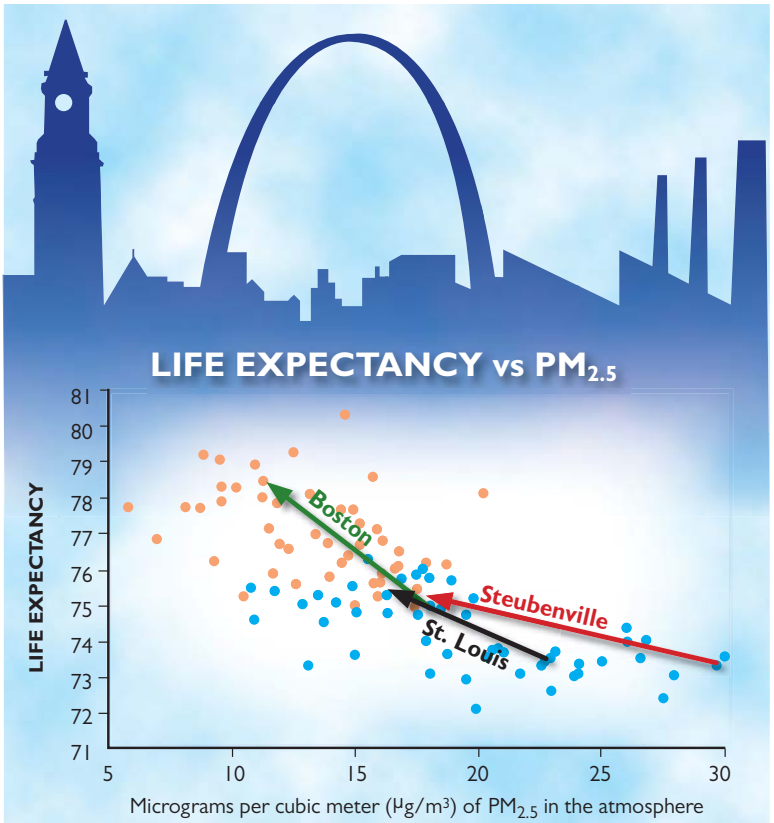


Particulate matter that is 2.5 microns or less in diameter ($PM_{2.5}$), the kind emitted from smokestacks and tailpipes, is known to be especially harmful. Reductions in such pollution lead to increased life expectancy. In Boston between 1980 and 2000, for example, as $PM_{2.5}$ concentrations dropped from 18 to 11 micrograms per cubic meter, local average life expectancy climbed four years. Of that increase, four-tenths of a year—or 10 percent of the total gain—was attributable to improved air quality.

ropolitan areas over time. Their findings validate the previous work.

During the roughly 20-year span studied, the overall average increase in lifespan was just under three years. Although much of this gain was due to other factors—including greater use of statin drugs, reductions in smoking, the increased prevalence of defibrillators, better diets, and better healthcare during the period—the cities with the biggest improvements in air quality invariably saw the biggest improvements in life expectancy. Even in a city like Boston, which registered relatively cleaner air, generally good healthcare, and an increase of four years in life expectancy, cleaner air accounted for 10 percent of the gain.

In those cities with the *largest* improvements in air quality, the increase in lifespan attributable to cleaner air was 10 months. "It is a dramatic gain," says professor of environmental epidemiology Douglas Dockery, the paper's senior author, who chairs the department of environmental health. Given the small changes in the overall levels of these all-but-invisible particles (whose average concentration dropped fewer than 7 micrograms per cubic meter), he notes, "It is startling that we can detect this effect at all." Yet an analysis by the federal Office of Management and Budget has shown that the public-health benefits of controlling fine-particle pollution vastly outweigh the costs. As an editorial stated in the *New England Journal of Medicine*, in which the new findings appeared, the results are significant because they provide "direct confirmation of the population health benefits of mitigating air pollution...."

The public-health benefits of controlling fine-particle pollution vastly outweigh the costs.

—Jonathan Shaw

DOUGLAS DOCKERY WEBSITE:
www.hsph.harvard.edu/faculty/douglas-dockery

DISK DRIVE

Fighting Disease *in Situ*

The disks at the center of Dr. David Mooney's current cancer research don't appear very powerful. Grayish-brown circles with the texture of a dry, hardened sponge, they are dwarfed by a fingertip and snap in half easily. But if recent work on melanoma therapies by the McKay professor of bioengineering and his team are any kind of harbinger, these tiny disks could become cancer's biggest challenger.

