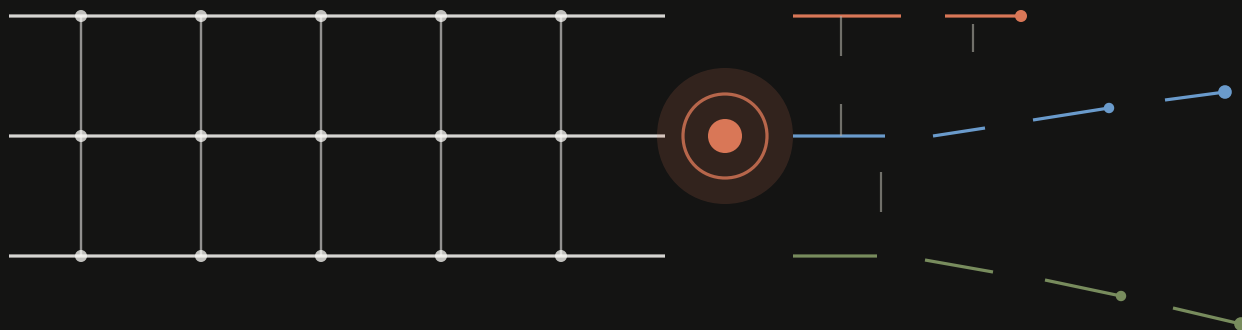


INFLECTION.

THE WEEKLY MAGAZINE OF INNOVATION

ISSUE 02 · FRIDAY, JULY 24, 2026 · DEEP DIVE — ANTIBIOTIC ADJUVANTS



THE RESISTANCE ISSUE

The Next Great Antibiotic Isn't an *Antibiotic*

A molecule that kills nothing has brought vancomycin back from the dead. The trick was to stop hunting for new drugs and start switching off the machinery bacteria built to survive the old ones. Resistance, it turns out, is not a wall. It is a component — and components can be disabled.

P.07 Eight qubits, run off a commodity 300 mm wafer line

P.07 A rocky world 48 light-years out, betrayed by leaking helium

P.09 Why the waste stream is the only channel a system can't lie on

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DISPATCH

Everything in this issue was solved by looking at what a system throws away.

Astronomers at Harvard confirmed the first atmosphere ever found on a rocky planet in a habitable zone — not by seeing the atmosphere, which is effectively invisible at that distance, but by catching the helium leaking out of the top of it. Chemists at Cold Spring Harbor and Scripps revived a failing antibiotic by attacking an enzyme the bacterium politely secretes into the water around itself. Two teams who will never meet, both finding the interior by measuring the exhaust.

That lens is more useful than it sounds. Most organizations treat waste as noise: the logs nobody reads, the heat, the retries, the exception that never breaks anything. But exhaust is the one part of a closed system you get to touch for free, and it is the only channel a system cannot lie on — because it isn't trying to communicate. It is simply what fell out.

The feature that follows is the sharpest version of this idea we have seen in years. Bacteria spent eighty years evolving defenses against our drugs, and in doing so they published a blueprint. They told us exactly which of their proteins are load-bearing, by the simple expedient of keeping them. This was the week somebody finally read it — and shipped a patch.

Un-Breaking Vancomycin

A 1950s antibiotic that superbugs had comprehensively defeated works again — because a molecule with no antibacterial activity of its own switched off the machinery of resistance.

BY THE INFLECTION DESK · 24 JULY 2026

On July 22, Cold Spring Harbor Laboratory announced something that sounds, at first hearing, like a category error. Its chemists, working with Howard Hang's group at Scripps Research, had restored vancomycin's ability to kill a drug-resistant bacterium — without changing vancomycin, and without inventing a new antibiotic. They added a second molecule, called pghi-4, which has no antibacterial activity whatsoever. On its own it does nothing at all. Paired with a drug the bugs had already beaten, it kills them.

