THE ARISING

Rebuilding Human Function

REGENERATIVE ENGINEERING



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What can medicine rebuild?

There is a practical difference between keeping a damaged organ alive and giving it back the work it has lost. Medicine has become extraordinarily good at the first. Dialysis can stand in for kidneys. Injected insulin can sustain a person whose pancreas no longer makes enough of it. Transplantation can replace a failing organ, but the supply is scarce and immune rejection remains a lifelong concern. Regenerative engineering begins with a different ambition: make living cells, tissues, or replacement organs perform the missing function.

The achievements are uneven, and that unevenness tells us something useful. A genetically corrected sheet of skin can renew itself after grafting. A cluster of insulin-producing cells can respond to blood glucose. A transplanted population of dopamine-producing cells may survive inside a brain. A liver can be maintained outside the body with oxygenated blood-like fluid long enough to assess its function. By contrast, assembling a complete kidney, with its intricate filtration units, drainage system, vessels, immune relationships and hormonal roles, remains far beyond routine bioprinting, the use of printing methods to arrange cells and supporting materials.

This issue asks what we can genuinely repair now, what early human studies are beginning to show, and how the formidable engineering problems fit together.

1. Four ways to return a lost function

The phrase *regenerative medicine* covers several very different operations. Confusing them makes progress appear faster than it is.

Repair cells already present. Exercise, nutrition and rehabilitation draw on normal adaptation and tissue maintenance. Experimental work on cellular reprogramming asks whether some damaged tissue can be made more resilient or regain selected functions. The challenge is to change cell behavior without wiping out its identity or triggering abnormal growth.

Replace missing cells. Researchers can manufacture islets, clusters of insulin-producing cells, or immature cells destined to make dopamine, a brain chemical involved in movement, from stem cells. Here the engineering question is not whether an entire organ can be printed. It is whether new cells survive, integrate and perform a defined task for a durable interval.

Build living tissue. Skin is more accessible than a kidney because it can be grown, handled and grafted as sheets. Other tissues require three-dimensional scaffolds, forces such as stretching or compression, blood-vessel networks and interactions among multiple cell types. Tissue engineered for a laboratory disease model is useful, but it is not necessarily implantable.

Replace an organ and support it through the transition. Human donor organs, machine perfusion (pumping oxygen-rich fluid through an organ) and gene-edited animal organs are different technologies.

Each addresses a separate bottleneck: supply, preservation or acceptance by the recipient’s immune system. None solves them all.

The strongest clinical story is not simply “we grew an organ.” It identifies the missing function, demonstrates restoration in patients, measures durability and harm, and compares the result with existing care.

2. A child's skin: regeneration that genuinely happened

In 2017, Hirsch and colleagues described treating a seven-year-old with a life-threatening form of junctional epidermolysis bullosa. The disorder damaged the adhesion between layers of skin. Investigators collected the child's own skin cells, corrected them with a functional copy of the gene using a modified virus as a delivery vehicle, grew more of the corrected skin stem cells, and grafted sheets that rebuilt a large area of working outer skin, or epidermis. Their tracking of the cells’ genetic signatures suggested that a limited pool of long-lived stem cells sustained renewal after transplantation S01.

It is difficult to overstate the biological achievement. A living protective surface was rebuilt from the patient's cells, with correction carried into the self-renewing population. But the description also defines its limits: a single exceptionally severe case, specialized manufacturing, the demands of gene delivery and graft surgery, and no proof that a similarly complex liver or kidney can be made the same way. A skin sheet meets the environment across a relatively accessible surface. A kidney needs millions of precisely arranged functional units, perfused vessels and working plumbing.

For future tissue engineering, this example gives a surprisingly specific design principle: the graft must contain not only useful mature cells but the renewing cells that sustain the tissue. A beautiful implant that cannot maintain itself is a temporary device, not a lasting biological replacement.

3. Insulin-producing islets: replacing a function, not an entire pancreas

The most instructive modern clinical example may be diabetes. In the 2025 *New England Journal of Medicine* report of the ongoing zimislecel program, researchers implanted stem-cell-derived, fully differentiated islet cells into adults with type 1 diabetes complicated by difficulty recognizing dangerously low blood sugar (hypoglycemia) and serious prior episodes. This was an early human study, called phase 1-2, in which participants and clinicians knew what treatment was given. It did not randomly assign people to the new treatment or modern standard care for comparison. All participants received medicines that suppress the immune system to prevent rejection S02 / S11. These results came from an analysis done while the study was still running, and the analysis had not been planned in advance. That makes confirmation in later studies especially important.

