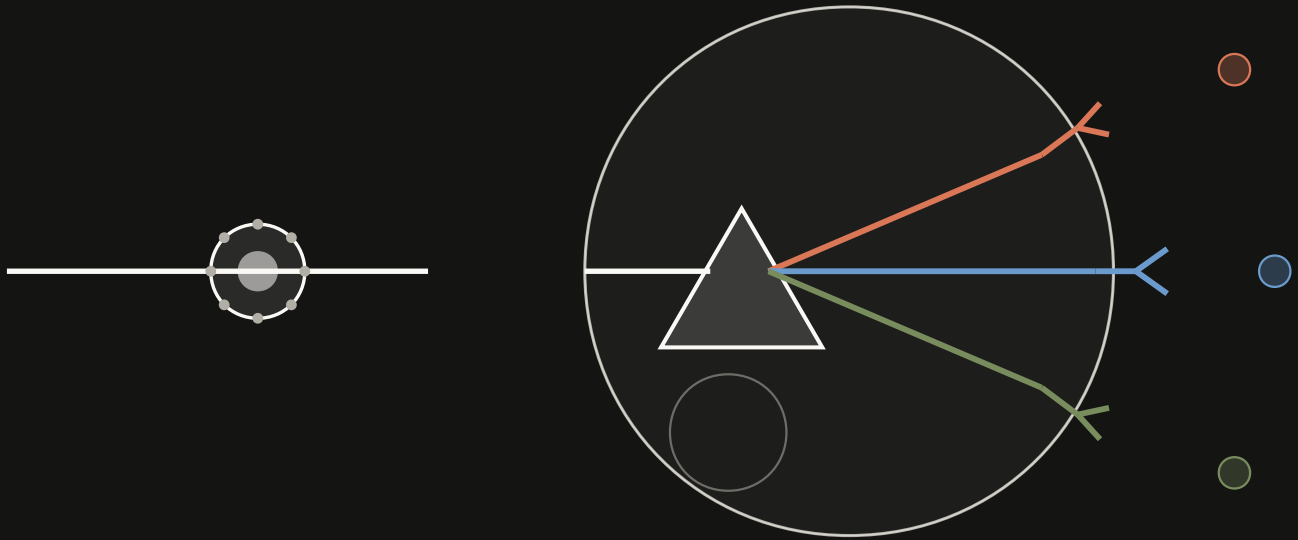


INFLECTION.

THE WEEKLY MAGAZINE OF INNOVATION

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DEEP DIVE — IN VIVO CELL THERAPY



BIOTECH · CELL THERAPY

The Factory *Disappears*

In eighteen months, big pharma has committed roughly \$14 billion to a technology that builds CAR-T cells inside the patient instead of inside a clean room. The bet is not on a better medicine. It is on deleting the building where medicine gets made — before a competitor deletes it for you.

- 01 Why a billion dollars changed hands on one patient's data
- 02 The Contrarian: in vivo CAR-T will win by being worse
- 03 A hydrogen turbine with no compressor — 303 seconds and counting

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DISPATCH**FROM THE EDITOR**

Two things happened this week that look unrelated and are not. In Karlsruhe, engineers ran a gas turbine for 303 seconds without a compressor — the component that normally eats about half of a turbine's own output. In New Brunswick, Johnson & Johnson paid \$785 million for the option to buy a company that makes CAR-T cells without a factory.

A compressor and a clean room do the same kind of work. Neither one is the point of the system. Both exist purely to prepare an input for the process that actually matters — squeezing air before combustion, engineering cells before infusion. And in both cases, the preparation stage had quietly become the most expensive, most fragile, most capital-hungry thing in the whole apparatus.

That is this issue's lens, and it is the one I keep returning to. Mature fields almost never advance by making the main event better. Combustion has been well understood for a century; CAR biology has been well understood for a decade. They advance when somebody looks at the elaborate machinery bolted to the front of the process and asks whether it needs to be there at all. The answer is usually no, and the answer is usually unwelcome — because that machinery is somebody's moat.