A very small substitution

Vancomycin has one job and it does it stupidly well. It clamps onto a two-amino-acid tail — D-alanyl-D-alanine — that hangs off the building blocks of the bacterial cell wall. By gripping that tail it physically blocks the cross-linking step that turns loose strands into a load-bearing mesh. No cross-links, no wall; the cell inflates and bursts. It is a beautifully dumb mechanism, which is exactly why it held for decades.

Resistant *Enterococcus faecium* defeats it with one substitution. A cluster of genes — the *van* operon, carried on mobile elements and traded between bacteria the way you'd install a package — rewrites that terminal alanine into a lactate. D-Ala-D-Ala becomes D-Ala-D-Lac. One nitrogen becomes one oxygen. One of the five hydrogen bonds vancomycin uses to grip its target simply stops existing.

The drug's affinity collapses by more than a thousandfold. Nothing has been destroyed. The antibiotic is still there, at full concentration; the target is still there, in the same place, doing the same job. The handshake just no longer completes.

Which is what makes vancomycin resistance so instructive. It is not brute force. It is a schema migration — and the organism kept backwards compatibility with everything except the drug.

The bill

The stakes are not abstract. The GRAM Project's analysis in *The Lancet*, the first global study of resistance trends over time, forecasts 39 million deaths directly attributable to bacterial antimicrobial resistance between 2025 and 2050. That is three deaths a minute, sustained for twenty-five years. More than a million people a year already died of it between 1990 and 2021, and the age profile is moving the wrong way: deaths in children under five fell by half over that period, while deaths in people over seventy rose by more than eighty per cent.

Enterococcus is a modest contributor by those global numbers and a genuinely frightening one by hospital logic. The CDC counted roughly 54,500 vancomycin-resistant enterococcal infections among hospitalized Americans in 2017, and 5,400 deaths. These are not infections you pick up out in the world. They are infections you pick up in the room you went to in order to get better.

For thirty years the field's answer to that arithmetic has been the same: find another drug. That answer has been failing — not scientifically so much as financially, for reasons we take up on page six. What follows is the other answer.

How You Un-Break a Drug

1 · Attack the adaptation, not the organism

An antibiotic adjuvant is a companion molecule that does not kill bacteria. It restores an antibiotic that used to. The underlying logic is almost embarrassingly simple: resistance is *work*. It costs the cell genes to carry, enzymes to express, and energy to run. And anything a cell must actively do, something else can actively stop.

The category is not new — the one unambiguous success story in antibacterial drug development is the β -lactamase inhibitor, the reason amoxicillin still works when paired with clavulanic acid. What is new is the target.

2 · The enzyme nobody was aiming at

The team went after SagA — secreted antigen A — a peptidoglycan hydrolase that *E. faecium* uses to trim and remodel its own cell wall as it grows.

Note what SagA is not. It is not a resistance gene. It does not modify vancomycin, it does not pump the drug out, and it is not encoded on the *van* operon. It is housekeeping. It is the enzyme equivalent of a maintenance cron job.

The finding, published in *Nature Communications*, is that switching SagA off — genetically or pharmacologically — makes resistant *E. faecium* susceptible to vancomycin again. Resistance turned out to depend not only on the operon that changes the target, but on the ordinary remodeling machinery that has to physically rebuild a working wall around the change. Break the builder and the workaround stops working.

Resistance is work. Anything a cell must actively do, something else can actively stop.

3 · Click chemistry as a search engine

The inhibitor came out of a method John Moses's lab at CSHL calls diversity oriented clicking: a family of reactions engineered to emit large numbers of structurally varied molecules quickly and reliably. The lab has built a library of more than 150 compounds this way.

It was never an antibiotics program. Molecules from the same collection have gone into cancer research. The library is a general-purpose instrument, and the group deliberately keeps it open to collaborators — which is how a Scripps immunologist ended up holding the key to an enzyme a Long Island chemist had never intended to inhibit.

4 · The molecule was already on the shelf

pghi-4 was first made in the Moses lab in 2020 — six years before anyone paired it with vancomycin. It sat in a freezer, fully characterized and entirely unassigned, until Hang's group went looking for a way to shut down SagA and discovered that somebody had already built the thing.