At this early analysis, 14 people had at least a year of follow-up; 12 had received the full dose. All 12 full-dose recipients had no severe low-blood-sugar episodes between day 90 and one year. All also had HbA1c below 7%, a measure of average blood sugar over recent months, and spent more than 70% of monitored time in the target glucose range. Ten of those 12 were not using external insulin at day 365. These are patient-relevant observations: fewer dangerous episodes and a restored capacity to regulate glucose. They are not evidence that the intervention is safe or effective in the much larger population living with type 1 diabetes.

Three participants experienced serious neutropenia, a shortage of infection-fighting white blood cells. Two participants died during follow-up, one from cryptococcal meningitis, a fungal infection affecting the tissues around the brain and spinal cord, and one from progression of an existing illness affecting brain function; the paper described their circumstances and the consequences of immunosuppression. The treatment creates living insulin secretion but does not yet remove the need to protect transplanted cells from immune attack. The registry has since expanded the program into a later-stage study, called phase 3, listed as ongoing in the cited registry record S11.

The engineering lesson is that a replacement tissue can succeed by supplying a single missing physiological function. The hardest next step may be reducing the price paid for that success: donor-cell rejection, immunosuppression, long-term surveillance, scaling manufacture and demonstrating durable benefit against current alternatives.

4. Replacing dopamine-producing cells in the brain

A related strategy appears in Parkinson's disease. In a 2025 phase 1/2 report from Kyoto University Hospital, seven patients received immature dopamine-producing cells made from induced pluripotent stem cells: adult cells reset to a state from which they can develop into different cell types. Surgeons implanted them on both sides of the putamen, a brain region involved in movement. At 24 months, the investigators reported no serious adverse events and no tumor overgrowth on MRI. All seven recipients nevertheless experienced adverse events: 72 were mild and one was moderate. Measures of dyskinesia, unwanted involuntary movements, worsened in six of seven patients, generally while their Parkinson’s medication was active. Tacrolimus, a medicine used to suppress rejection, added its own side-effect concerns and need for monitoring. Imaging suggested dopamine-related activity from grafts. Among six people included in the preliminary assessment of benefit, movement scores improved for some but not all participants S03.

Seven recipients and an uncontrolled early study cannot establish a reliable treatment effect. Surgery, medication adjustments, patient selection and natural variation all complicate interpretation. Still, the question has moved beyond whether these cells can be developed into the desired cell type in a laboratory. The trial tests whether they can survive in a human brain and perform a part of the missing biological work. Long-term tumor surveillance, unwanted movements, immune compatibility and clinical-function outcomes matter much more than a dramatic photograph of neurons in a dish.

The next generation of cell replacement must do two things at once: make the right cells and help them join the right circuit. In the brain, cellular identity is only the beginning of function.

5. Edited blood stem cells: the patient as the manufacturing source

Regenerative engineering can also occur outside the body and then return to it. In a phase 3, single-group study of exagamglogene autotemcel for severe sickle cell disease, investigators collected patients' own blood-forming stem cells and related immature cells. They edited a stretch of DNA that controls fetal hemoglobin, an oxygen-carrying protein normally made before birth that can help prevent sickling. Before the modified cells were returned, patients received intensive treatment to clear existing blood-forming cells from the bone marrow, called myeloablative conditioning. Of 30 participants with enough follow-up for the primary evaluation, 29 remained free of severe vaso-occlusive crises for at least 12 consecutive months. These are painful episodes caused by blocked blood flow. The study did not use a concurrent randomized control S04.

That is a powerful restoration of blood function, and a reminder that not all therapies bearing the label *gene editing* are a simple injection. Cell collection, specialized gene modification, quality testing, chemotherapy-like conditioning, hospitalization and prolonged monitoring are integral to the process. The harms of conditioning and the demands of specialized care are central, not footnotes. This path illustrates why a remarkable molecular intervention can remain inaccessible to many people who might benefit.