The deep dive that follows is about cell therapy, but do not read it as a biotech story. Read it as a case study in what happens to an industry when its hardest-won capability — the thing it spent a decade and several billion dollars learning to do — turns out to have been scaffolding.

THE THESIS, IN ONE SENTENCE

*When a process learns to generate its own preconditions, the apparatus that used to supply them stops being an **asset** and starts being a **liability**.*

THE FEATURE

The Factory Disappears

Cell therapy was never really a drug. It was a bespoke manufacturing service wearing a drug's regulatory clothing. A wave of deals this summer is a bet that the manufacturing is about to become optional — and that the plants everyone built are the industry's biggest liability.

BY INFLECTION · REPORTING WEEK OF 31 JULY – 6 AUGUST 2026

On 28 July, Johnson & Johnson wrote Sail Biomedicines a cheque for \$785 million — \$465 million of it as equity — plus up to \$140 million in milestones, and took an exclusive option to buy the company outright for another \$2.58 billion. Total potential value: north of \$3.5 billion. Sail's lead programme, SAIL-0839, has not reported human data. What J&J bought, on the merits, is a delivery vehicle: nanoparticles carrying circular RNA to CD4- and CD8-positive T cells, and a promise that those cells will build their own chimeric antigen receptors without ever leaving the body.

A drug that is actually a supply chain

To see why a pharma giant pays billions for an unproven delivery system, you have to look at what conventional CAR-T actually is. The approved therapies — Yescarta, Carvykti, Breyanzi and the rest — are autologous, meaning each dose is built from the patient's own cells. The sequence is unforgiving. Book an apheresis slot. Draw the patient's blood and separate the T cells. Freeze them. Ship them, in a cryogenic container, to one of a handful of licensed facilities. Thaw, activate, transduce with a viral vector, expand for a week or two, run release testing, freeze again, ship back, and infuse — after first destroying the patient's remaining lymphocytes with chemotherapy so the new cells have room to grow.

Vein-to-vein, that loop takes four to eight weeks. Somewhere between five and ten per cent of builds fail outright, and in sicker cohorts the reported failure rate runs higher still. A single Carvykti infusion lists at \$465,000 before the hospital, the conditioning chemotherapy or the intensive-care monitoring, which is why total US cost of care routinely lands between half a million and a million dollars.

None of that is a pricing problem. It is a throughput problem wearing a pricing problem's costume. You cannot serve a population from a build queue.

And the population just got enormous

For CAR-T's first decade the queue was tolerable, because the eligible population was small: patients with relapsed blood cancers who had exhausted every other option. Then, in 2022, Georg Schett's group in Erlangen pointed the same CD19-directed cells at autoimmune disease, on the theory that if you delete the B-cell compartment thoroughly enough, the immune system reboots without its pathological memory.

It worked, and it worked in a way that embarrassed sixty years of immunology. In the group's fifteen-patient case series — eight with lupus, three with inflammatory myositis, four with systemic sclerosis — every lupus patient reached DORIS remission, and every patient stopped immunosuppressive therapy entirely. Median follow-up was fifteen months; some patients have since passed two years drug-free.

That result detonated the market logic. Refractory blood cancer is measured in tens of thousands of patients a year. Lupus, rheumatoid arthritis, myositis and scleroderma are measured in millions. A therapy that requires a clean-room slot per patient cannot reach them. Something has to give, and it is not going to be the biology.

BREAKTHROUGHS

Ship the compiler, not the binary

The particle with an address

The enabling trick is targeted delivery. A lipid nanoparticle is a fat bubble that fuses with whatever cell it bumps into — and left alone, what it bumps into is the liver. Roughly speaking, LNPs are hepatocyte-seeking missiles by default, which is fine for a clotting-factor therapy and useless for a T-cell therapy.

