

INFLECTION.

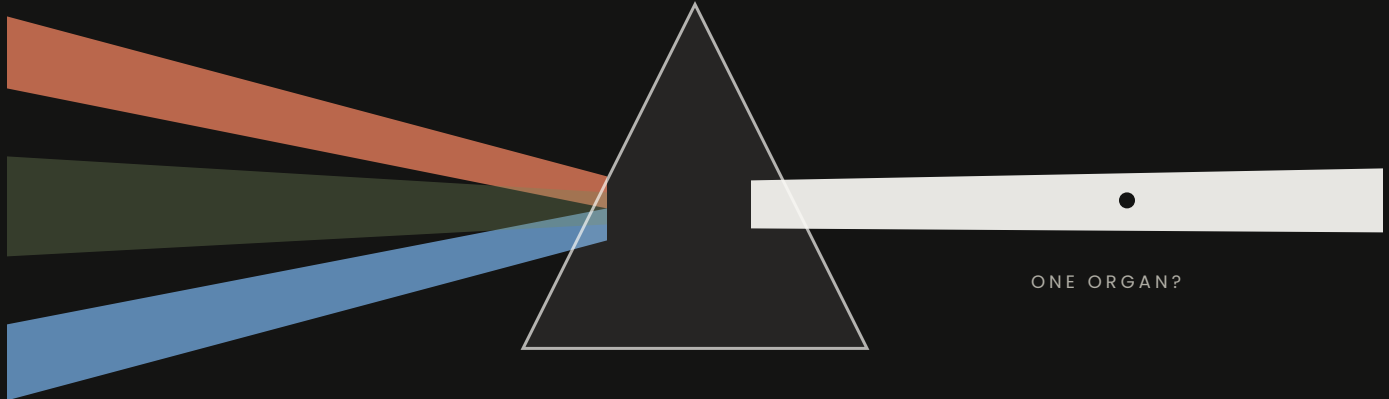
THE WEEKLY MAGAZINE OF INNOVATION

ISSUE 02

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DEEP DIVE — THE TWO-ORIGIN BRAIN

OTX2 · FOREBRAIN + MIDBRAIN



GBX2 · HINDBRAIN

DEVELOPMENTAL NEUROSCIENCE · STANFORD / NATURE NEUROSCIENCE

Your Brain Is a *Merger*, Not a Monolith

For a century we drew the brain as one tree with one root. This week, lineage tracing found two roots — separate from the embryo's first days, conserved for 550 million years. The payoff isn't trivia: it's the neurons nobody could grow.

AGAINST THE GRAIN

Lineage is the new spec sheet — why provenance, not the end product, decides what you can build.

SIGNALS

Sound makes a quantum jump; DOE bets \$99M on hot rock; a telescope doubles its life in one burn.

THE LONG VIEW

Initial conditions are destiny — and the cheapest place to win.

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DISPATCH

Start at the
fork, not the
finish line.

FROM THE EDITOR

Here is a pattern worth stealing. For decades, stem-cell labs tried to manufacture hindbrain neurons — the cells that run breathing, swallowing and the face — and kept failing. They were optimising the destination. This week a Stanford team showed the failure was baked in at the departure gate: the cells they started from had already committed to the *other* half of the brain.

That is this issue's lens: **outcomes are downstream of lineage**. What a thing can become is often decided long before anyone looks at it — in an embryo's first days, in a spacecraft's first burn, in the first well drilled into a new geothermal field. All three stories are in these pages.

For a CTO the translation is blunt. When a migration, a reorg or a model refuses to become what you want, stop tuning the last step. Walk back to where the paths diverged, and check whether you are trying to convert something that was never able to get there.

THE FEATURE

Two Brains, One *Skull*

A lineage-tracing study in *Nature Neuroscience* argues the vertebrate brain is a composite organ: front and back grow from separate progenitors that never mix. It explains a decades-old lab failure — and fixes it.

BY THE INFLECTION DESK · 7-MINUTE READ

Picture a river delta in reverse. Textbooks taught that the brain begins as one stream — a single pool of neural progenitor cells — that later branches into forebrain, midbrain and hindbrain. On September 18, a 24-author team led by Kyle Loh at Stanford Medicine, with colleagues at Caltech and UCSF, published evidence that there is no single stream. From gastrulation onward, the earliest moment the body plan takes shape, two separate pools of progenitors emerge side by side. One builds the forebrain and midbrain. The other builds the hindbrain. They never overlap.

The textbook picture

The adult brain is conventionally split three ways. The forebrain handles what we think of as thought: language, abstract reasoning, self-reflection. The hindbrain — the brainstem — handles what keeps us alive: breathing, heartbeat, sleep, hunger, and the muscles of the face, tongue and throat that let us speak and swallow.

The dominant developmental model held that all three regions trace back to one common starting population, which then diversified. It is a tidy tree with a single root, and it shaped how a generation of stem-cell biologists tried to make brain cells in a dish.