This is the most quietly radical part of the story, and it has nothing to do with microbiology. The rate limiter in drug discovery is usually assumed to be synthesis: making the molecule. Here the molecule existed for six years. The rate limiter was *indexing* — knowing what you already have, and knowing which lock it fits.

Anyone who has inherited a large codebase will recognize the failure mode exactly. The function you need has already been written, by someone who has left, under a name that describes what they were doing rather than what it does. The expensive work is not writing. It is finding.

From Bench to Bedside — and the Gap Between

The honest state of play

pghi-4 plus vancomycin has restored killing in resistant *E. faecium*. That is a laboratory result, not a therapy. No patient has received it; no pharmacokinetics have been published.

The team says it is already building second-generation derivatives that couple the inhibitor directly to vancomycin — one molecule rather than two. Read that as a tell. The hardest problem with any two-drug combination is pharmacokinetic matching: both molecules must arrive at the same tissue, at the same time, in something close to the right ratio, and stay there. A great many adjuvants have died in precisely that gap. Fusing them into a single chemical entity is the standard escape route, and it is not a cheap one.

Where it goes next

The group names drug-resistant tuberculosis and methicillin-resistant *Staphylococcus aureus* as candidates for the same strategy. Both are conditions where the drugs we already have are genuinely good and the organisms have simply learned to ignore them — which is exactly the situation in which an adjuvant is worth more than a discovery program.

Who paid for it

The NIH and the National Cancer Institute, the Australian Research Council, New York State's Biodefense Commercialization Fund, and two private foundations. Note what is absent from that list. This was not a pharmaceutical antibiotics program, because in 2026 there are barely any pharmaceutical antibiotics programs left.

The commercial shape

Here is the part that should interest anyone who allocates capital. An adjuvant is a new, patentable molecule that rides on an off-patent generic whose safety profile, dosing, manufacturing, and clinical familiarity were paid for decades ago. You inherit seventy years of pharmacovigilance and you only have to prove the new half. Set against a novel-scaffold program, the risk-adjusted arithmetic is not close.

The catch is the mirror image of the advantage. Pairing with a cheap generic caps what you can charge, and payers will reasonably ask why a ten-dollar drug plus a companion should cost hundreds. The antibiotic market's central pathology — that the products society most needs are the ones it least wants to buy — is not repealed by better chemistry. It is only made survivable.

FIELD NOTES · HOW IT WORKS

- 1 The grip.** Vancomycin clamps onto a D-Ala-D-Ala tail on cell-wall precursors, physically blocking cross-linking. No cross-links, no wall. The cell bursts under its own pressure.
- 2 The dodge.** Resistant *E. faecium* swaps that tail for D-Ala-D-Lac. One atom's difference. Vancomycin's grip weakens more than a thousandfold and the drug becomes a bystander.
- 3 The counter.** The dodge still requires the cell to rebuild a working wall around the modified precursors — work done by remodeling enzymes such as SagA. Inhibit SagA with pghi-4 and the rebuild stalls. Vancomycin, entirely unchanged, starts killing again.

GLOSSARY

ADJUVANT

A molecule with no antibacterial activity of its own that restores the potency of one that has it.

PEPTIDOGLYCAN

The mesh of sugar strands and peptide cross-links that forms a bacterial cell wall. Vancomycin's battlefield.

SAGA

"Secreted antigen A." An *E. faecium* enzyme that trims and remodels peptidoglycan during growth. Not a resistance gene — which is why nobody was aiming at it.

RESISTOME

The full set of genes and proteins an organism uses to survive drugs. A target library that annotates itself.

The Resistome Is the Best Target Library in Medicine

The consensus says antimicrobial resistance is a discovery crisis — the pipeline is empty, we need novel scaffolds, and the fix is money. Here is the read that looks wrong until you run the arithmetic.