6. The vascular problem: how do cells breathe?

If there is a single engineering problem that separates a living tissue from an organ-sized replacement, it is the need for supply lines. A tiny cluster of cells can exchange oxygen and nutrients by diffusion, the natural movement of molecules into and out of the surrounding fluid. An organ-sized mass cannot simply rely on that. Cells deep inside a thick graft will fail unless vessels deliver adequate flow, oxygen, nutrients and waste removal. Moreover, flow is not just a supply mechanism: pressure and the friction of flowing fluid help cells mature and shape their behavior.

Two 2026 laboratory studies illustrate the present frontier. Filatova and colleagues formed tiny round clusters of human liver tissue with vessel-like networks. They combined developing liver cells, blood-vessel lining cells, and supporting stem cells known as mesenchymal stem cells. The networks had hollow channels and, inside devices that control very small fluid flows, connected with channels lined by blood-vessel cells outside the clusters. The researchers also assembled interconnected layers S07. That is progress toward vascular architecture, not a transplant-ready human liver.

Separately, a printed model of liver fibrosis, or scarring, used temporary material that could be removed to leave open channels. Fluid could then flow through spaces resembling the liver's small blood vessels. Researchers separately adjusted the stiffness of the material supporting the cells. In these laboratory tests,

fluid flow and material stiffness changed the behavior of scar-forming cells and the function of liver cells S08. Such devices may improve disease modeling and drug tests; they do not demonstrate that the same construct will replace an organ in a person.

A realistic manufacturing roadmap therefore starts with an unglamorous series of measurements: which cells are present, whether channels stay open, how evenly oxygen reaches tissue, whether flow damages the blood-vessel lining, whether immune cells can enter, and whether the construct performs its job after implantation. Scale amplifies every neglected problem.

7. A liver outside the body: preservation as engineering

Not every advance needs a new organ. Keeping an existing donor organ alive and assessable for longer can improve transplantation logistics. In a randomized trial involving 220 liver transplants, Nasralla and colleagues compared machine perfusion at near-body temperature with conventional storage kept cold without circulation. Perfused livers showed about half the measured liver-cell injury, estimated from enzymes released by damaged cells; the investigators also reported a lower organ-discard rate and longer preservation intervals. However, important outcomes such as survival of the transplanted liver, survival of the recipient and bile-duct complications did **not** show a clear difference beyond the uncertainty in this trial’s results. That does not prove the methods are equivalent; it means this trial did not establish an advantage on those outcomes S05.

This distinction is instructive. Better enzyme levels and fewer discarded livers are meaningful operational signals, but the trial did not establish a survival advantage. The machine controls flow, oxygenation, temperature and composition, while clinicians assess viability and coordinate transplantation. It is already a more practical model of regeneration's engineering future than a picture of a laboratory-grown organ. A working system joins biology to monitoring, a supply chain, clinical decisions and a procedure that can be repeated safely.

8. A genetically edited pig kidney: a real bridge, and a real failure

A 2026 *Lancet* report described one patient who received a kidney from a genetically engineered pig through a U.S. expanded-access arrangement allowing experimental treatment outside a standard clinical trial. The kidney functioned after surgery, and the recipient avoided dialysis for 271 days. Early rejection driven by immune cells called T cells resolved with treatment. After approximately six months, immunosuppression was reduced during a bacterial infection that was not transmitted from the pig; later damage to tiny blood vessels led to failure and surgical removal of the transplanted kidney. The patient subsequently received a human kidney; the authors did not find clinically significant evidence of an immune response that would make a later human donor kidney harder to match, or transmission of pig infections in the reported follow-up S06.

One person's course cannot establish population-level safety, a routine replacement strategy or a definitive risk of infection. Yet it provides something stronger than an aspirational press release: a longitudinal record of function, rejection, failure and the possibility of another transplant afterward. The most important scientific question may be what injured the microvessels despite conventional crossmatch tests, which check for antibodies that might attack a donor organ. Immunology, endothelial biology and long-term organ monitoring converge there.

The goal is not to declare animal organs equivalent to human organs. It is to learn which barriers can be engineered away and which cannot. An edited donor genome is necessary for this approach but does not guarantee lasting acceptance by the recipient’s immune system, good function or absence of infection.