So you decorate the outside. Capstan Therapeutics — bought by AbbVie for \$2.1 billion in June 2025 — builds targeted LNPs studded with antibody fragments that latch onto CD8, plus a bespoke ionisable lipid, L829, engineered specifically to reduce liver uptake. Its lead candidate CPTX2309 carries mRNA encoding an anti-CD19 CAR and is in Phase 1 in lupus and rheumatoid arthritis. Critically, it is dosed without lymphodepleting chemotherapy at all.

Sail takes a different route to the same place: circular RNA, which resists the exonucleases that chew up linear messages, giving longer and more stable CAR expression from a single delivery. Orna Therapeutics — acquired by Eli Lilly in February for up to \$2.4 billion — is built on the same circular-RNA chemistry. EsoBiotec, which AstraZeneca bought for up to \$1 billion, skips RNA entirely and uses an engineered lentiviral vector that integrates permanently.

The first human evidence

It is genuinely early. The most substantial published dataset is EsoBiotec's: four patients with relapsed, refractory multiple myeloma, dosed in Wuhan, written up in *The Lancet* in July 2025. All four responded. Two had their disease disappear completely — one by day 28. That is a real, checkable result from a single intravenous infusion, with no cells manufactured anywhere.

It also came with a bill. All four patients developed cytokine release syndrome, three of them at grade 3. One developed neurotoxicity. Three needed pressors for low blood pressure. Skipping the factory did not make the immunology polite.

In autoimmune disease, the first in vivo programme to report clinical data is HN2301, and its numbers are startling for a different reason: circulating B cells fell measurably within six hours of the first dose, were fully depleted at the 4 mg dose, and stayed depleted for seven to ten days. At three months, all five patients showed reduced disease activity. Six hours, against four to eight weeks.

AstraZeneca committed up to a billion dollars on the strength of results from a single patient, presented at a January investor conference.

THE PRICE OF AN OPTION ON THE FUTURE

The stampede, tallied

Set the science aside and read the cheques. AstraZeneca–EsoBiotec, up to \$1 billion. AbbVie–Capstan, \$2.1 billion. Gilead's Kite–Interius, \$350 million. Bristol Myers Squibb–Orbital, \$1.5 billion, for a preclinical asset. Lilly–Orna, up to \$2.4 billion. Lilly–Kelsonia, \$3.25 billion upfront. J&J–Sail, more than \$3.5 billion in potential value.

That is roughly \$14 billion of headline value in eighteen months. The figure mixes committed cash with milestone-contingent payments and should be read as an upper bound, not a wire transfer. But even the committed portion is extraordinary set against the denominator: a published human dataset you could fit on one page.

SO WHAT

What it means when a modality loses its moat

The strategic content of these deals is not "we found a better CAR-T." It is "the asset class we spent a decade capitalising may be about to stop mattering." Every large cell-therapy player owns or contracts licensed manufacturing capacity — suites, vector supply, cryogenic logistics, a trained workforce. That capacity is what makes the business defensible, and it is also what caps it.

If an in vivo product works, the defensibility migrates. It moves out of the plant and into the delivery chemistry: which ionisable lipid, which binding moiety, which RNA topology, which patent. Those are molecules, and molecules ship in vials at ordinary cold-chain temperatures to ordinary infusion centres. A community rheumatologist can administer that. A community rheumatologist cannot run an apheresis-to-infusion loop.

So the sensible thing for an incumbent to do — the only sensible thing — is to buy a call option on the technology that would strand its own assets. That is exactly what the tally on the previous page describes. Read as therapeutics investing, \$14 billion against a page of data looks reckless. Read as insurance against your own factories, it looks cheap.

Watch three markers over the next eighteen months. First, human tropism data: does the targeting hold in people, or does the liver win? Second, redosing: does anti-vector or anti-PEG immunity blunt the second dose? Third, and most consequential, whether anyone runs an in vivo therapy in a community setting rather than an academic centre. That last one is the whole thesis.

