

Positional Memory: How Cells Know What to Rebuild

ABSURD HEALTH INSTITUTE — MEDICAL CONCEPT PAPERS · VOLUME SIX · PAPER 07

Research series: Lost Instructions of Regeneration

Article URL upon publication: <https://absurd.health/research/volume-six/positional-memory-how-cells-know-what-to-rebuild/>

Abstract (original summary). Regeneration requires cells to reconstruct the correct structure in the correct location. Axolotl work on the Hand2–Shh feedback circuit supplies a concrete example of maintained and experimentally alterable positional identity. This paper explores the difference between cellular proliferation and anatomical information, and outlines the substantial barriers to translation into human repair.

Regeneration has a geography problem

Growth without positional information cannot reconstruct an organism. Cells in an amputated limb must distinguish anterior from posterior, proximal from distal and inner from outer structures. Developmental signaling coordinates supply this information during embryogenesis, but an adult regenerating limb must recover it after injury. A 2025 axolotl study described a Hand2–Shh positive-feedback mechanism involved in preserving posterior positional identity. That finding is specific, experimentally useful and more impressive than the vague suggestion that cells somehow 'remember' the body's ideal design.

Information stored in biology

The study connects lingering developmental transcriptional identity with a capacity to reactivate Sonic hedgehog signaling during regeneration. Feedback helps explain why the system can maintain a regional identity even when an active patterning signal is absent in uninjured tissue. Researchers showed that positional memory could be altered experimentally under defined conditions, revealing that anatomical identity is not entirely fixed. This demonstrates one molecular implementation of memory in axolotls; it does not establish a universal organism-wide map or an accessible human limb blueprint.

Why it changes the therapeutic question

Many proposed regenerative strategies prioritize cell expansion and delivery. Positional-memory biology suggests a separate requirement: cells need information about where they are and which structure they should contribute to. A transplanted progenitor could survive and proliferate while producing an anatomically inappropriate result if contextual signals are incorrect. This is especially relevant to complex reconstructions requiring bones, tendons, nerves, vessels and skin to meet in the right arrangement.

Boundary of inference

A Hand2–Shh circuit cannot be equated with a human clinical therapy. These pathways influence growth and development, and misexpression can produce malformations or oncogenic risks depending on context. Competing explanations of species-level regenerative differences include immune organization, wound epithelial behavior and evolutionary constraints. The Institute's new synthesis is that regeneration should be evaluated as an information-and-execution problem, but that proposal must not erase tissue-specific biology.

A clinical thought experiment

A growing blastema could generate enough cells to replace a missing digit yet produce extra or misplaced digits if positional signaling is wrong. This is the difference between regenerative quantity and information. The

Hand2–Shh work gives a concrete circuit for one axis of axolotl limb identity, while leaving other axes and species differences unresolved. The same molecular pathways are powerful during development, precisely because their spatial control matters.

What would discriminate among explanations

A translation program should ask whether adult human target cells retain any comparable regional identity and whether experimentally manipulating it changes structure rather than only gene expression. A negative result would be valuable: it would show that an axolotl solution does not transfer to that human tissue. No therapeutic conclusion should follow merely because developmental genes are detectable.

Position is information, not merely location

In normal development, cells respond to positional signals that allow tissue structures to form in ordered arrangements. A bone must occupy the proper region relative to muscle, nerve, tendon and skin; digits require appropriate identity and spacing. The same logic applies to regeneration: surviving cells around a wound must establish not only what tissue types to make, but which missing structures belong between the stump and the distal end. A failure of positional information could produce inadequate rebuilding even if cells retain the capacity to divide and differentiate.

This creates a useful contrast between replacing a cell population and replacing an organ. A suspension of progenitor cells can contain every relevant lineage potential while providing almost none of the spatial relationships required for a functioning structure. Patterning requires gradients, local feedback, mechanical constraints and interactions between cell populations over time. More cells may make a larger mass. Correct information can make an organized organ.

Evidence that positional memory is molecular

A 2025 Nature study in axolotl limbs identified an interaction between Hand2 and Sonic hedgehog (Shh) signaling that helps maintain posterior identity and can alter the positional character of anterior blastema cells. The work supports a striking principle: adult tissue can maintain a developmental memory that remains actionable after injury. Its experimental demonstration is specific, however. It concerns certain anterior–posterior positional features of axolotl limb regeneration, not a complete molecular map for all vertebrate tissues. Nor is it evidence that adult human cells will respond similarly to the same perturbation.