9. Reprogramming: can a damaged cell be persuaded to repair itself?

Cell replacement is not the only route. In partial reprogramming experiments, selected proteins that control gene activity temporarily change which genes cells use, without changing the underlying DNA sequence while investigators try to avoid complete loss of identity. A 2026 study in aged mice reported smaller areas of early damage from interrupted blood flow and better short-term movement-and-sensation measures after repeated activation of reprogramming proteins known as Yamanaka factors. Researchers also found changes involving oligodendrocytes, cells that produce the protective insulation around nerve fibers called myelin, and better preservation of that insulation S09. These findings are experimental mouse observations near 48 hours after interrupted blood flow, not proof of recovery or prevention of stroke in people. The genetic model, schedule and delivery mechanism matter.

A treatment called ER-100 addresses a different but related question in people. The cited ClinicalTrials.gov record describes an early safety study that enrolls small groups one after another, without assigning treatments at random. It includes people with open-angle glaucoma or nonarteritic anterior ischemic optic neuropathy, two conditions that damage the nerve carrying visual information from the eye to the brain. It is designed primarily to evaluate safety and tolerability of a reprogramming-based gene-therapy approach; the record listed recruiting status and a planned enrollment of 18 in that registry entry S10. A registry record is a study plan, not evidence that vision improved.

The possibility is scientifically substantial. Before making it a patient-facing recommendation, however, investigators must show control over dose and duration, sustained cell identity, tissue-specific benefit, absence of uncontrolled growth and safety over meaningful intervals. For now, “rejuvenation” should be used with a clear statement of what improved and whether it was tested in cells, animals, or people, not as a synonym for clinical age reversal.

10. The engineering sequence that matters

A replacement tissue is best judged as a working system. Its design review ought to follow the biological job from beginning to end.

Specify the function. Is the goal glucose-responsive insulin secretion, a load-bearing cartilage surface, sustained blood filtration, or dopamine signaling? A tissue may look anatomically convincing and still fail its job. Choose outcomes that matter to people, then choose laboratory tests that help explain those outcomes.

Select a cell source. Autologous cells, taken from the patient, reduce some compatibility problems but can be expensive and slow to manufacture. Allogeneic cells, taken from another person, can be produced at scale but bring immune challenges. Gene editing can remove a defect or alter compatibility, but also creates a separate safety and quality-control problem.

Give cells an environment. The extracellular matrix, the material surrounding cells, provides physical support and chemical signals. Bioreactors, controlled containers for growing living tissue, regulate oxygen, nutrients, flow and sometimes motion. The liver fibrosis platform S08 shows why the same cell population behaves differently in a stiff, perfused matrix than in a static flat dish. A useful model needs a stated question and a clear test of how well it represents real tissue.

Build supply and integration. Thick tissue needs vascular architecture; nerves and immune cells may be necessary for normal physiology. Host vessels must connect. Secreted products must reach the right destination. Long-term function must survive inflammation, infection, scar formation and the changing body into which the graft is placed.

Manufacture the same product twice. The right cell types, adequate biological activity, freedom from contamination, stable genetic material, and consistent quality from batch to batch are not minor details. A single bespoke surgical triumph is evidence of possibility. It is not proof of an affordable, scalable health service.

Compare honestly. A new graft should be measured against the actual alternatives: donor transplant, medical therapy, rehabilitation, assistive devices, dialysis, or standard cell transplantation. Follow patients for events that matter-survival, function, hospital use, quality of life and serious harms-not just biological markers. Cost and access are outcomes of another kind.

This sequence helps explain why regenerative engineering progresses in islands. A small cell population restoring one task may reach human trials sooner than a complete, multi-organ system. A vascularized liver spheroid can be an excellent research model while remaining years of engineering decisions away from a clinical graft; its actual arrival date cannot responsibly be inferred from the model.

11. Where mathematics, AI and robotics genuinely help

Robotics can automate reproducible cell handling, imaging and bioreactor control. Image-analysis software can check cell shapes and flag possible contamination. Mathematical models can estimate how oxygen and nutrients move, how fluids flow, and how forces affect tissue. AI may help find good growing conditions and flag unusual results. None of those tools removes the need to test cells and outcomes in the real world.

