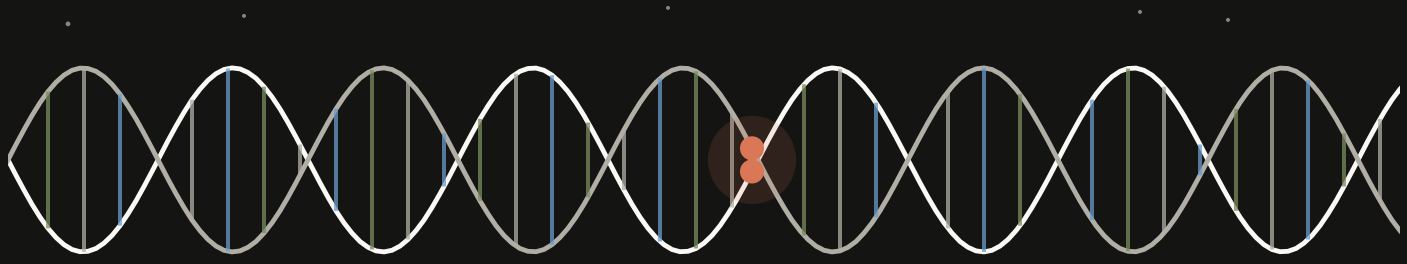
INFLECTION.

THE WEEKLY MAGAZINE OF INNOVATION

ISSUE 03 · FRIDAY, 20 NOVEMBER 2026 · DEEP DIVE — GENE EDITING



ONE LETTER, REWRITTEN
NO DOUBLE-STRAND CUT

THE DEEP DIVE

The Edit Is Not the *Product*

Base editing has just cleared its first pivotal trial, and the cleverest thing in the therapy is not the edit. It is the hospital stay wrapped around it. Read the week through the step that did not improve.

- Why 31 patients and 12 months may matter less than the chemotherapy that comes first
- Casgevy went from 5 patients to 64 in a year: what that slope says about who wins
- Signals: a magnet that survives at atomic thinness · quantum memory that vibrates · the carbon budget's four-year clock

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THE DISPATCH

A cure has two halves: the molecule and the procedure.

> *The procedure is the product.*

Ask a pharmacist what a drug is and she will name a molecule. Ask a patient with sickle cell disease what the treatment is and you will hear about collecting stem cells, a course of chemotherapy, weeks in hospital, and somewhere in the middle, an edit. This week the edit passed its pivotal test. The rest of the procedure did not change.

On 10 November, Beam Therapeutics said its base-edited therapy, risto-cel, met the primary goal of its BEACON trial: freedom from severe pain crises for at least twelve months. Beam plans to file for approval as early as the end of the year, which could make it the first base-editing therapy submitted to the FDA. Most coverage asks whether the edit works. We ask something more useful: what, exactly, is being sold?

This issue's lens is to find the step that has not improved. That is where the next decade of value, and of risk, tends to sit. Our three Signals each hide one too.

— THE EDITORS

THE FEATURE

One Letter at a Time

Beam's risto-cel rewrites a single letter of DNA without cutting the double helix, and it has just cleared its pivotal trial. Here is what that proves, and what it leaves open.

BY THE INFLECTION DESK · RESEARCH DRAWN FROM BEAM THERAPEUTICS, BIOPHARMA DIVE AND PHARMAPHORUM · 9-MINUTE READ

Sickle cell disease is a one-letter typo. A single point mutation, known as E6V, in the beta-globin gene makes hemoglobin clump into long, rigid molecules that bend red blood cells into sickles. The sickled cells jam blood vessels and die early, and the result is anaemia, severe pain crises, infections, stroke, organ failure and early death. It is the most common inherited blood disorder in the United States, affecting an estimated 100,000 people there and roughly eight million worldwide.

The problem: fix the typo, or sidestep it

The obvious cure is to correct the typo. Risto-cel does something sneakier: it switches on a backup gene. Fetal hemoglobin, or HbF, is the main hemoglobin during development and early life, and it does not sickle. Babies are protected until the body turns HbF off. The switch is a protein called BCL11A, which sits on the promoters of the HBG1 and HBG2 genes and holds HbF down.

