Someday, these culture systems may be able to mimic whole organs sufficiently well to permit their use as surrogates in toxicology testing (M. Shuler, Cornell).

Signaling proteins that control differentiation of progenitor cells are under investigation (D. Anderson, CalTech; N. Mahanthappa, Ontogeny). Whereas most of the discovery and testing of these proteins has occurred in developing animals, these proteins are also active in adult tissues, suggesting new pharmacological approaches for tissue regeneration. For example, administration of growth factors or signaling proteins such as those from the sonic hedgehog family could initiate repair in bone or the nervous system.

The delivery of novel agents requires precise spatial as well as temporal control necessitating new delivery strategies—for example, gene therapy is being used to target signaling proteins to specific tissue sites, such as arteries (A. Clowes, Washington) and bone (J. Bonadio, Michigan). Novel gene delivery techniques may be particularly useful: a gene gun is being used to deliver plasmids encoding transforming growth factor β to skin cells (J. Davidson, Vanderbilt). *In vivo* gene therapy of skeletal muscle results in physiological levels of erythropoietin in the circulation of mice and monkeys (J. Leiden, Chicago). Although it is apparent that novel activities can be introduced into tissues in this fashion, controlling the level of expression of the transgene and the life span of genetically-modified cells remains a challenge (G. Krueger, Utah).

The central importance of new materials for the construction of artificial matrices was highlighted in the keynote address by Robert Langer[3] (MIT). Langer described ways to engineer the correct physical, chemical, and morphological characteristics into polymeric tissue scaffolds. The basic principles involved appear to be quite general: the versatility of synthetic polymer chemistry and modern polymer processing technology permit application of artificial matrices to the repair of a plethora of tissues including cartilage, skin, bone, tendon, intestine, and nerve.

Novel materials can be used to present immobilized signaling peptides[4] (J. Hubbell, Swiss Federal Institute of Technology) or growth factors, which promote the migration of cells necessary for tissue repair and guide them to the site of injury (P. Letourneau, Minnesota). Polymeric materials presenting tethered epidermal growth factor signal hepatocytes to differentiate[5] (L. Griffith, MIT), and implants that provide controlled delivery of nerve growth factor enhance the survival of transplanted neurons[6] (M. Saltzman, Cornell). It has long been known that cells depend on intrinsic signals as they sort into aggregates. More recent results suggest that this sorting can also be influenced by adhesion to different surfaces (M. Steinberg, Princeton).

Almost every presentation articulated the need for synergy between materials engineers, biologists and clinicians. Difficulties in mimicking native tissue responses using synthetic approaches, and the need for quantitative methods to describe and predict responses, were articulated by those describing fundamental studies on receptor-mediated cell migration (D. Lauffenburger, MIT), cell interactions with matrix (B. Eckes, Cologne), autocrine signaling (S. Wiley, Utah), and mechanical loading (the forces applied during growth) of tissues (A. Banes, North Carolina; A. Grodzinsky, MIT). The next generation of engineered tissue will be more rational in design, as the biological basis for tissue responses becomes clearer. It may never be possible (or desirable) to engineer a human head onto a lion's body, but less mythical tissue recombinations are already on the horizon.

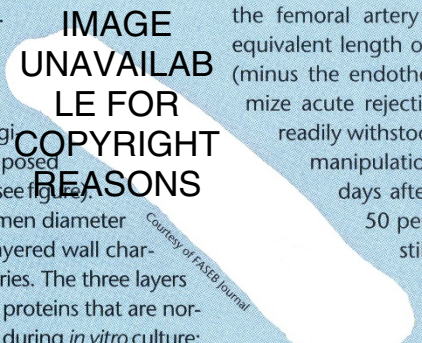
1. Aebischer, P. *et al.* Gene therapy for amyotrophic lateral sclerosis (ALS) using a polymer-encapsulated xenogeneic cell line engineered to secrete hCNTF. *Human Gene Therapy* **7**, 851–860 (1996).
2. Soon-Shiang, P. *et al.* Insulin dependence in a type I diabetic patient after encapsulated islet transplantation. *Lancet* **343**, 950–951 (1994).
3. Langer, R. & Vacanti, J.P. Tissue engineering. *Science* **260**, 920–932 (1993).
4. Hern, D.L. & Hubbell, J.A. Incorporation of adhesion peptides into nonadhesive hydrogels useful for tissue resurfacing. *J. of Biomed. Materials Res.* **39**, 266–276 (1998).
5. Kuhl, P.R. & Griffith-Cima, L.G. Tethered epidermal growth factor as a paradigm for growth factor-induced stimulation from the solid phase. *Nature Med.* **2**, 1022–1027 (1996).
6. Saltzman, W.M. Growth factor delivery in tissue engineering. *MRS Bulletin* **21**, 62–65 (1996).

School of Chemical Engineering
Cornell University
Ithaca, NY 14853, USA

Artificial arteries—all wrapped up

During heart by pass surgery, large arteries such as the aorta can be successfully replaced with synthetic blood vessels, but replacing smaller arteries (lumen size <5 mm) with such synthetic grafts has proved to be much more difficult. To address this shortcoming, Auger and colleagues (Laval University, Quebec) set out to 'grow' their own biocompatible arteries from human cells (*FASEB Journal*, **12**, 47–56, 1998).

They cultured human fibroblasts and vascular smooth muscle cells separately in media supplemented with ascorbic acid, which encouraged the cells to grow as sheets. The muscle cell sheet was then wrapped around an inert plastic tube (diameter 3 mm) to form the medial (middle) layer of the arterial wall. The adventitial (outer) cell layer was forged by enclosing the muscle layer in a sheet of fibroblasts. Following culture in a bioreactor (to encourage the two cell layers to merge), the plastic tube was removed and the resulting lumen was seeded with human endothelial cells, which proliferated to fashion the intimal (inner) layer of the arterial wall.



Courtesy of FASEB Journal

After three months of careful nurturing, the Canadian team emerged with an engineered artery composed entirely of human cells (see figure). Their creation had a lumen diameter of 3 mm and a three-layered wall characteristic of normal arteries. The three layers each expressed marker proteins that are normally lost or diminished during *in vitro* culture: endothelial cells re-expressed von Willebrand factor, muscle cells re-expressed desmin. Auger and co-workers were pleasantly surprised by the high burst strength (2000 mmHg) of the engineered blood vessel, which was comparable to that of a normal human artery.

Although the artificial artery 'looked the part', the authors wanted to know if it could 'play the part'. So, they replaced 5 cm of the femoral artery in six dogs with the equivalent length of the engineered artery (minus the endothelial cell layer, to minimize acute rejection). The arterial grafts readily withstood suturing and surgical manipulation. Angiography seven days after surgery revealed that 50 percent of the grafts were still patent (that is, capable of maintaining normal blood flow). The next step, the investigators say, is to graft engineered arteries into other animals (perhaps pigs) and monitor the grafts for a longer period.

Orla Smith is the News & Views editor of Nature Medicine