We do not have an antibiotic discovery problem. We have an antibiotic *repair* problem — and repair has a far better search space than discovery does.

Consider what resistance actually is. It is not a wall the organism hides behind. It is machinery the organism built, at real metabolic cost, out of proteins. Ligases, hydrolases, efflux pumps, remodeling enzymes. Every one of them is, in principle, a drug target. Which means the resistome is not an obstacle. It is a library.

And it is a library with a property no screening collection has ever had: **it annotates itself**. Organisms under drug pressure tell you which of their proteins are load-bearing by the simple act of keeping them. You do not have to guess which nodes matter. Evolution has already run the ablation study — at planetary scale, over eighty years, for free — and published the results in the genomes of the survivors.

Then the economics, which is what actually decides this. Novel antibiotics are commercially dead by construction. A good new antibiotic must be reserved; that is what stewardship means. So approval guarantees low volume. Achaogen's plazomicin was approved by the FDA in June 2018 for multidrug-resistant infections and booked under one million dollars of sales in its first year. The company filed for bankruptcy in 2019. Most small sponsors of an FDA-approved antibacterial since 2010 have gone bankrupt or exited below invested cost. Post-approval obligations alone run to roughly \$350 million over a decade.

An adjuvant inverts nearly every term. It is new and patentable, but it rides on a generic whose safety, manufacturing, and clinical-familiarity burden was amortized in the twentieth

century. You are not shipping a new operating system. You are shipping a patch.

Why the consensus disagrees — and it has good reasons

It is preclinical. pghi-4 plus vancomycin has cleared resistant bacteria in a flask, not a bloodstream. Combination pharmacokinetics is where most adjuvants die, and the team's own move toward fused single-molecule derivatives is a candid admission of it.

Adjuvants are themselves selection pressure. Bacteria will evolve around SagA inhibition — variant enzymes, efflux, redundant hydrolases. You are buying time, not immunity. The ratchet still turns; you have only slowed the pawl.

Real resistance is layered. The *van* operons, penicillin-binding-protein substitutions and biofilms all contribute. Disabling one remodeling enzyme in vitro is not the same as clearing a bloodstream infection in an immunocompromised patient.

The precedent is real but narrow. β -lactamase inhibitors — clavulanic acid with amoxicillin, avibactam with ceftazidime — prove adjuvants work. They also prove the strategy generalizes slowly: decades on, it still has not travelled far beyond the β -lactams. SagA may be another one-off.

And the deepest objection: adjuvants can only extend mechanisms we already possess. If a mechanistic class is genuinely exhausted, no amount of lock-picking helps. Some fraction of true discovery is non-optional.

The synthesis is not *repair instead of discovery*. It is that the field funds repair as a footnote when the arithmetic says it should be the base case — and discovery the expensive, necessary hedge.

8

qubits, foundry-made

QUANTUM

Eight qubits, off a commodity wafer line

Imec and the Australian startup Diraq reported the first coherent operation and readout of an eight-qubit silicon spin array fabricated on a 300 mm CMOS-compatible foundry process — the same class of production line that made the processor in your laptop. The work was led by Andreas Nickl and Tuomo Tanttu of UNSW Sydney and Diraq, with Diraq founder Andrew Dzurak among the senior authors. The number to watch is not eight. It is that scaling readout to eight required no significant increase in sensor count, wiring density, or thermal load. Rivals now count logical qubits in the dozens. This platform counts wafers — and wafers are the only unit that has ever scaled.

SOURCE · IMEC PRESS RELEASE, 13 JULY 2026 · NATURE COMMUNICATIONS

48

light-years away

ASTRONOMY

A rocky world that kept its air

Harvard's Collin Cherubim and colleagues confirmed the first atmosphere ever found on a rocky planet inside another star's habitable zone: LHS 1140 b, 48 light-years out. They did it backwards. Rather than hunting for the atmosphere, they predicted from a model that helium should be streaming off the top of it, booked time on the WINERED spectrograph at Magellan in Chile, and caught the leak. A second planet in the same system transited on the same night and showed nothing at all — a clean internal control. The atmosphere is estimated to have survived more than three billion years.