FIELD NOTES

How you build a CAR-T cell without a factory

1 Address the envelope.

A lipid nanoparticle — or an engineered viral vector — is coated with antibody fragments that bind one specific surface marker, typically CD8 or CD4. The particle is the envelope; the antibody is the address line. Without it, the package goes to the liver.

2 Deliver the instruction.

Inside is mRNA, or a circular RNA loop, coding for a chimeric antigen receptor — usually one that recognises CD19, the marker on B cells. The particle fuses with the T cell's membrane and drops the message in the cytoplasm. With RNA, nothing is written to the genome. The cell simply reads a note.

3 Let the cell build the weapon.

The T cell's own ribosomes translate the message into CAR protein and display it on its surface. For a few days that cell hunts and kills CD19-positive B cells. Then the RNA degrades, the receptor is lost, and the cell reverts to being an ordinary T cell.

GLOSSARY

AUTOLOGOUS / EX VIVO

Made from the patient's own cells, outside the body. Every dose is a one-off build with its own batch record, its own release tests and its own chance of failing.

TROPISM

Where a delivery vehicle naturally ends up. Untargeted lipid nanoparticles have hepatic tropism — they go to the liver. Beating that default is the central engineering problem of the field.

LYMPHODEPLETION

Chemotherapy given before infusion to clear space for the engineered cells. Effective, unpleasant, and a major reason conventional CAR-T needs a hospital. In vivo approaches aim to skip it.

CYTOKINE RELEASE SYNDROME

The inflammatory storm that follows rapid immune-cell activation. Ranges from fever to organ failure, graded 1 to 5. It is a consequence of the killing, not of the manufacturing — so in vivo does not avoid it.

MOVE 37 • THE CONTRARIAN

In vivo CAR-T will win by being *worse*

Every write-up of this summer's deals frames in vivo delivery as an upgrade. It probably isn't. Judged as medicine, it looks like a downgrade — and that is precisely the reason to expect it to take the market.

Put the two products side by side for a single patient. Conventional ex vivo CAR-T gives you a characterised, potency-tested, expanded cell population that engrafts and persists, with fifteen autoimmune patients in drug-free remission at a median of fifteen months and some past two years. In vivo mRNA CAR-T gives you a few days of receptor expression, B cells returning inside a fortnight, and no durability data whatsoever.

If you were choosing a therapy for your own mother, you would choose the factory-built one. Nobody is choosing for one patient.

The binding constraint in cell therapy was never efficacy. It was throughput. An ex vivo dose is not a product; it is a work order — an apheresis slot, a cryoshipper, a clean-room suite, a four-to-eight-week cycle time, a build-failure rate, and a \$465,000 sticker before the hospital adds its own. That is a managed service with a plant as its moat, and a plant has a capacity ceiling. Millions of lupus and rheumatoid patients do not fit under it.

In vivo collapses the work order into a vial. The instant it does, the industry's most defensible asset — licensed manufacturing capacity — reclassifies as a stranded cost. Which is the actual explanation for \$14 billion moving against a page of human data. Pharma is not buying better medicine. It is buying the right to obsolete its own factories on its own schedule.

Software people have watched this film. Ex vivo is ahead-of-time compilation: ship the source to a specialised build

farm, compile it, test it, ship the binary back. In vivo is just-in-time: ship the compiler to the target machine and compile in place. JIT output is, as a rule, slower than AOT output. JIT won anyway — because deployability beat performance, and it wasn't close.

Why the consensus disagrees — and might be right

This is a thesis, not a forecast, and there are four honest ways it breaks.

Tropism may not survive humans. Almost every targeting result in this field is preclinical. Capstan had to invent a new ionisable lipid just to get its particles out of the hepatocyte, and mouse biodistribution is a notoriously flattering mirror.