Why the old model mattered

If everything shares a root, then any early neural cell should, with the right chemical nudges, be steerable toward any brain

region. That assumption turned into protocol. And for human hindbrain neurons, the protocols kept stalling — a serious gap, because brainstem tissue cannot be sampled from living patients.

That gap has real casualties. Spinal muscular atrophy is a leading genetic cause of death in children under one. ALS is typically diagnosed between 40 and 70. In both, specific hindbrain neurons progressively fail, and patients can lose the ability to swallow and, eventually, to breathe. Without human cells to study, researchers have been working partly blind.

The new paper's contribution is to say: the stall was not bad chemistry. It was a wrong map.

WHAT THEY FOUND

Four findings, *one* rewritten origin story

1 • A fork at gastrulation

Co-first authors Rayyan Jokhai and Carolyn Dundes traced cell lineages in mouse embryos back to gastrulation. They found two populations from the start. Cells expressing the gene *Otx2* are destined for forebrain and midbrain; cells expressing *Gbx2* become hindbrain. The hindbrain is not a late branch off the forebrain's path — it runs on a parallel track from day one.

Think of two assembly lines that share a building, not one line with a late switch. The paper calls them anterior and posterior neural ectoderm.

2 • Chromatin as a one-way door

Chromatin is the packaging that decides which genes a cell can even reach. The two progenitor pools showed fundamentally different chromatin landscapes that already foreshadowed their future identities. In software terms, the build flags are set before compile time: you cannot patch a front-brain progenitor into a hindbrain one, because the relevant code paths are physically packed away.

The team's reading of prior failures follows directly: earlier protocols probably tried to coax forebrain/midbrain progenitors into hindbrain fates they were never able to adopt.

“The front of the brain arises from a totally different progenitor cell.”

KYLE LOH, STANFORD MEDICINE

3 • The neurons nobody could make

Starting instead from posterior-type progenitors, the team steered human pluripotent stem cells into hindbrain motor neurons specific to rhombomeres 5 and 6 — segments that control facial and swallowing muscles, and cells the paper describes as hitherto difficult to generate in vitro. The cells fired action potentials and carried the region-specific protein markers of the real thing.

4 • A 550-million-year-old seam

The same two-origin arrangement appears in chickens, zebrafish and acorn worms — seafloor animals whose lineage split from ours more than 550 million years ago. Jellyfish, which diverged 600–700 million years ago, carry two nervous systems at opposite ends of the body. The authors' hypothesis: evolution took two pre-existing neural systems and pushed them together. The seam survived because the build process never changed.

FROM LAB TO MARKET

What changes *now*

Disease models, finally human

The most immediate value is a supply of human hindbrain neurons for ALS and SMA research. The failing cells in both diseases sit in tissue you cannot biopsy from a living person. A reproducible dish-grown version turns a black box into an assay: you can watch degeneration, test compounds, and compare patient-derived lines.

The appetite circuit

The hindbrain also hosts neural circuits that regulate hunger — among the systems influenced by GLP-1 drugs such as semaglutide. Human hindbrain cultures give pharmacologists a way to study those interactions in human cells rather than inferring from rodents. Given how much capital now flows through obesity medicine, that is a commercially loud use case for a quiet developmental-biology paper.

A new QC question for the whole field

The subtler implication: every lab making neurons from stem cells now has to ask *which progenitor pool* it started from. If regional identity is locked in at the ectoderm stage, the starting recipe becomes a quality variable, not a footnote. Expect differentiation protocols — and organoid datasets built on them — to be re-examined through this lens.

What's next

The team says it will trace where the spinal cord comes from developmentally and pin down how SMA and ALS disrupt hindbrain neurons. Regenerative therapy is the stated long-term goal; it is also, realistically, years away.

FIELD NOTES

How the two-origin brain works

- 1 The fork.** At gastrulation, two progenitor pools appear at once: Otx2+ (front) and Gbx2+ (back). No shared parent pool.
- 2 The lock.** Each pool packs its DNA differently. Chromatin makes some fates reachable and others effectively impossible.
- 3 The build.** Begin from the posterior pool and human stem cells mature into working hindbrain motor neurons (rhombomeres 5/6).

GLOSSARY

Gastrulation

The early embryonic stage when the basic body layers and axes form.

Neural ectoderm

The embryonic tissue that gives rise to the nervous system.

Chromatin

DNA plus its packaging proteins; controls which genes are accessible.

Rhombomere

One of the repeating segments of the developing hindbrain; r5/6 feed face and swallowing muscles.

THE CONTRARIAN · MOVE 37

Lineage Is the New *Spec Sheet*

The headline says “your brain is two organs.” The consequential read is duller and bigger: in biology’s manufacturing era, *provenance* becomes the product.

The move that looks wrong

Everyone will chase the endpoint — better ALS neurons, better organoids. The sharper bet is on the ledger behind them. If a cell’s possible futures are fixed at the ectoderm stage, then a vial of neurons is only as trustworthy as its lineage record: which progenitor pool, which chromatin state, which day it forked. That is a bill of materials for living parts.

