tivity provide the mathematical tools that we need to curve space. The space transformations that have been used previously to design cloaks can locally compress and stretch space in all directions, but despite this huge design freedom, the result is still a flat space without any intrinsic curvature to bend the path of light. The use of curved spaces allows new designs to be explored.

To introduce a curved space in the design of a cloak, it must be mapped on a three-dimensional physical space. A two-dimensional example of such a map is the Mercator projection that represents the curved spherical surface of Earth on a flat sheet of paper. This kind of operation also results in equivalent optical properties but with a much greater variety of designs for cloaks. Leonhardt and Tyc have proposed a very skillful transformation from a carefully chosen curved space where a natural cloaking effect exists that results from the sophisticated paths that light takes around the hidden region. Translated into equivalent properties in Euclidean space, this scheme allows an invisibility cloak to be designed without singularities in the optical properties of the materials. Nevertheless, the required optical properties are still demanding.

Although the use of metamaterials solves many problems in cloaking, their properties are sensitive to the wavelength. Realizing the required optical properties across the entire visible spectrum presents an additional hurdle, especially when extreme values must be reached. Indeed, such values require resonances, that is, phenomena tuned to specific frequencies. Thus, bringing the material properties to moderate values is a necessary step for a cloak to work for all colors.

Theoretical work on cloaking has shown that, in principle, an invisibility device may be possible, but how will engineers design and manufacture such a device? The development of a real cloak will likely involve numerical modeling (*5*), as well as trial-and-error optimization, with little reference to the initial ideas. Concerning applications, fictional literature has made us acquainted with some frightening aspects of invisibility. However, the theory of cloaking can be translated to other kinds of waves encountered everywhere in physics. Indeed, the first practical applications of invisibility may well be the protection of small islands against dangerous sea waves (*6*).

References

1. U. Leonhardt, T. Tyc, *Science* **323**, xx (2009).
2. J. B. Pendry, D. Shurig, D. R. Smith, *Science* **312**, 1780 (2006).
3. B. Gralak, G. Tayeb, S. Enoch, *Opt. Express* **9**, 567 (2001).
4. W. X. Jiang *et al.*, *Appl. Phys. Lett*. **93**, 194102 (2008).
5. F. Zolla, S. Guenneau, A. Nicolet, J. B. Pendry, *Opt. Lett*. **32**, 1069 (2007).
6. M. Farhat, S. Enoch, S. Guenneau, A. B. Movchan, *Phys. Rev. Lett.* **101**, 1345011 (2008).

10.1126/science.1168456

CHEMISTRY

Repair or Replacement: A Joint Perspective

Insights into the molecular origins of cartilage lubrication could lead to more efficient tissue repair and to longer-lasting prostheses for hip and knee joints.

Jacob Klein

The ultra-low friction coefficients between the articulating cartilage surfaces in human hips or knees cannot be duplicated even by the most sophisticated technological means. Breakdown of this lubrication can lead to wear of the cartilage and to osteoarthritis. As human longevity increases, over 50% of populations may eventually suffer from debilitating osteoarthritic pains or joint breakdown due to such cartilage wear. In adults, damaged or worn cartilage has little capacity for self-healing, largely due to the low intrinsic density of chondrocytes (the cells responsible for synthesis of cartilage components, including the type II collagen from which its network is formed). Recent research into regeneration or replacement of damaged joints (*1*) points to directions that could improve prospects for osteoarthritis sufferers.

Efforts to repair cartilage often introduce chondrocyte cells, or stem cells which can differentiate into chondrocytes, to the damaged region, where they can regenerate tissue. The matrix (scaffolding) containing such cells, which is implanted in the tissue, must resist removal by friction as the cartilage surfaces slide past each other at high pressures. This underlines the importance of lubrication for articular cartilage repair. Better lubrication can also greatly increase the lifetime of hip or knee prostheses when joint replacement becomes necessary.

In a classic treatment for cartilage regeneration, known as microfracture, mesenchymal stem cells are released from marrow in the underlying bone to permeate the damaged cartilage area (*2*). There the stem cells undergo chondrogenesis (differentiation to chondrocyte-like cells) to accelerate tissue healing, although the resulting tissue is fibrillar, in contrast to the low-friction, smooth hyaline cartilage (see the figure). More recently, for early-stage osteoarthritis, chondrocytes harvested from a healthy cartilage region have been culture-expanded in vitro and transplanted into damaged regions to promote tissue regeneration (*2*). Synthetic biology may hold considerable future promise for such approaches. In one approach, somatic cells may be programmed to dedifferentiate to pluripotent stem cells (*3*), which could then be embedded in the cartilage to undergo chondrogenesis. Other approaches, still in their infancy (*4*), would seek to reprogram cells to their regenerative format as native chondrocytes. Ideally, these should, with the appropriate external cues, regenerate the native hyaline cartilage in damaged tissue.