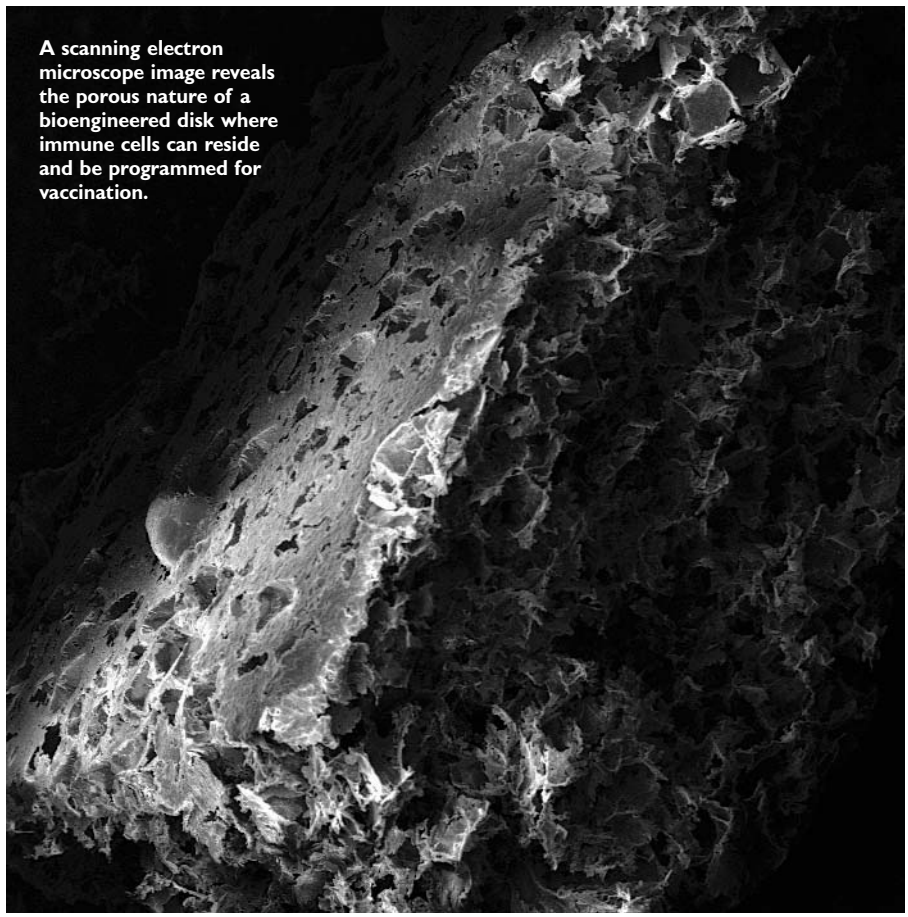
Cancer is a tough enemy. Against most diseases, the human immune system is a stalwart defender, equipped with a huge arsenal of molecular weapons to fight off bacteria, viruses, and all sorts of other harmful foreign invaders. But cancer flies under the radar: created by the body, it is camouflaged by familiar proteins the system has learned to view as harmless.

The relatively new field of cancer immunotherapy seeks to resolve this quandary by retraining the body's defenses to seek out and destroy cancer cells it would normally pass by. So far, the vaccines and therapies developed using this approach typically involve removing cells from a patient's body, programming them externally, and then reinjecting them. At that point, the hope is that the cells will travel to the lymph nodes and activate tumor-fighting killer T-cells.

"But there are limitations with that protocol," says Omar Ali, a postdoctoral fellow and a principal collaborator with Mooney. "Specifically, when you inject the cells back into the patient, many of them—which you have spent so much time programming—will die." Once trained outside their natural environment, Ali says, the cells have trouble readjusting to the body, leaving only 1 to 2 percent to mobilize cancer-fighting T-cells.

Mooney's team has solved this problem by finding a way to deliver cancer therapy from within. Mooney had been working with biomaterials and implantable systems in his research for years, stimulating

Chart by Stephen Anderson



A scanning electron microscope image reveals the porous nature of a bioengineered disk where immune cells can reside and be programmed for vaccination.