Risto-cel is a one-time therapy made from the patient's own CD34+ blood stem cells. Those cells are base-edited in the promoter regions of HBG1/2 so that BCL11A can no longer bind, without disrupting BCL11A itself. HbF production goes up. The design mimics natural gene variants in people whose fetal hemoglobin never switches off.

Scissors versus pencil

Older CRISPR is scissors: cut both strands of DNA and let the cell patch the gap. Base editing is a pencil with an eraser. It changes individual letters in place, and, in contrast to older CRISPR approaches, it does not cut through the DNA. Casgevy, the first CRISPR-made therapy approved for sickle cell, also works by raising fetal hemoglobin, but it is built on a different underlying technology.

Both are made the same way round: extract the patient's cells, re-engineer them in a lab, and transplant them back, where they settle in the bone marrow and begin making new blood cells. Hold on to that last sentence. It is the one the rest of this issue turns on.

What the trial actually showed

A pivotal result, without the numbers

BEACON is an open-label, single-arm, multicentre Phase 1/2 study. As of the 20 October 2026 data cutoff, 39 adults and 10 adolescents had been treated, and 31 had completed the follow-up needed for the main endpoint. That endpoint, called VF12, is freedom from severe vaso-occlusive crises (VOCs) for at least 12 consecutive months, judged by independent adjudication.

Beam says the study met it, met all primary safety endpoints at a prespecified interim analysis, and met every secondary efficacy endpoint, including freedom from inpatient hospitalisation for severe VOCs for 12 consecutive months. What Beam did not release is any percentage, any count of patients who stayed crisis-free, or any detailed safety table.

When the detail arrives

An earlier data cutoff goes to an oral presentation at the American Society of Hematology meeting in New Orleans on 12–15 December. Full pivotal results are planned for a medical meeting in 2027. The company expects to submit a Biologics License Application as early as year-end 2026.

> *"These are the first Phase 3 results to deliver on the much-heralded promise of in vivo CRISPR gene editing."*
>
> JOHN LEONARD · CEO, INTELLIA THERAPEUTICS

The cousin that skips the transplant

The same week's clinical story has a twin. Intellia's lonvo-z targets the KLKB1 gene in hereditary angioedema, and it is edited inside the body in a single outpatient infusion. In the HAELO Phase 3 trial it cut investigator-confirmed attacks by 87% versus placebo from week five to week 28, and 62% of patients were attack-free over six months against 11% of controls. Intellia has begun a rolling application and is aiming for a launch in the first half of 2027.

Why the comparison matters

Risto-cel and lonvo-z are not rivals; they treat different diseases. They do show two ways to deliver the same idea. One edits cells outside the body and returns them after a transplant. The other goes straight to the liver cells and needs no transplant. If you are building anything in this field, that fork is the strategic choice.

Beam says the safety it has seen so far is consistent with the known effects of its procedure: plerixafor to mobilise stem cells, the cell collection itself, myeloablative conditioning with busulfan, the transplant, and the underlying disease. That sentence deserves a second look on page six.

FROM LAB TO MARKET

What it means, and what it does not

Proven: a single-letter edit to a fetal hemoglobin switch can keep severe pain crises away for a year in a single-arm study, as judged by independent reviewers. **Not yet shown:** how long it lasts beyond that, how it compares head to head with approved options, and what it will cost to deliver at scale. Beam itself flags that treatment effects may not prove durable over longer follow-up.

Risto-cel would arrive third in a market that has been slow. Casgevy and Lyfgenia both sold slowly at first. Genetix, the company formerly known as bluebird bio, sold itself after struggling to market Lyfgenia and its other gene therapies. Only five people received Casgevy in the second half of 2024. The number receiving treatment rose to 64 in 2025, bringing $116 million in revenue, and Vertex booked $219 million in Casgevy sales in the first nine months of 2026.