Toxicity is not part of what gets deleted. All four EsoBiotec myeloma patients developed cytokine release syndrome, three at grade 3, one with neurotoxicity. Removing lymphodepletion removes one hazard. It does not remove the cytokine storm, and an uncharacterised in-body product is harder to titrate than a released batch.

Transience may be fatal to the value proposition. Ex vivo's entire pitch is one infusion, years of freedom. If transient RNA means chronic redosing, a cure becomes a subscription — commercially attractive, clinically much less so, and vulnerable to anti-PEG or anti-vector immunity blunting dose two.

The incumbents are not standing still. Rapid-manufacturing platforms are already compressing vein-to-vein time toward days rather than weeks. If ex vivo gets fast and cheap enough, the disruption thesis loses its wedge entirely.

THE FALSIFIER

ONE OBSERVATION
THAT WOULD SETTLE IT

An in vivo CAR-T dose given outside an academic centre, by a community rheumatologist, with no ICU on standby. If that happens inside three years, the plants are stranded. If every dose still needs a tertiary hospital in 2029, in vivo bought convenience, not scale.

SIGNALS

THREE ITEMS FROM OTHER DOMAINS

303

SECONDS OF CONTINUOUS
RUN TIME — BEATING NASA'S
250

ENERGY

A gas turbine that makes its own pressure

On 4 August, the Karlsruhe Institute of Technology ran a compressorless hydrogen gas turbine for 303 seconds — long enough to stop being a stunt. Conventional turbines spend roughly half their own output driving a mechanical compressor that squeezes air before combustion. KIT's design generates that pressure inside the combustion chamber instead, using detonation waves that form from a fluid-mechanical instability in the flowing gas. Earlier attempts lasted fractions of a second before the chamber melted. The team says it is the first to couple such a burner to a turbine and actually produce electricity. Fewer moving parts, no compressor stage, and hydrogen — which reacts fast enough to give a stable pressure rise — as the natural fuel.

SOURCE · KARLSRUHER INSTITUT FÜR TECHNOLOGIE, PRESS RELEASE 2026-010, VIA SCIENCEDAILY, 4 AUG 2026

10×

LOWER CLAIMED COST PER
TOKEN VERSUS BLACKWELL

COMPUTE

Rubin reaches customers

NVIDIA's Vera Rubin platform, in full production since June, begins landing with customers this month across eight cloud partners. The headline claims are 5× the rack-level inference performance of Blackwell, 10× lower cost per token, and 10× more inference throughput per watt — with mixture-of-experts training needing roughly a quarter as many GPUs. Read the fine print: the 10× figure is an MoE-specific number. For dense inference the honest improvement is closer to 2–3×. The interesting consequence is not the speed. It is that per-token economics are now improving faster than model sizes are growing, which quietly changes which products are viable to build.

SOURCE · NVIDIA NEWSROOM; TOM'S HARDWARE, VERA RUBIN NVL72 LAUNCH COVERAGE

12

LANGUAGES AND DIALECTS
ITS FIRST HUMANOID SPEAKS

ROBOTICS

BYD's first robot is a salesperson

BYD unveils its first humanoid, Xiao Di, this month — 1.61 m, 58.5 kg, able to translate between six Chinese dialects and six foreign languages. Note where it is being deployed: not the assembly line, but the company's Di Space experience centres, two to three units per store, greeting visitors and explaining vehicle features. Everyone modelling humanoid economics assumes factory labour is the beachhead. BYD is betting the first defensible use is retail presence, where a robot that is merely charming and multilingual clears the bar — and where the motors, batteries and control stacks already amortised across millions of cars transfer over almost for free.

SOURCE · SOUTH CHINA MORNING POST, 31 JUL 2026; THE NEXT WEB; CNEVPOST

THE COMMON THREAD

All three delete a stage rather than improve one. Karlsruhe removes the compressor; Rubin removes GPUs from the training run; BYD removes the R&D cycle by reusing an automotive drivetrain. Nobody made the core process better this week — they made the surrounding apparatus unnecessary.