OMAR ALI

blood-vessel growth and bone regeneration using small subcutaneous disks: just the kind of device that might allow researchers to recruit immune cells and activate more efficient attacks on the cancer.

As they detail in a recent issue of *Nature Materials*, Mooney's team began their research by locating a good internal recruiter—a special protein that attracts dendritic cells, the immune-system workers that instruct T-cells to attack.

Their delivery method was a thin, eight-millimeter polymer disk that they implanted under the skin of mice with an aggressive melanoma. Reacting to the internal recruiter, dendritic cells sought out the disk, where they were activated by two additional items it harbored: antigens to train the cells to seek their specific cancer target, and so-called "danger signals," which mimic infection and energize the cells. Then the dendritic cells migrated to the lymph nodes to create armies of tumor-specific T-cells.

The addition of the "danger signals" proved crucial, sending 13 percent of the cells toward the lymph nodes, an improvement of more than 10 percentage points over results from external treatments. That outcome, coupled with the apparently more lasting benefit of internal manipulation by the activated dendritic cells, produces a qualitative as well as quantitative effect, says Mooney. The mice—which had been dying from the melanoma at around the twenty-fifth day—began surviving at a rate of 90 percent.

In addition to the promising results, there were other practical benefits: the disks cost only about $300 to manufacture; external treatments, Ali says, can take up to a month to prepare and can cost up to $10,000.

Working with Harvard's Office of Technology Development (see "Retooling Tech Transfer," January-February 2008, page 57), the findings have become the foundation of a start-up company, InCyTu (a play on *in situ*, and a nod to Mooney's bioengineering models). The team expects to begin clinical trials by the end of the year, and hopes for reasonably quick acceptance because the Food and Drug Administration has already approved most of the elements they are working

with, including the disk. They see the possibility of treating a host of diseases beyond cancer, including administering stem-cell treatments, with this novel delivery method.

Even if the clinical trials result in something more modest than a cure, says Ali—if the technique enhances survival rates or gives chemotherapy a better chance to work—it could be a huge advance in the fight against cancer, exciting enough for him to postpone a planned move to Malaysia's burgeoning biotech community. The *in situ* approach is "very easy to reproduce" and inexpensive, "so it could be used in both developed and developing countries." Yet he retains a healthy cynicism. "I'm always a bit skeptical," he explains, "because we haven't made the translation" from mice to humans. ~DAN MORRELL

DAVID MOONEY E-MAIL ADDRESS:
mooneyd@seas.harvard.edu
OMAR ALI E-MAIL ADDRESS:
alio@seas.harvard.edu
DAVID MOONEY WEBSITE:
www.seas.harvard.edu/mooneylab

INDULGENT ENVIRONMENTS

"Dissing" Evolution

PROFESSOR of anthropology Daniel Lieberman believes we can better understand the history and future of human evolution by pondering a single theme: how we take in and expend energy. This theme, he suggests, is crucial to understanding why the human lineage thrived, and influential in modern social and individual ills.

Lieberman's own research focuses on how evolution shaped the human body. The book project he is just beginning aims to synthesize his own and others' recent work in evolutionary biology, including new discoveries from genetics and the fossil record, in an attempt to frame the big picture in a new way.

That story begins seven million years ago, with climate change in Africa at the end of the Miocene Era. As the milieu changed from dense forest to a more open habitat of trees and brush—dispersing customary food sources—our ancestors' anatomy and physiology changed, too. They became bipeds—an ingenious strategy on nature's part, Lieberman notes, because walking upright uses 75 percent less energy than knuckle-walking.

Then, between two and three million years ago, during the late Pliocene Era, the continent cooled still more, and vegetation became even less dense. This time, evolution provided a different response to the changing foodscape: our ancestors became endurance runners, and that enabled them to become carnivores. Gradually, *hominins* (the preferred term for primates—such as the extinct Neanderthals and australopithecines—more closely related to humans than to chimpanzees) also lost their fur and gained an enhanced ability to sweat. That allowed them to stay cool while running long distances at speeds that force animals to gallop and thus eventually overheat and collapse (because they can't simultaneously pant to cool themselves). These physical changes were critical because spear points, the earliest hunting implements, first appear millions of years later. Lieberman believes the high-arched feet and springy legs that enable us to run marathons are not mere flukes of evolution or byproducts, but among the crucial features that enabled the human genus to go forth and prosper.

