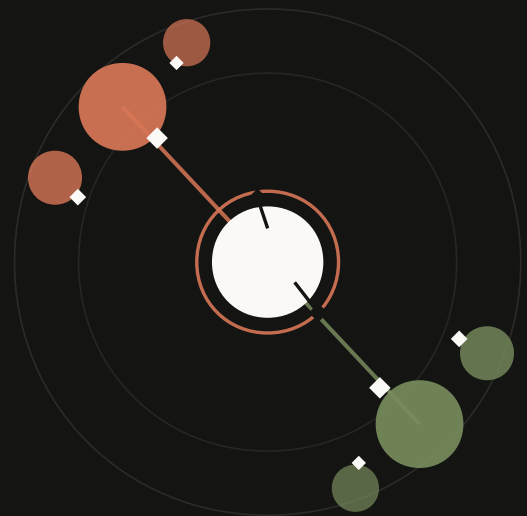


THE MOVE 37 BREAKTHROUGH

To kill the deadliest brain cancer, aim at the cells *protecting* it.

A *Nature* paper this week inverted a decade of immunotherapy dogma. Instead of arming T-cells to survive a tumor's hostile guards, researchers found one molecular badge worn by both the cancer *and* its guards — and built a single therapy to clear them together. In mice, the tumors vanished.



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DISPATCH · EDITOR'S NOTE

The durable fix rarely targets the thing you're angry at.

Every so often a result matters less for what it does than for what it assumes. This week's came from oncology — the field that has spent a generation teaching humility to people who thought biology was an engineering problem.

Faced with a hostile system, the instinct is to harden your agent against it: more armor, more redundancy, more resistance. Glioblastoma has punished that instinct for years. The tumor's genius isn't toughness — it's *recruitment*. It conscripts your own immune cells and turns them into guards.

So the move that matters isn't a better soldier. It's a change of target: one badge worn by both the cancer and its captured guards, cleared in a single stroke. Hold that lens over the rest of the issue — a chip built for one workload, a reactor built on an abandoned magnet, a sky surveyed instead of a single star. The theme of the week is *aim*.

THE EDITORS · INFLECTION

The Shared Badge

A hunt through the glioblastoma's molecular junk drawer found a single marker on both the cancer and its bodyguards — and rewrote the rules of solid-tumor immunotherapy.

BY THE INFLECTION EDITORS • JULY 3, 2026

Glioblastoma is the tumor that has humbled oncology. It is the most common malignant brain cancer in adults, and after six decades of surgery, radiation, and chemotherapy the median patient still lives roughly fifteen months. Fewer than seven in a hundred are alive at five years. The cruelty is not that we lack weapons — it is that the tumor turns our own immune system into its staff, then dares us to fire on our own troops.

For blood cancers, the last decade belonged to CAR-T. Engineers take a patient's T-cells, bolt on a synthetic "chimeric antigen receptor" that recognizes a molecular badge on the cancer, and reinfuse an army trained to hunt. In leukemia and lymphoma the results can look like miracles: durable remissions where chemotherapy failed.

Then the same idea met solid tumors and stalled. In glioblastoma, CAR-T aimed at antigens such as EGFRvIII, IL13R α 2, and HER2 produced flickers of response followed by relapse. The problem was never that the cells couldn't find the tumor. It was *where* they had to fight.

A glioblastoma is not a lump of cancer cells. Up to half of its mass is immune cells — tumor-associated macrophages, the body's cleanup crew, recruited and then corrupted into a suppressive state that switches off the very T-cells we send in. The tumor digs a swamp and staffs it with turncoat guards.

Why does that microenvironment beat a T-cell? Partly physics: the tumor is a disorganized fortress of leaky vessels

that keeps infused cells from reaching the core. Partly chemistry — a fog of suppressive signals, much of it exhaled by those conscripted macrophages. A cell that breaches the wall often arrives too exhausted to fight.

For ten years the field's answer was to armor the soldier: engineer T-cells to resist exhaustion, secrete their own fuel, or ignore the tumor's "stand down" signals. Useful, incremental — and never enough. The swamp always won on points.

The obvious countermove is a tougher soldier. The non-obvious one is to change the question: what if the molecule that marks the cancer also marks its defenders? Then a single receptor might dismantle the fortress and its garrison in one motion.

This week, a North American consortium led by neurosurgeon-scientist Sheila Singh published a different move. They stopped trying to help the soldier survive the swamp. They went looking for a way to drain it.

The badge on **both** uniforms

Rather than begin with the cancer cell, the team ran a multi-omic hunt across the entire tumor — malignant cells and immune cells alike — for a surface marker they had in common. They found one: **GPNMB**, glycoprotein non-metastatic melanoma protein B, sitting on both the glioblastoma cells and, crucially, on the immunosuppressive macrophages doing the shielding.