Even mathematical claims need careful checking. A public October 2026 critique documented differences between a written Navier-Stokes proof and portions of its machine-checked Lean formalization, including an extra mathematical requirement in one estimate. The computer had therefore checked a statement with different requirements from the written version. Its authors did not decide whether the written mathematical proof was correct. The Clay Mathematics Institute still listed the Navier-Stokes problem, about equations describing fluid motion, as Active S12 / S13.

For a tissue bioreactor, the practical counterpart is straightforward: a numerical fluid model is trustworthy only if the equations, boundary conditions, material parameters, code and real measurements agree within stated limits. A computer checking the logic of a mathematical proof is not the same as showing that a fluid-flow simulation matches real measurements. The distinction matters if a simulation is being used to keep living tissue supplied with oxygen.

12. What would count as the next leap?

The next meaningful gains will probably look modest before they look spectacular: a cell product that avoids chronic immunosuppression; a more reliable way to perfuse thick tissue; a reliable test of biological activity that predicts how a graft will work after implantation; longer follow-up for neurological grafts; a controlled comparative study showing a patient outcome that existing care does not achieve; or a production method that maintains quality across many independent batches.

A complete implantable kidney made by printing cells alone is not established. A fully functional printed heart is not established. Whole-body rejuvenation in humans is not established. These remain ideas to investigate, not clinical destinations with dependable calendars. What is established is more useful than hype: individual living functions have been restored in patients, and each success makes the next hard question more precise.

Reader's scientific map

Path	Demonstrated capability	Current limit	Next decisive test
Corrected skin from the patient	Working outer skin regenerated in one severe case S01	Specialized manufacturing; not a general organ blueprint	Durable outcomes and reproducible availability
Stem-cell-derived islets	Insulin secretion and 10/12 full-dose participants insulin-independent at one year in uncontrolled study S02	Immunosuppression; limited follow-up and population	Comparative efficacy, long-term safety and access
Dopamine-cell grafts	Graft survival and dopamine activity in seven-person early study S03	Exploratory benefit; surgery and surveillance	Controlled function and long-term tumor/dyskinesia monitoring
Edited blood stem cells	Strong single-group clinical outcome in sickle cell disease S04	Intensive bone-marrow preparation and complex care	Durability, safety, equity and simpler conditioning
Organ perfusion	Reduced measured graft injury and discard in randomized liver trial S05	No proven survival advantage in that trial	Recipient outcomes, practical implementation
Pig-to-human kidney	Dialysis-free support for 271 days in one reported recipient S06	Rejection, graft failure, infectious surveillance	Multi-patient long-term results
Engineered liver tissue	Fluid-carrying laboratory networks and a laboratory disease model S07 / S08	Not transplant-ready organs	Integration in a living body and scalable, verified function
Partial reprogramming	Mouse resilience signals and phase 1 human safety study underway S09 / S10	No established human rejuvenation or vision benefit	Human safety and functional outcome evidence

What these advances mean

We are learning how to repair selected living functions rather than merely compensate for their loss. The best work is often beautifully specific: a sheet of skin that renews, an islet that senses glucose, a donor liver kept functioning on a machine, a graft that buys a patient time. Those examples give us a method for thinking about every more ambitious claim. Ask what biological job has been restored, in whom, for how long, at what cost and risk, compared with what. The answers will change. That is why FRONTIERS is a living reference rather than a collection of promises.

Sources and further reading

- **S01** - one-patient gene corrected epithelial stem-cell reconstruction
- **S02** - phase 1/2 allogeneic stem-cell-derived islet therapy in 14 evaluable patients
- **S03** - seven-patient iPS dopaminergic progenitor transplantation
- **S04** - phase 3 single-group exa-cel gene-edited stem-cell transplant
- **S05** - randomized normothermic liver machine perfusion trial, 220 transplants
- **S06** - gene-edited porcine kidney in one living person with subsequent human allotransplantation
- **S07** - engineered human liver spheroids with vascular networks in vitro
- **S08** - sacrificially bioprinted perfused liver fibrosis model
- **S09** - cyclic Yamanaka factors in aged stroke mice
- **S10** - ER-100 first-in-human open angle glaucoma/NAION safety protocol
- **S11** - zimislecel VX-880 phase 3 protocol/continuation
- **S12** - written vs machine-checked Navier-Stokes proof semantic mismatch critique
- **S13** - Navier-Stokes equation: Millennium Prize Problem status

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