The feedback architecture matters. A transient signal can initiate a state that persists after the signal is withdrawn, because the network maintains itself. Such memory is mechanistically different from a cell continuously receiving an external morphogen gradient. In developmental systems, positive feedback and gene-regulatory loops can stabilize identity. But stable memory also makes reprogramming asymmetric: shifting a cell into one identity may be easier than reversing it. A regenerative therapy would need to anticipate both directions, not assume every induced state can be switched off at will.

Anatomy contains several distinct maps

One coordinate system may tell cells whether they lie anterior or posterior; another may encode proximal versus distal position; another concerns tissue layer or organ boundary. These maps need not use identical molecular pathways. Axonal projections add a further form of mapping when a tissue must be reconnected to sensory and motor networks. Vessels impose yet another geometry: capillaries must serve metabolically active cells at appropriate distances. Rebuilding one map while neglecting others can produce a tissue that looks organized

microscopically yet lacks effective function.

An instructive comparison is engineered cartilage. Producing chondrocytes and cartilage matrix is not equivalent to reconstructing the layered, mechanically integrated surface of a joint. Even when a graft is biologically viable, integration with adjacent cartilage and subchondral bone can be limiting. Positional information in this context includes biomechanics and border conditions, not only developmental transcription factors. The concept becomes valuable when adapted to each tissue rather than invoked as a universal hidden code.

How the hypothesis could be tested

A strong experiment would distinguish a cell's intrinsic positional memory from instructions supplied by its environment. Researchers could compare cells taken from different anatomical regions in controlled grafting or organoid systems, measuring whether their identities persist, adapt or become inappropriate after relocation. Perturbing defined signaling circuits could then test causality. Functional outcomes would include correctly oriented tissue, appropriate connection to neighboring structures and sustained performance after the signaling intervention ends.

In humans, claims must remain considerably narrower. Evidence from developmental biology and animal regeneration motivates hypotheses about wound architecture and cell identity, but current clinical medicine cannot regenerate amputated adult limbs by rewriting a known positional code. The central insight is nonetheless profound: adequate stem-cell numbers may be irrelevant if the body cannot specify what it is supposed to build.

When a map is complete enough

The success of a regenerative map should ultimately be judged by whether it specifies the correct boundaries and connections, not by resemblance to fetal gene expression alone. Developmental transcription factors can appear in adult injury responses without recapitulating normal development. A regenerating structure may need to stop growing at an appropriate size, integrate into existing blood vessels and transmit force through neighboring tissues. A patterning program that lacks termination signals could create malformed tissue despite accurately recreating an early developmental stage.

Thus the experimental challenge is also one of restraint. A researcher attempting to alter positional identity must demonstrate that the induced program switches off appropriately and does not disturb adjacent healthy tissue. Such constraints distinguish a meaningful tissue-engineering strategy from merely showing that a powerful morphogen can change cell behavior. The latter finding can be biologically valuable without being a treatment.

Anatomy offers an unusually strict standard of success

For an appendage, correct regeneration can be judged by number and arrangement of skeletal elements, muscular attachment, vascular supply, innervation and usable movement. The apparent simplicity of counting digits can mislead, because a normally shaped structure may still have poor sensation or motor control. Conversely, a structurally incomplete reconstruction might support surprisingly useful function. Both observations matter when moving from developmental biology to regenerative medicine.

Human tissue-engineering studies should distinguish local patterning, which produces appropriate short-range geometry, from the larger problem of whole-organ integration. A cell's positional gene expression may look correct even when a transplant fails to connect to its host. Evidence of a maintained developmental memory is therefore only one component of a successful regenerative outcome.

Selected scientific readings

- Molecular basis of positional memory in limb regeneration. Nature (2025). <https://www.nature.com/articles/s41586-025-09036-5>

This is an evidence-informed conceptual essay, not a systematic review, clinical trial, validated diagnostic instrument, or treatment recommendation.

Editorial status: substantially revised conceptual article. Evidence-informed, not peer-reviewed, not a systematic review or clinical treatment guidance.