BY THE NUMBERS

SEVEN FIGURES WORTH REMEMBERING

\$14B

Headline value of in vivo CAR-T deals struck by large pharma in eighteen months. Mixes committed cash with milestone-contingent payments — read it as an upper bound.

\$2.58B

Johnson & Johnson's option price to acquire Sail Biomedicines outright, on top of \$785 million already paid.

4

Patients in the *Lancet* case series behind AstraZeneca's billion-dollar in vivo bet. The deal itself was triggered by data from one.

6 hrs

Time from first in vivo CAR-T dose to measurable depletion of circulating B cells, in the first autoimmune programme to report clinical data.

4–8 wks

Vein-to-vein time for a conventional autologous CAR-T dose — apheresis, shipping, transduction, expansion, release testing, shipping back.

\$465K

US list price of a single Carvykti infusion, before hospital, conditioning chemotherapy and monitoring costs are added.

~50%

Share of a conventional gas turbine's own power output consumed by its air compressor — the number that makes Karlsruhe's compressorless 303-second run more than a curiosity.

EVERY FIGURE ABOVE IS TRACEABLE TO A NAMED SOURCE LISTED ON PAGE 09. WHERE A DEAL VALUE BLENDS UPFRONT CASH WITH CONTINGENT MILESTONES, WE SAY SO RATHER THAN ROUNDING UP.

THE LONG VIEW

The preparation stage is optional

A compressor and a clean room are the same machine. Not literally — one squeezes air, the other engineers lymphocytes — but structurally. Neither produces the thing you want. Both exist only to condition an input so that the real process can run. And in both, that conditioning step had swollen until it consumed about half of everything: half a turbine's power, half a cell therapy's cost and nearly all of its cycle time.

What makes this week instructive is that two disconnected fields arrived at the same move in the same seven days, and neither did it by improving the main event. Combustion chemistry did not change in Karlsruhe. CAR biology did not change in New Brunswick. What changed is that somebody looked at the elaborate apparatus bolted to the front of a working process and asked whether the process could generate that condition itself. Pressure from the flame. Receptors from the patient.

This is the least glamorous kind of breakthrough and reliably the most valuable, because the preparation stage is where the capital sits. It is the compressor stage that makes turbines heavy, and the clean room that makes cell therapy a service business. Delete it and you do not get a faster version

of the old thing. You get a different category of thing — one that fits in an aircraft nacelle, or a community rheumatology clinic.

Which is also why these moves are so consistently resisted, and resisted most fiercely by the people best placed to make them. The preparation stage is somebody's moat. It is the reason the incumbent is the incumbent. Choosing to delete it means writing down the exact asset that justified the last decade of investment, on the evidence of a four-patient case series, before you are sure. Every one of the buyers on page four made that choice this year and none of them will say so out loud.

So the question worth carrying out of this issue is not about lipid nanoparticles or detonation waves. It is architectural, and it applies to whatever you happen to be building. Somewhere in your system there is a stage that produces nothing, exists only to make an input acceptable to the next step, and quietly consumes a disproportionate share of your cost, latency or headcount. You almost certainly consider it load-bearing. It probably is — right up until the moment the main process learns to do it for itself.

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NEXT ISSUE · FRIDAY

THE LENS

*What in your system exists only to
prepare an input for the real work —
and what breaks if you **delete** it?*

NEXT ISSUE

We follow the compressor out of the power plant and into the nacelle. Pressure-gain combustion changes the thermodynamic cycle itself — the first such change in roughly a century — and the payoff is far larger in flight than on the grid. Plus: what a 303-second run has to prove before it becomes a 30,000-hour one.

Researched, written & designed with Claude.
Typeset in Poppins & Lora on the Anthropic palette.
Every figure verified against a named source.

