The Regenerative Engineering: Prime Example of Convergence.

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## REGENERATIVE ENGINEERING IN THE BODY

**Introduction**

If salamanders lose their tails or a leg, they can regrow them, at any point during their lifetime. What if people too, aided by advanced regenerative engineering strategies, could also regrow damaged or amputated body parts? Think of all the wounded warriors, the failing knees of an aging population, the long waiting list for transplanted kidneys. There have been significant advances in prosthetics—electromechanical replacement limbs—but they still do not restore the sense of touch and normal feedback in movement. Organ transplant techniques have also improved, but infection and rejection of the alien tissue are still significant problems, quite aside from the huge shortage of donor organs. And people do continuously regrow both skin and blood cells throughout their lives—so why not more complex tissues or whole limbs?

In fact, advances in regenerative engineering offer the hope of bringing these techniques into routine clinical use. Already, artificial skin developed for burn patients is widely used. New techniques to foster bone growth are on the market. And more significant opportunities are emerging, some already in clinical trials. These new approaches define convergence: they require sophisticated new materials compatible with the human body to provide a lattice for new tissue to grow on; the use of adult stem cells derived from the patient to generate new tissue that won’t be rejected; advanced developmental biology to stimulate cell and tissue growth; carefully engineered bio-reactors to provide nutrients and controlled growing conditions; and even genetic approaches to turn on or off specific genes. Recent innovations illustrate the potential for such convergent approaches.

**Recent Advances**

One area of importance for regenerative engineering is the use of adult stem cells, found in fat, blood and other parts of the body, or even ordinary skin cells that have been re-programmed to act as stem cells. Such cells—unlike those from developing embryos—are easily obtainable from a patient and can be stimulated to grow into new tissues. They can be loaded into a 3-D printer cartridge, allowing new tissues to be printed in the sizes and shapes desired, or simply “painted” onto an existing protein structure, placing millions of cells in a very short time. This makes it possible, in principle, to regrow damaged parts of the body with tissue that the body recognizes as its own—in effect, to harness the body’s own internal healing mechanism, and to accelerate them.

**Ligaments and Tendons**. Some 200,000 people tear an anterior cruciate ligament (ACL) every year in the U.S. alone. Surgeons can repair these by transplanting a tendon from elsewhere in the patient’s body or from a cadaver, but it doesn’t always work. Recent work at the University of Connecticut shows that it’s possible to prompt the body into re-growing the ligament. The approach utilizes the torn stump of the ACL, which contains stem cells, other tissues, and nutrients needed for regrowth, but also implants a specially engineered matrix that provides immediate support for the knee, but also a structure for cells to attach to and grow on.[[1]](#endnote-1) Then a specialized bioreactor is placed around the knee for 12-18 months to protect the growing tissue and provide additional nutrients. After successful experiments with rabbits and sheep, the new engineered ligament is now in human clinical trials. A similar approach in underway to regrow injured Achilles tendons. A biodegradable polymer is used to supply stem cells (obtained from fatty tissue) and growth stimulating peptides to the injured site, enabling the stem cells to develop into tendon tissue and regrow the tendon.

Re-growing bone is already possible, but advanced approaches are likely to involve advanced materials such as polymer/ceramic composites and will create a matrix that includes stem cells, nanomaterials, and growth factors, each of which must be provided in the correct order for optimal growth.

The ultimate goal is to regrow more complex tissues, such as a limb or a whole knee, inside a bio-reactor attached to the patient. It’s not possible yet, but that is the opportunity, especially with improved understanding of the developmental biology of stem cells—which turn out to be present throughout the adult human body—and with more precise ways to get growth genes, normally silent in adults, to turn on in damaged tissues.