Tissue engineering (*5*, *6*) for cartilage regeneration generally uses a combination of scaffolding, cells, and signaling molecules to induce chondrogenesis. Scaffolding matrices are implanted, self-assembled, or gelled within cartilage lesions; implanted scaffolds may also be glued to the tissue. Hydrogels of synthetic or naturally occurring macromolecules (including components of cartilage), self-assembling nanofiber networks, or plugs of healthy transplanted cartilage have been used as scaffolds, and several of these are undergoing clinical trials. The incorporated cells are typically mesenchymal stem cells; signaling molecules for chondrogenesis are often growth factors or genes(*5*).

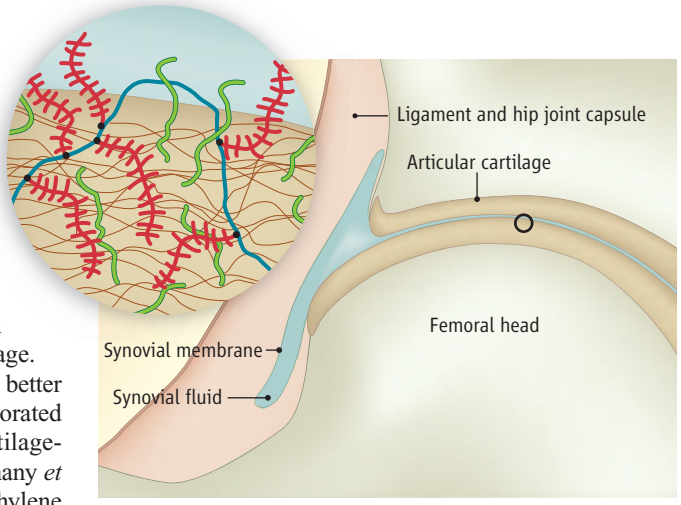
An optimal scaffold environment would be biocompatible, have mechanical and permeation properties similar to those of healthy cartilage (*7*), not be broken down prematurely by tissue enzymes (*8*); and biodegrade eventually and be removed, in parallel with the

Department of Materials and Interfaces, Weizmann Institute of Science, Rehovot 76100, Israel. E-mail: jacob.klein@weizmann.ac.il

growth of new tissue. Recent attempts to optimize some of the properties of scaffolds include the following examples.

Moutos *et al.* (*7*) have described a scaffold woven from polyglycolic acid yarn, and consolidated with a biocompatible hydrogel. The permeability and mechanical properties of this matrix mimic those of healthy articular cartilage. This matrix should therefore provide a better supportive environment for the incorporated cells, and thereby improve their cartilage-regeneration properties. Gonen-Wadmany *et al.* (*8*) have developed protein-poly(ethylene glycol) conjugates for creating hydrogel scaffolds; poly(ethylene glycol) protects the protein backbone against the enzymatic breakdown that often affects scaffolds consisting of proteins alone. Capito *et al.* (*9*) vary the traditional scaffolds: They create closed sac-like containers made of robust membranes through self-assembly of hyaluronic acid and peptide amphiphiles. The sacs are permeable to signaling molecules but not to cells. Sacs encapsulating mesenchymal stem cells and cultured in appropriate media readily undergo chondrogenesis, as revealed by expression of type II collagen. A different, promising approach uses sophisticated scaffolding matrices designed to recruit existing cells from the surrounding tissue. The cells then cause scaffold breakdown and release of signaling molecules previously stored in the matrix; these in turn stimulate the cells to more vigorous regeneration of new, normal tissue (*10*).

A crucial requirement for cartilage repair is that the scaffolding is attached at the cartilage lesions and integrates with the tissue; the attachment must be sufficiently robust to resist being torn off as a result of stress at an articulating joint. Wang *et al.* (*11*) have developed an adhesive based on chondroitin sulfate [a major component of the bottle-brush-like macromolecules, called aggrecans, that permeate the native cartilage (see the figure)]. The adhesive can be readily applied to glue (and integrate) scaffolding directly to the cartilage lesion. The resulting interfacial shear strength is ~50 kPa; for typical pressures of ~5 MPa at human hips or knees, this requires the friction coefficient at the scaffold surface during articulation to be <0.01 to avoid detachment of the scaffold. Similarly, high friction, and hence wear, may arise in regenerated tissue if it does not mimic the healthy, smooth native cartilage sufficiently closely (as happens for example with the microfracture technique). Efficient lubrication is therefore crucial not only in healthy joints, but also for tissue engineering of cartilage, and it is very important to understand its molecular origins.