It is an almost literary detail. One badge, worn by both the enemy and its bodyguards — and, better still, GPNMB is displayed most heavily by exactly the suppressive macrophages that make the tumor untouchable. The marker of the disease and the marker of its defense turned out to be the same molecule.

"They didn't teach the T-cell to survive the swamp. They pointed it at the swamp."

One receptor, **two** enemies

The researchers built a CAR-T cell against GPNMB and turned it loose in the hardest test beds immunology has: orthotopic patient-derived xenografts — human tumors grown in the mouse brain — and fully immunocompetent mouse gliomas. The engineered cells did two jobs at once.

They killed GPNMB-positive tumor cells, and they selectively deleted the immunosuppressive macrophages while largely sparing the pro-inflammatory ones. Clearing the guards flipped the microenvironment from hostile to permissive, and

the attack began to compound on itself: fewer suppressors meant fitter T-cells, which cleared more tumor, which recruited fewer suppressors.

The test bed matters, too. An immune-deficient mouse can flatter a therapy by stripping out the very defenses that sink it in patients; a fully immunocompetent animal keeps the hostile microenvironment intact. It is the harder, more honest trial — and the one where most solid-tumor CAR-T quietly fails.

Eradicated — and staying **gone**

Across multiple models, including patient-derived tumors, the therapy eliminated all detectable tumor and produced durable, disease-free survival. Not slower growth — animals that lived on, cancer-free.

In a disease where "progress" usually means a few extra weeks, complete and lasting clearance in immunocompetent models is the kind of result that makes cautious scientists

reread the methods section twice. The mechanism, not just the outcome, is what earned the *Nature* cover.

Durability is the tell. Debulked tumors regrow; tumors whose supporting niche has been dismantled often do not. These animals were not merely tumor-free at the final measurement — they stayed that way.

The honest timeline

A mouse cure is not a human cure — least of all in glioblastoma, whose history is a museum of therapies that erased tumors in rodents and failed in people. What travels is the *strategy*, not the promise. Expect IND-enabling toxicology, manufacturing, and then early-phase trials measured in years, not quarters.

Why a strategist should care

The reusable idea is target *selection*, not the target. If you can find one antigen shared by a tumor and its support system, you convert the microenvironment from a shield you must survive into a target you can attack — with the therapy you already built.

That reframes a decade of solid-tumor immunotherapy. The field spent years optimizing the soldier. This paper optimizes the *map* — choosing a target whose geometry already spans the enemy and its infrastructure. GPNMB CAR-T programs exist for other solid tumors; a dual-compartment rationale gives them a logic competitors lack.

There is a caution folded into the optimism: a target that spans the tumor and immune compartments is potent precisely because it is not tumor-specific — which is also why it could be dangerous. Hold that thought for the next page.

GLOSSARY · FOUR TERMS

CAR-T

T-cells re-engineered with a synthetic receptor that targets a chosen surface marker.

TAM

Tumor-associated macrophage — an immune cell conscripted to suppress attack; up to half a glioblastoma's mass.

GPNMB

The surface glycoprotein found on both glioblastoma cells and suppressive macrophages — the shared badge.

Orthotopic PDX

A patient's tumor grown in its native site — here, the mouse brain — the most realistic preclinical test.

FIELD NOTES

How it works, in three steps

1 Find the shared badge

Scan the whole tumor for a surface marker common to the cancer cells and their suppressive macrophages. Here: GPNMB.

2 Build one receptor

Engineer the patient's T-cells with a single CAR that recognizes that badge — one receptor, two cell types in its sights.

3 Clear crop and soil

Infused cells kill tumor cells *and* delete the suppressive guards, flipping the microenvironment so the attack sustains itself.

The trick is not a stronger weapon. It is a target that touches both the disease and its defense.

The headline is "CAR-T cures brain cancer in mice." The real signal is that the *objective function* just changed.

For a decade the field optimized T-cell *durability* — how to keep a soldier alive in a poisoned field. This paper optimizes target *topology*: choosing an antigen whose geometry spans both the tumor and its defenses. That is a Move 37. It looks like a targeting error — why aim your cancer gun at immune cells? — until you see that those immune cells are the tumor's regenerative infrastructure. Cut the supply line and the visible enemy starves.

The lesson generalizes past oncology. In any adversarial system, the resilient move is often to retarget the enabling structure rather than the loud symptom. The badge, not the soldier.

Consider what "objective function" means here. For a decade the metric that mattered was persistence — how long an engineered cell keeps killing inside a suppressive tumor. Every clever fix optimized that one number. This work swaps the metric for coverage: how much of the tumor's operating system a single target can touch.

A strong player, asked to design a glioblastoma therapy, would not spend the antigen budget on immune cells. It looks like waste — until you see that those cells are what regrow the tumor and shield it from everything else.

