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BODY, HEAL THYSELF

ENGINEERED GELS MAY PROMPT THE BODY TO REPAIR ITSELF AS NEVER BEFORE.

Kristi S. Anseth, the first engineer to become an HHMI investigator, has invented new classes of hydrogels—synthetic bioinspired micro-environments that support and interact with living cells. Working with clinicians, chemists, and biologists, the University of Colorado at Boulder researcher and her colleagues are developing a form of tissue engineering to coax the body to heal itself.

Imagine that a soldier could quickly regrow the bones of his shattered leg, that a skier could donate a bit of her own cartilage to rebuild the protective cushion in her damaged knee, or that an implant of tailor-made brain cells could cure the shaking of Parkinson's disease.

That is the promise of tissue engineering, a field often called regeneration medicine. Clinicians, engineers, biologists, chemists, and materials scientists are joining forces to marshal the body's developmental and repair mechanisms to heal wounds, rebuild damaged tissues, and replace essential cells.

In my laboratory, our challenge is to design customized biomimetic gels, also called hydrogels, that imitate some aspects of the extracellular matrix—the natural three-dimensional microenvironment that encourages cell growth during development and wound healing and during normal tissue homeostasis. These artificial matrices already are being tested as structural supports for cell-built treatments such as joint repair. The next generation of gels will support cells' metabolic functions, such as insulin regulation for diabetes, and encourage cell-to-cell connections, as with neurons in the brain.

A second challenge is to learn the biomimetic cues that cells require to perform a desired repair. We may discover that our task is less to control natural processes than to trigger the right conditions so that the cells themselves can take on the job of building and organizing tissue.

A treatment now in clinical trials to repair the cartilage worn away from a skier's painfully damaged knee offers a simple example of the way a biomimetic gel works. Injected into the space within the joint, the hydrogel—which combines water with large macromolecules—is activated by beams of light to form a molecular mesh. This mesh forms a firm but flexible scaffold, rather like organized Jell-O, built in the presence of the patient's own cartilage-forming cells, which secrete tissue components that decorate the lattices of macromolecules like vines on a trellis. Stimulated by cues from the three-dimensional scaffolding, the cartilage-built structure gains strength and the artificial scaffolding begins to dissolve. Meanwhile, the skier exercises her knee, and mechanical forces refine the shape. Instead of a titanium joint replacement, she has regrown a natural cushion of her own cartilage to support her knee.

In nature, the extracellular matrix provides not only support but also a location for molecular signals that are traded back and forth as the cells build a specific structure or organ. Taking advantage of this cell-gel crosstalk, Jeffrey A. Hubbell and his group at the École Polytechnique Fédérale de Lausanne (Switzerland) have shown in animal studies that a synthetic gel can provide a matrix that stimulates the animal's bone marrow to fill the gaps between fragments with strong bone cells. The matrix is laced with encapsulated doses of a growth-promoting protein that are only released, dose by dose, when growing bone-marrow cells send an activating signal to a cache of the protein within the gel.

With further advances, artificial gels may also be tailored to support stem cells—an important requirement for any cell-based treatments of Parkinson's disease or type 1 diabetes, which so far do not provide lasting benefits in the body. A customized gel could guide the process of coaxing precursors to become the desired cell type. The gel would then protect the therapeutic cells with molecular barriers. And it would be embedded with further instructions for cell therapy—signals to be activated once the cells were implanted in the body. Brain cells, for example, could be encouraged to send out axons and perhaps be guided to connect with specific types of neurons.

The technical advances needed to take advantage of these opportunities will require synergistic efforts across disciplines. Scientists and engineers working together will advance gel niches from their infancy to mature, sophisticated environments, illuminating the possibilities for cell-based strategies to repair tissues.

INTERVIEW BY JANET BASU. *Kristi Anseth does research and teaches at the University of Colorado at Boulder.*