**Growing Whole Organs for Transplant**. Another area of active research is growing whole organs. The need is clear—at any given time in the U.S., nearly a million people are waiting for transplants of various kinds. The ideal is to take cells from the patient and regrow an organ that could be then put back into the patient. That may well be possible for relatively simple organs—already, in a few cases, replacement bladders and veins have been successfully made to work in animal models and in a few humans. But for more complex organs—livers, kidneys, hearts—several researchers at Massachusetts General Hospital and the Texas Heart Institute are following a different approach.[[2]](#endnote-2) They start with donated cadaver organs, then wash away all of the cells from the donor, leaving only the structural protein framework of the organ, typically composed mostly of collagen. Then they add cells from the intended recipient and nutrients and growth factors, and let the new organ tissue regrow on the collagen structure. That is much simpler, in principle, than trying to create all of the tiny micro-tubules in the kidney, or the precise structure of arteries and valves in the heart. And the resulting organ would be immunologically identical to the recipient, so there are no rejection risk—it would be like getting a new heart that is really your own.

Success is not assured, but the potential is a much larger supply of transplantable organs than could ever be obtained from living donors—indeed, the donor organ does not even have to be from a human; pig organs seem to work fine and are often stronger and healthier than those from human cadavers. But scientists are still sorting out which kinds of cells work best. The sheer numbers are daunting—the heart has billions of cells. And getting the new cells to take root on the protein structure and grow, and then to become functioning parts of a beating heart—is trickier. So researchers put the heart in a bioreactor that mimics the sensation of beating with a pump and often use electrical signals to help synchronize the actions of the individual cells. In animal experiments, some hearts eventually beat on their own, if not yet fully efficiently.[[3]](#endnote-3) The final challenge will be to implant such a heart and connect it to all the vascular plumbing of a living animal or human. At the very least, scientists doing this work expect to learn a lot about the cell types within organs and how they work together, which may suggest still other therapeutic approaches.

**Restoring Organ Function**. Whether or not complex organs can be regrown, there is another approach that could significantly improve human health. It stems from the recognition that the human body has remarkably redundant capacity—organs such as the kidney or the liver can function even with only a fraction, perhaps 10-20 percent, of their normal capacity. In fact symptoms of organ failure in a patient usually don’t occur until that point. So the idea being pursued by researchers at Wake Forest university is to insert a wedge of healthy tissue, equal to 10 or 20 percent of the organ, in such patients and keep them alive and with a high quality of life.

For a patient with kidney failure, for example, the process might go something like this: extract some healthy kidney cells from the patient and grow them; remove cells from a health pig kidney, leaving only the protein structure; then repopulate the pig organ with the patient’s cells. Insert a segment of the new kidney tissue into the patient’s failing organ, where it is recognized and accepted as “self” and can quickly begin to function. In principle, such partial transplants are much easier, and perhaps more likely to work, than re-growing whole organs. This approach is not yet in human clinical trials, but animal trials already show promise.

*These examples illustrate the potential power of convergence approaches that combine developmental biology, bio-engineering, and clinical innovation to dramatically improve the quality of life for those with damaged or dysfunctional body parts. The same research efforts will also advance basic understanding of the developmental process that generates the organ in the first place. For example, to make synthetic organs will require stems cells with the right structure and signaling characteristics, so these cells generate the complex tissues needed to function as bone or tendon. The nature of signaling between muscle, vascular and neuronal tissue, currently poorly understood, can be studied in these synthetic organs bioreactors. In another area of science, these types of organ bioreactors are also important for investigating migration of cancer cells into tissue forming metastatic growths, a central problem in control of this disease. Convergence science will not only advance innovations in healthcare but will also advance fundamental knowledge of biological systems.*

1. Freeman, J.W. et al. Evaluation of a hydrogel-fiber composite for ACL tissue engineering. *J Biomech* **44**, 694-9 (2011). [↑](#endnote-ref-1)
2. Ren, X. et al. Engineering pulmonary vasculature in decellularized rat and human lungs. *Nat Biotechnol* **33**, 1097-102 (2015). [↑](#endnote-ref-2)
3. Ott, H.C. et al. Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. *Nat Med* **14**, 213-21 (2008). [↑](#endnote-ref-3)