muscle and immune cells are much harder. And cheap generic antivirals set a brutal price benchmark.

OUR CALL

Watch safety across patients, not headline potency. The winner is the chassis regulators learn to trust.

Signals.

THREE MOVES FROM OTHER FRONTIERS THIS WEEK

37,075

TRIALS READ IN ~6 HOURS

AI · DRUG DISCOVERY

Stanford builds a "virtual biotech" staffed by AI agents

James Zou's team modeled a drug company as an AI chief scientific officer that hands work to thousands of specialist agents. Assigned one agent per trial, the system pulled outcomes for 37,075 Phase II and III trials in about six hours. It found that drugs aimed at switch-like genes active in few cell types were 48% more likely to reach market, with 32% fewer adverse events. Using only pre-2025 data, it proposed a B7-H3 lung-cancer strategy that a major drugmaker later took down the same path.

SOURCE · SCIENCE (SEPT 2026); SINGULARITYHUB, SEPT 18

2 ms

PHONON RING-DOWN TIME

QUANTUM · SENSING

Scientists watch sound make a quantum jump

Stanford's Amir Safavi-Naeini and colleagues coupled a chip-scale mechanical resonator to a superconducting qubit and watched single phonons, the quanta of sound, drop from state 1 to 0 in real time. The resonator rings for two milliseconds, the equivalent of an ordinary tuning fork humming for hours. That leaves time for hundreds of measurements. Uses include error detection for quantum computers and sensors that could identify proteins.

SOURCE · SCIENCE 393, 1217 (2026); STANFORD VIA SCIENCEDAILY, SEPT 22

22 yrs

OF FUEL, VS 10 PLANNED

SPACE · ASTRONOMY

NASA's Roman telescope may have more than doubled its life

Roman's first mid-course correction on August 31 burned just 40 lb of propellant against a 441-lb budget, a saving of more than 90%, and hit its target with better than 99% accuracy. The observatory also turned out lighter than its conservative budget, 17,760 lb against 21,605 lb, so it launched with extra propellant. NASA now estimates at least 22 years of fuel.

SOURCE · NASA SCIENCE, ROMAN BLOG, SEPT 14; SCIENCEDAILY, SEPT 18

By the Numbers.

250M+

People living with chronic hepatitis B worldwide.

NATURE, SEPT 21, 2026

<10%

Share of patients treated 10+ years who can stop their daily antivirals without a severe rebound.

NATURE, CITING F. ZOULIM

17 mo

Longest durable biomarker repression seen so far after a single TUNE-401 infusion.

TUNE THERAPEUTICS, EASL 2026

100%

Share of TUNE-401 participants at dose levels 2–4 showing HBV biomarker repression.

TUNE THERAPEUTICS, EASL 2026

90%

Share of mice with undetectable HBV surface antigen and DNA at CRMA-1001's highest dose.

NCHROMA BIO, AASLD 2025

1 yr+

Length of liver-gene silencing in monkeys after one dose of the same effector and nanoparticle.

NCHROMA BIO, AASLD 2025

≈1%

Approximate yearly rate of functional cure under today's therapies. This is the baseline every silencer is racing to beat.

TUNE THERAPEUTICS RELEASE, CITING PUBLISHED LITERATURE

THE LONG VIEW

Editing the instructions *about* the instructions.

Line up this week's stories and a pattern appears. In the liver, the breakthrough didn't change the viral DNA. It changed the layer that decides whether that DNA is read. At Stanford, the virtual biotech didn't invent a better molecule. It built a better way to decide which molecules deserve a trial. In the quantum lab, the advance wasn't a new kind of sound. It was a qubit that could watch sound without disturbing it. Even Roman's extra decade came from precision in the control layer, not a bigger tank.

That is the mark of a maturing technology. Early on, progress comes from raw power: stronger

cuts, bigger models, more fuel. Later, the leverage moves up a level, to control, selection and observation. The substrate stays put, and the instructions about it get smarter.

For builders, the lesson travels. The riskiest change to any complex system is a rewrite of its core. The cheapest, safest and often most scalable change is to the layer that governs it. Epigenetic editing is biology's feature flag, and it arrived first for a disease that affects hundreds of millions of people, not a handful. Whether the silence lasts ten years is still open. But the question has changed from "can we cut it?" to "do we need to?"

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INFLECTION.

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THE LENS · THIS WEEK'S QUESTION

*In the systems you run, what are you
rewriting that you could simply **stop**
reading?*

NEXT ISSUE · FRIDAY

Issue 03 lands October 2. A new deep dive from a different frontier: energy, robotics, materials or space, wherever the week's biggest surprise turns out to be.

RECURRING

The Contrarian · Signals · By the Numbers · The Long View. Every figure is sourced, and every source is listed.