A close-up view of the articular cartilage surface. Schematic section through part of a hip joint. The friction coefficients between the articular cartilage layers, compressed to 50 atmospheres or more in a hip joint, can be as low as 0.001 (*18*). (**Inset**) The detailed structure at the outer cartilage surface is thought to include charged macromolecules (*16*)—mainly hyaluronic acid (blue), to which are attached aggrecans (red), and lubricins (green)—that extend from the surface to form a brushlike layer. Synthetic charged brushes lead to low friction similar to that in articular cartilage (*12*), although, to date, only up to much lower pressures than in human joints.

Recent efforts to elucidate these molecular origins have focused on nanotribological studies of surface-attached molecules in aqueous media, seeking to emulate those at the cartilage surface (see the figure). Raviv *et al.* (*12*) showed that synthetic polyelectrolyte brushes attached to opposing surfaces can provide remarkable lubrication when mutually compressed to moderate pressures and made to slide past each other, with friction coefficients similar to those in healthy joints. Briscoe *et al.* (*13*) found that boundary lubrication under water was far superior to that in air or oil, and mediated by the hydrated surfactant headgroups. These and other studies (*14*, *15*) emphasize the importance of hydration layers surrounding charges in aqueous media as a basic lubrication element (*16*).

These nanotribological studies do not mimic the actual cartilage surface or the macromolecules emanating from it (see the figure), but rather provide insight into the origins of the very efficient lubrication in living joints (*16*). One difficulty is that at pressures of ~ 5 MPa, normal in hips or knees, friction coefficients attained in the laboratory to date have been much higher than the values of ~0.001 typical of human joints. Nonetheless, the insights gained from nanotribology can have immediate benefits for improved prostheses. For example, Moro *et al.* (*17*) achieved a massive reduction in wear-generated debris particles of the concave plastic cup of a hip prosthesis when they grafted polymer brushes to the plastic surface. Such debris particles are a major cause of failure of prosthetic implants through bone softening and consequent loosening of prostheses; their reduction through brush lubrication is thus a substantial potential benefit.

Future materials challenges will be to design scaffolds that provide optimal environments for the progenitor cells that they bring to the damaged tissue, or to stimulate indigenous cells; and to develop bioadhesives that promote tissue integration and prevent scaffold detachment during joint articulation. In replacement strategies, surface treatments that suppress the wear leading to implant failure may allow a closer approach to "lifetime" prostheses for the most widely used polymer-metal implant combinations. Thus, both for repair and replacement, a better understanding of the molecular mechanisms underlying the remarkable lubrication afforded by healthy articular cartilage at the high pressures in human hips and knees remains an urgent goal.

References and Notes

1. Some of these developments were discussed at the Royal Society of Chemistry conference "Chemistry in the New World of Bioengineering and Synthetic Biology," Oxford, 22 to 24 September 2008.
2. E. B. Hunziker, *Osteoarthr. Cartil.* **10**, 432 (2001).
3. J. A. Byrne, *Hum. Mol. Genet.* **17**, R37 (2008).
4. E. Andrianantoandro, S. Basu, D. K. Karig, R. Weiss, *Mol. Syst. Biol.* **2**, 2006.0028 (2006).
5. F. H. Chen, R. S. Tuan, *Curr. Rheumatol. Rev.* **4**, 161 (2008).
6. D. G. Anderson, J. A. Burdick, R. Langer, *Science* **305**, 1923 (2004).
7. F. T. Moutos, L. E. Freed, F. Guilak, *Nat. Mater.* **6**, 162 (2007).
8. M. Gonen-Wadmany, L. Oss-Ronen, D. Seliktar, *Biomaterials* **28**, 3876 (2007).
9. R. M. Capito, H. S. Azevedo, Y. S. Velichko, A. Mata, S. I. Stupp, *Science* **319**, 1812 (2008).
10. M. P. Lutolf, J. A. Hubbell, *Nat. Biotechnol.* **23**, 47 (2005).
11. D.-A. Wang *et al.*, *Nat. Mater.* **6**, 385 (2007).
12. U. Raviv *et al.*, *Nature* **425**, 163 (2003).
13. W. H. Briscoe *et al.*, *Nature* **444**, 191 (2006).
14. D. Gourdon *et al.*, *Langmuir* **24**, 1534 (2008).
15. S. Lee, N. D. Spencer, *Science* **319**, 575 (2008).
16. J. Klein, *Proc. Inst. Mech. Eng. Part J* **220**, 691 (2006).
17. T. Moro *et al.*, *Nat. Mater.* **3**, 829 (2004).
18. C. W. McCutchen, *Wear* **5**, 1 (1962).
19. I thank A. Klein, D. Seliktar, and S. Safran for critical comments. Supported by the McCutchen Foundation, the Israel Science Foundation, and the Minerva Foundation at the Weizmann Institute.

10.1126/science.1166753