Drug programs that screen on the wrong-origin neurons get confident answers to the wrong question. So the durable value may accrue to whoever standardises lineage verification — the “SOC 2 for cells” — rather than to any single cell line.

There is an architecture lesson too. Evolution kept two systems with different jobs — reflex and deliberation — physically adjacent but developmentally separate, for half a billion years. Loh notes a single organ would probably be more efficient. Nature kept the seam anyway. Teams merging their “fast path” and “thinking path” into one model or one service might ask why.

Why the consensus disagrees

The markers are not new. *Otx2* and *Gbx2* have marked the front and back of the early neural plate in textbooks for decades. The claim is about *timing* — separate from gastrulation — and that rests mainly on mouse lineage tracing.

“Two organs” is framing. Functionally the brain is one tightly wired system. Separate origins do not mean separate operation.

One neuron type is not a platform. The human result covers rhombomere 5/6 motor neurons. Other hind-brain populations, scale-up and batch consistency are unproven.

Replication pending. The paper is fresh and closed-access; independent labs have yet to reproduce the protocol.

Therapy is far. Disease models can arrive in a few years; regenerative treatments for ALS or SMA are a much longer road.

Verdict: bet on the ledger, not the lab trick — but size the bet for a decade, not a quarter.

SIGNALS

Elsewhere this week

1→0

QUANTUM

Sound makes a quantum jump, live

Stanford physicists led by Amir Safavi-Naeini watched a single phonon — a quantum of vibration — vanish from a chip-scale mechanical resonator in real time, published in *Science*. Quantum jumps were first seen in trapped ions in 1986 and photons in 2007; sound was the holdout. The trick: a resonator that rings for 2 milliseconds (a tuning fork with that relative staying power would ring for hours), read out hundreds of times by a superconducting qubit without destroying the state. Uses on the table: error detection for quantum computers and ultra-sensitive sensors — the team is exploring protein detection with Caltech.

SOURCE · Makihara et al., *Science* 393:1217 (2026); Stanford via ScienceDaily, Sept 22, 2026

\$99M

ENERGY

DOE bets on engineered hot rock

On September 21 the Department of Energy committed more than \$99 million to 21 geothermal projects, including five field-scale tests of enhanced geothermal systems — among them Fervo in Idaho and Quaise near Oregon's Newberry Volcano, targeting 265–365°C at the bottom of the hole. Context: the U.S. had about 2.68 GW of utility-scale geothermal as of June 2026, roughly 0.4% of generation in 2025. Field data will be published to DOE's Geothermal Data Repository — the quiet win, because shared subsurface data compounds.

SOURCE · CarbonCredits.com, Sept 22, 2026, citing DOE and EIA

22 yrs

SPACE

A telescope doubles its life in one burn

NASA says the Nancy Grace Roman Space Telescope now has fuel for at least 22 years of science against a 10-year design budget. Its first mid-course correction on August 31 hit more than 99% accuracy and used about 18 kg of propellant versus a 200 kg allocation. Roman also launched lighter than budgeted — 8,056 kg against a conservative 9,800 kg — so the tanks were filled to capacity. Precision early bought a decade later.

SOURCE · NASA Science, Roman mission blog, Sept 14, 2026

BY THE NUMBERS

Seven figures that *moved*

550M

Years the two-origin brain plan appears conserved — from acorn worms to humans.

2 → 0

Brain progenitor pools found at gastrulation — and their overlap.

24

Authors on the Stanford-led *Nature Neuroscience* paper, with Caltech and UCSF.

2 ms

How long Stanford's resonator rings — long enough to watch one phonon disappear.

18 / 200

Kilograms of fuel Roman's first burn used, versus kilograms budgeted.

22 yrs

Roman's new minimum fuel horizon — up from a 10-year design life.

2.68 GW

U.S. utility-scale geothermal capacity as of June 2026 — the baseline DOE's \$99M across 21 projects aims to break out of.

THE LONG VIEW

Initial conditions are *destiny*

Read this week's stories side by side and one idea keeps surfacing. An embryo commits two pools of cells to two futures before a single neuron exists. A telescope's first 18-kilogram burn quietly buys it twelve extra years. A geothermal industry stuck near 2.7 GW is being funded not to build plants first, but to drill, measure and publish — to fix its starting knowledge.

In each case the leverage sits at the fork, not the finish. And in each case the fork is invisible from the end:

nobody looking at an adult brainstem, a telescope in orbit, or a power plant can see the decision that made it possible.

That is uncomfortable for leaders, because we are measured at the finish. The practical habit is simple. When something stubbornly will not become what you need, ask what it was committed to before you arrived — and whether the cheaper move is to start again from the right pool.

SOURCES & FURTHER READING

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INFLECTION.

THE WEEKLY MAGAZINE OF INNOVATION

NEXT ISSUE · FRIDAY

A new deep dive, a new domain, the same promise:
one idea that looks wrong until it doesn't.

THE LENS

*What would have to be true for the obvious
answer to be **wrong**?*

This week's version: what in your stack is a merger pretending to be a monolith?