SOURCE · SCIENCE, 16 JULY 2026 · DOI 10.1126/SCIENCE.AEA9708

140

megawatts, one country

COMPUTE

A nation buys itself a reflex

NVIDIA and Japan's Ministry of Economy, Trade and Industry announced what they describe as the world's first national AI infrastructure for physical AI: a Vera Rubin facility with 13,750 Vera CPUs and 27,500 Rubin GPUs drawing 140 megawatts, built with Noetra Corp under METI's FRONTia Project. FANUC, Hitachi, Kawasaki, Kubota, Sony and Yaskawa intend to join the associated Cosmos Coalition. Read it as industrial policy rather than a sale. Japan is not buying compute; it is buying a shared perception layer for a robotics sector it already leads. (Company announcement — framing is the vendor's.)

SOURCE · NVIDIA NEWSROOM, 16 JULY 2026

39 million

Deaths directly attributable to bacterial antimicrobial resistance forecast between 2025 and 2050 — roughly three every minute, for twenty-five years.

1,000×

The collapse in vancomycin's binding affinity when a resistant cell swaps one nitrogen for one oxygen in its cell-wall precursor.

< \$1M

First-year sales of plazomicin, approved in 2018 for multidrug-resistant infections. Its maker filed for bankruptcy the following year.

54,500

Vancomycin-resistant enterococcal infections among hospitalized Americans in 2017, and 5,400 deaths.

150+

Compounds in the Cold Spring Harbor click-chemistry library that happened to contain the inhibitor, six years before anyone knew what it was for.

8

Silicon spin qubits run coherently off a 300 mm CMOS foundry line — with no significant increase in wiring or thermal load.

48

Light-years to LHS 1140 b, the first rocky habitable-zone planet confirmed to have kept an atmosphere.

Measure the Exhaust

Two of this week's results were obtained the same way by teams who will never meet.

Cherubim's group could not see the atmosphere of LHS 1140 b. Atmospheres on small rocky planets orbiting red dwarfs at 48 light-years are close to invisible to direct transmission spectroscopy — which is the entire reason the question stayed open for twenty years. So they stopped trying to see the thing and looked instead at what it was losing. Helium escaping from the top of an atmosphere is a far louder signal than the atmosphere itself. The leak proved the reservoir.

Moses and Hang's teams did not attack the resistance mechanism either. The *van* operon is a miserable target: redundant, mobile, and it deforms the very thing the drug binds. So they went after *SagA* — an enzyme *E. faecium* secretes into the space around itself while doing routine maintenance. Secreted, accessible, unglamorous, load-bearing. The exhaust, not the engine.

There is a principle in here worth more than either result. In any closed system, the parts you can measure and the parts you care about are usually different parts. The reflex is to keep improving

the instrument until it can see the thing you care about. The better move, more often than anyone admits, is to find what the system is throwing away and prove that its waste is a faithful function of its interior.

Engineers know this instinct as observability and chronically under-rate it, because logs and traces feel like overhead rather than physics. They are not overhead. A system's waste stream is the one channel it cannot help but be honest on — precisely because it isn't trying to communicate. It is simply what fell out.

Imec's eight qubits belong to the same family of insight. The interesting variable was never the qubit count; eight is a rounding error against the millions fault tolerance will eventually demand. The interesting variable was the wiring, the sensor count, the thermal budget — the overhead everyone files under plumbing. That is where the constraint actually lives, and this week somebody measured it and found it flat.

Bacteria have been publishing their internals for eighty years. This was the week somebody read them, found the maintenance routine, and switched it off.

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THE LENS

*What in your stack isn't broken — only **disabled**?*

Somewhere in your system is a capability that still works perfectly and simply cannot complete a handshake. You have almost certainly been budgeting to replace it. Try costing the patch first.

NEXT ISSUE · FRIDAY

Another domain. Another Move 37.

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