Beam's management told analysts in September that uptake has been held back by supply constraints rather than weak demand or reimbursement. RBC analysts add that risto-cel could be attractive because it has a shorter manufacturing process and needs fewer cycles of treatment to mobilise the cells. On the day of the news, Beam's shares fell by as much as 10%.

For the CTO. Treat a therapy like a pipeline, not a product. Throughput is set by the slowest stage. In ex vivo gene therapy that stage is the clinic (stem cell collection, conditioning, a transplant bed), not the lab. A better edit raises quality. It does not raise capacity. That is our inference, not Beam's claim.

Timeline: BEACON data cutoff 20 Oct → topline 10 Nov → ASH oral 12–15 Dec → BLA as early as year-end 2026 → detailed results in 2027.

FIELD NOTES · HOW A BASE-EDITED CELL THERAPY IS MADE

1. **Mobilise and collect.** A drug called plerixafor pushes blood stem cells out of the marrow, and the patient's CD34+ cells are collected.
2. **Edit.** A base editor rewrites the promoters of HBG1/2 so BCL11A can't bind, and fetal hemoglobin switches back on.
3. **Clear and return.** Busulfan chemotherapy clears the marrow, and the edited cells are infused back as a transplant.

GLOSSARY

Base editing. Changing a single DNA letter in place, with no double-strand cut.

HbF. Fetal hemoglobin, a non-sickling form made early in life.

VOC. Vaso-occlusive crisis: the severe pain episode caused by sickled cells blocking vessels.

Myeloablative conditioning. High-dose chemotherapy that clears the bone marrow before a transplant.

THE CONTRARIAN

The Bottleneck Is *the Product*

Everyone is grading the edit. Grade the hospital bed.

The unfashionable read

Read the safety line in Beam's own press release again. The findings are described as consistent with the known and intended effects of plerixafor, cell collection, busulfan conditioning, the transplant, and the underlying disease. The edit is not on that list. What the patient has to endure, in other words, is the procedure.

Now add the market. Five Casgevy patients in the second half of 2024. Sixty-four in 2025. Beam's own management points to supply constraint, not demand. If the limiting factor is how many people the system can collect, condition and transplant, then a more elegant edit improves outcomes without widening the funnel.

What follows (our inference)

First, the edit commoditises. Casgevy is already on the market and risto-cel may follow, and both work by switching fetal hemoglobin back on. Differentiation moves to cycle time, number of mobilisation cycles and bed-days. Second, the long-run threat to any ex vivo therapy is the in vivo route, and Intellia has just shown that route can win a Phase 3 in another disease. We found no pivotal in vivo result for blood stem cells. Third, the scarce asset may be treatment-centre capacity, not the molecule.

WHY THE CONSENSUS DISAGREES

01 **The evidence is thin by design.** A single-arm, open-label study with 31 patients evaluable for the main endpoint, and no figures released. The consensus reads "met every goal" as a strong signal; we cannot yet check it.

02 **Twelve months is not a cure.** Beam's own risk language notes that effects may not prove durable. A better edit could still show its value over years.

03 **The supply argument is not independent.** It comes from Beam management, relayed in an analyst note. The data on throughput is not public.

04 **Precision may matter more than we say.** Editing without a DNA cut could carry safety advantages that topline data cannot reveal. Safety signals from other gene editing programmes, such as the liver-toxicity hold on Intellia's nex-z, show how organ-specific risks can surface late.

MATERIALS

few Å

A magnet that stays alive when you shave it to atoms

Multiferroics let a tiny voltage flip both an electrical and a magnetic state, which could mean memory and logic that need far less energy. The catch has been the “dead layer”: thin enough to fit in a chip, the material stops working. Brown University grew bismuth ferrite on a dysprosium scandate base, which squeezes it into the right structure, and added a metallic layer to cancel interfering electric fields. The film stays ferroelectric and magnetic down to a few angstroms, and shows altermagnetism, a magnet type that is fast like an antiferromagnet yet readable like a ferromagnet. It is a lab result; more development is needed before it reaches commercial chips.