WHY CONSENSUS DISAGREES

It's mice. Glioblastoma's graveyard is full of rodent cures — EGFRvIII CAR-T among them — that evaporated in humans. Preclinical eradication is table stakes, not proof.

GPNMB isn't tumor-exclusive. It appears at lower levels on normal macrophages, dendritic cells, and skin. The last drug to chase it, the antibody-drug conjugate *glembatumumab vedotin*, cleared safety but missed efficacy in breast cancer and melanoma and was shelved. On-target, off-tumor toxicity is a live risk.

Deleting macrophages cuts both ways. Selectivity for the suppressive subset is the whole ballgame; if it slips in humans, normal immunity pays.

Solid tumors fight physics. Getting cells into the brain, antigen escape, manufacturing, cost.

No human data yet. This is a preclinical proof of mechanism; the first-in-human trial that would truly test it does not exist in these results.

The consensus isn't wrong to be cautious — it has been burned before. But cautious people should still notice when the objective function changes. Even if this therapy fails in trials, the design principle — make the microenvironment a target, not an obstacle — will outlive it.

9
months

COMPUTE

OpenAI and Broadcom unveil "Jalapeño"

A reticle-sized inference ASIC, co-developed from first design to manufacturing tape-out in nine months — billed as the fastest advanced-node ASIC cycle ever, with OpenAI using its own models to accelerate the design. Early data claims performance-per-watt "substantially better" than today's best, with gigawatt-scale deployment by year-end. The recursive loop — models designing the chips that run the next models — just tightened another turn.

SOURCE · OPENAI / BROADCOM · JUN 24 2026

<\$50
per MWh

ENERGY

Fusion's abandoned architecture returns

Realta Fusion unveiled *Hammir-DT*, billed as the first modern axisymmetric tandem magnetic-mirror power-plant design: ~500 MW of fusion power, continuous rather than pulsed, on high-temperature-superconductor magnets, with a modeled cost of electricity under \$50/MWh. The twist is historical — the magnetic mirror was fusion's dead end, mothballed in the 1980s. It is back because the magnets finally caught up to the idea.

SOURCE · REALTA FUSION · JUN 2026

161
new mergers

COSMOS

The black-hole census goes industrial

The LIGO-Virgo-KAGRA catalog GWTC-5.0 added 161 new black-hole collisions, lifting the all-time tally of gravitational-wave detections to 390 — including GW250114, the clearest signal ever recorded, at a signal-to-noise of 76.9. In a decade, black-hole mergers went from once-in-history events to a routine survey, and the population is exposing a hidden class of "second-generation" holes built from earlier collisions.

SOURCE · LIGO / CALTECH · 2026

BY THE NUMBERS

Seven figures that frame the week.

6.8%

Five-year survival for glioblastoma — the cancer this week's feature targets.

15_{mo}

Median survival with the full standard of care — surgery, radiation, chemotherapy.

30–50%

Share of a glioblastoma's mass made of tumor-associated macrophages — the "soil."

9_{mo}

Design-to-tape-out for OpenAI's Jalapeño — a claimed record for advanced ASICs.

390

Total gravitational-wave detections after this year's catalog — 161 of them brand-new.

\$50/_{MWh}

Target electricity cost for Realta's magnetic-mirror fusion plant.

76.9

Signal-to-noise of GW250114, the clearest gravitational wave ever heard — a merger of two near-identical black holes, ~32 and ~34 times the mass of the Sun.

The frontier this week wasn't stronger tools. It was *better-chosen targets.*

Read the issue back to back and a single throughline surfaces. In cancer, the win came from aiming at the macrophage instead of only the tumor. In silicon, from a chip narrowed to one workload instead of a general-purpose accelerator. In fusion, from a magnet architecture everyone had written off. In astronomy, from surveying the whole sky rather than chasing a single spectacular event.

None of these was primarily a story about raw power. Each was a story about *aim* — choosing the right thing to point at, and then letting a modest tool do outsized work because it was pointed correctly. That is the quiet pattern behind a lot of what gets called a breakthrough: not a bigger hammer, but a better-read map.

The glioblastoma result is the sharpest version because its target looks, at first, like a mistake. Firing on your own immune cells is exactly the kind of move a careful person would rule out — until you notice those cells are the tumor's infrastructure. Move 37 was ruled out by every strong human player too. The lesson for anyone building in an adversarial system is the same: before you harden the soldier, ask whether you're aiming at the right enemy.

It will be years before we know whether this particular therapy survives contact with human biology. The design principle almost certainly will.

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Aim is the cheapest lever in innovation — and the least evenly distributed. The teams that win this decade may not be the ones with the most compute or the biggest labs, but the ones asking, before every build: are we pointed at the right thing?

THE LENS · A QUESTION TO SIT WITH

When the fix is to change *what you aim at*,
how do you know you've chosen the right
target — and not just a clever one?