Becoming meat-eaters not only gave our ancestors the energy to cover more ground but also released a caloric constraint on brain size. The shift enabled them to eat and store the fuel needed to power big brains and the attendant benefits: speech, memory, the use of complicated tools. Once that constraint was released, *Homo* brains grew quickly: the fossil record shows little difference in brain size between australopithecine and other early hominin specimens, but modern human brains are twice that large.

With the genus *Homo*, evolution devised a way of living that was more costly in terms of energy—breast-feeding australopithecines (with their very high energy needs) required about 1,600 calories a day, while the lactating *Homo erectus* female required 2,500—but also more productive, because of the larger brain. Comparison to chimpanzees (our closest living primate relatives) reveals another way modern humans use energy intensively: we produce offspring more frequently. Chimps can give birth only once every five to six years.

All this leads to the current era—which Lieberman casts as an energy crisis in more ways than one. Humans' evolved taste for energy-rich foods, high in sugar and fat, no longer gives a competitive advantage; when food is abundant and procuring it doesn't require physical activity, diseases such as diabetes result. Treat-

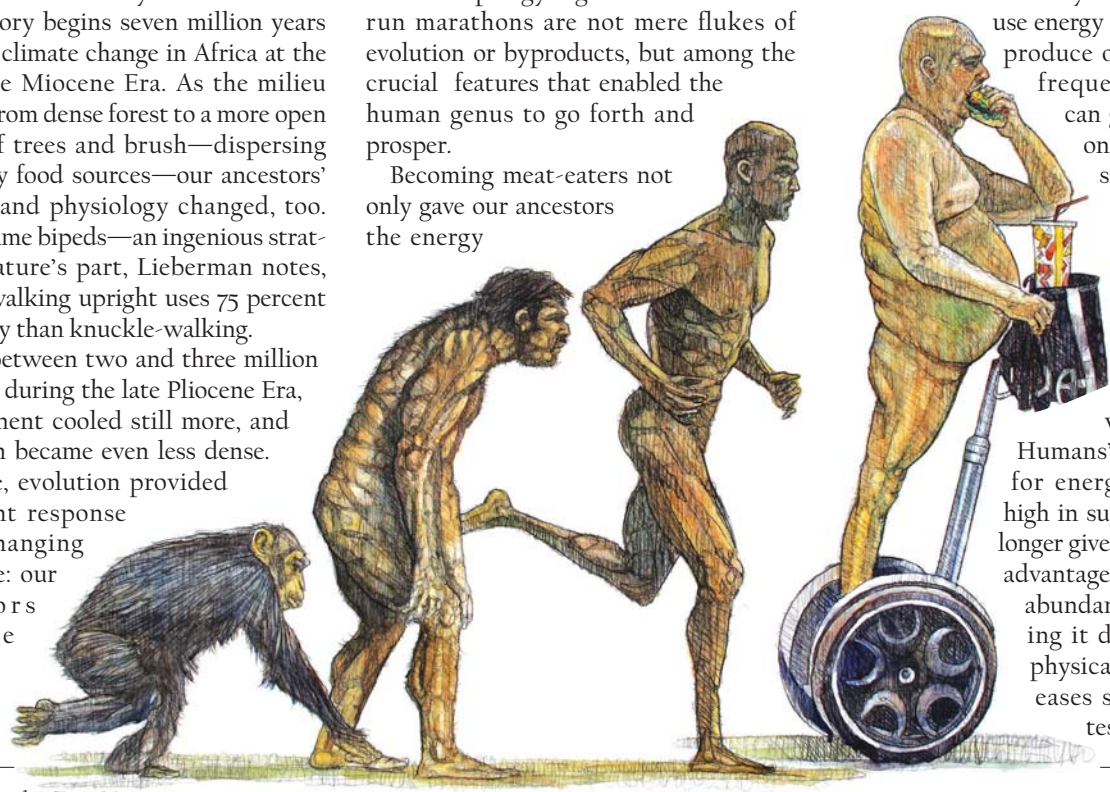


Illustration by Tom Mosser