SOURCE · ScienceDaily / Brown University, 12 Nov 2026 · sciencedaily.com/releases/2026/11/261111005853.htm · Nature Materials, doi:10.1038/s41563-026-02786-1

QUANTUM

1st

Quantum memory that vibrates like a guitar string

At ETH Zurich, Yiwen Chu’s team stores quantum information in tiny mechanical vibrations and pairs it with a superconducting qubit, much like a CPU working with RAM. It is the first experimental demonstration that mechanical resonators can work with superconducting qubits to carry out quantum computations. The team ran the quantum Fourier transform and a period-finding algorithm, and the architecture can in principle perform all the operations needed for arbitrary quantum computation. Vibrations are compact, can hold many patterns, and can keep states for longer. The open question is scaling to larger systems while keeping precision.

SOURCE · ScienceDaily / ETH Zurich, 11 Nov 2026 · sciencedaily.com/releases/2026/11/261109205416.htm · Science 392(6801):972, doi:10.1126/science.aef4139

CLIMATE

−0.4%

Fossil emissions dip, but the clock on 1.5°C is under four years

The Global Carbon Budget projects fossil CO2 emissions to fall 0.4% in 2026, to 38.2 billion tonnes, partly thanks to solar and wind and partly due to disruptions linked to the Iran conflict. Including land-use change, total emissions are set to hit 43.3 billion tonnes, up from 42.8. The remaining budget for 1.5°C is about 150 billion tonnes, under four years at current rates. Solar, wind and EVs are meeting roughly two-thirds of the extra energy demand, yet novel carbon removal offsets less than 30 minutes of annual fossil emissions. As one author put it, a one-year drop is not a peak unless it is driven by structural change.

SOURCE · ScienceDaily / University of Exeter, 10 Nov 2026 · sciencedaily.com/releases/2026/11/261109205358.htm · Earth System Science Data, doi:10.5194/essd-2026-895

49

Patients treated in Beam's BEACON trial as of 20 October: 39 adults and 10 adolescents.

31

Patients who had completed the follow-up needed for the 12-month crisis-free endpoint.

5 → 64

People receiving Casgevy: second half of 2024 versus the whole of 2025.

$219M

Vertex's Casgevy sales in the first nine months of 2026.

87%

Fewer hereditary angioedema attacks than placebo with Intellia's lonvo-z, weeks 5 to 28.

62% vs 11%

Attack-free over six months: lonvo-z against the control group.

8 million

People living with sickle cell disease worldwide, by Beam's estimate. About 100,000 are in the US.

Change the architecture around the thing, not the thing

Four stories this week, one pattern. Beam edited the right letter, and the part patients feel is still the chemotherapy and the transplant around it. Brown did not make a better multiferroic; it changed the strain and the electric field around the film, and the dead layer went away. ETH did not build a better qubit; it split processing from memory, as classical computers have done for decades.

The climate numbers carry the warning label. A fall in fossil emissions caused partly by a geopolitical shock is an event, not a structure. The honest caveat for every item here is that it is early: 31 patients, one film, one chip, one year. The cost of being early is risk. The cost of ignoring the pattern is discovering that the part you did not examine was the part that set the limit.

What to watch: whether Beam files its BLA by year-end, what the December ASH presentation reveals about durability and the procedure, and whether Intellia's first-half 2027 launch shows how fast a no-transplant route can grow.

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8. **Further reading:** HAELO trial record, ClinicalTrials.gov NCT06634420 — https://clinicaltrials.gov/study/NCT06634420

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THE LENS · A QUESTION FOR YOUR WEEK

Which step in your pipeline is quietly setting your throughput, and when did you last improve it?

NEXT ISSUE · FRIDAY, 27 NOVEMBER 2026

A fresh deep dive from a different domain, three new Signals, and a contrarian column that argues with the consensus.

RESEARCHED, WRITTEN & DESIGNED WITH CLAUDE. TYPESET IN POPPINS & LORA ON THE ANTHROPIC PALETTE.