Biomaterials for Drug Delivery and Tissue Engineering

Robert Langer

Abstract

The following article is an edited transcript based on the Von Hippel Award presentation by Robert Langer of the Massachusetts Institute of Technology on November 30, 2005, at the Materials Research Society Fall Meeting in Boston. Langer was honored with MRS's highest award for his "pioneering accomplishments in the science and application of biomaterials in drug delivery and tissue engineering, particularly in inventing the use of materials for protein and DNA delivery, and for his achievements in interdisciplinary research which have generated new medical products, created new fields of biomaterials science, and inspired research programs throughout the world."

Keywords: *biological, biomedical, microstructure, tissue.*

Introduction

I am greatly honored to receive the MRS Von Hippel Award, and I am also excited to see biomaterials as a field recognized by this award. In this presentation, I would like to talk about how I became involved in the field of biomaterials and about some of the research my group and I have conducted to understand and create biomaterials that could be useful in various areas of medicine.

First, let me provide a bit of motivation for improved drug delivery systems. Whenever, we, as patients, take drugs, whether by swallowing pills or taking injections, the level of the drug in our bloodstreams usually starts out very low, then rises, and then goes down again. We then take the drug again, and the same thing happens. At the peaks, those drug levels could be toxic, while in the valleys, the drug might not be effective at all. Yet almost all drugs are administered in this problematic way. More than 100,000 deaths every year can be attributed to people taking prescription drugs in the correct way, often because of that very fact.[1,2] That figure, by the way, is four times the number of deaths caused annually by AIDS in the United States. We and others wanted to find a method of administering drugs in such a way that they would go into the desired range and stay there, something that very few drugs do. Accomplishing that would be a major step toward preventing side effects. Controlling drug delivery could also lead to new medical therapies, as I will later demonstrate.

Polymer-Based Drug Delivery Systems

During the past 25 years, a whole new field of materials-based drug delivery systems has emerged. These polymer-based systems have had a dramatic impact on safe and effective drug delivery. One of the earliest developments, for example, was a nitroglycerin patch used to treat angina. This patch, approved in the early 1980s, is a thin polymer system containing nitroglycerin. Placed on the skin, it delivers the drug over a 24-hour period.

Systems like these can be used also to deliver drugs for much longer time periods. One of the more familiar systems, the contraceptive Norplant, was approved in the United States in 1991 and is now in use in more than 50 countries around the world. Norplant is composed of little tubes of silicone rubber no bigger than matchsticks. The drug diffuses out from the center of these tubes for over 2,000 days, or five years, after which the device is removed.

In 1980, controlled drug delivery systems were virtually nonexistent. Last year, the drug delivery field saw nearly 100 million people worldwide using polymer-based systems. Annual sales in the United States alone for these systems are about $30 billion; it's probably double that on a worldwide basis.

Before I describe how these polymer-based systems were developed and evolved, let me tell you a bit about how I got involved in this field. I received my ScD degree in chemical engineering from the Massachusetts Institute of Technology (MIT) in 1974. At that time, somewhat like today, we were involved in an energy crisis. As such, many chemical engineers ended up getting lucrative jobs with oil companies. I received four job offers from Exxon alone. One in particular made an impression on me—it was a job offer from Exxon in Baton Rouge, Louisiana. At the interview, they told me that if I—or anyone, for that matter—could improve the yield of oil by 0.1%, it would be worth billions of dollars to them.

While flying back home to Boston that night, I realized that I didn't want to do that. Rather, I wanted to see if there was a field where I could apply my chemical engineering background to some endeavor that would help people's health or education. I applied to different places for teaching positions, but didn't get any of those jobs. Then I started applying to hospitals. One of my colleagues suggested that I write to a surgeon named Judah Folkman, which I did. Dr. Folkman later called and told me about a problem he had been working on—figuring out how blood vessels grow in the body. He wanted to see if there was some way to isolate a substance that could stop this blood vessel growth, something he called an "angiogenesis inhibitor." When I started working with him, angiogenesis inhibitors were only theoretical, and many people did not agree with Dr. Folkman's concept. Moreover, this area of blood vessel growth was difficult to study. We realized that in order to solve this problem, we would not only need to isolate an angiogenesis inhibitor, which is often in the form of a large molecule, but we would also need to find an assay. We chose the eye of a rabbit, because there are normally no blood vessels in the eye. We put a tumor in the eye that would mimic what happens in the human body. Over time, blood vessels grew from the edge of the cornea to the tumor. At that point, we wanted to stop those blood vessels, but to do that we needed a controlled-release polymer that could deliver the different molecules I was isolating. Since there were no such systems at that time, I decided to try to develop one. I can trace my interest in the drug delivery field back to this project.

That was 32 years ago. It took 30 years, from that initial study in 1974 until 2004, before the first angiogenesis inhibitor, a drug made by Genentech called Avastin, was approved. Medicine, unlike many of the areas in which materials researchers work, is extremely slow in terms of moving from concept to production. Yet, for those who follow that field, the angiogenesis inhibitor has been a spectacular success and could become the most successful anticancer drug of all time.

In 1974, one of my goals was to see if we could release different molecules that I might isolate from cartilage, the tissue I was then studying. A lot of the molecules were large. At that time, there were no systems for delivering these kinds of molecules for long time periods and in a way that would be safe in the human body. So the work I was doing was somewhat basic—to help in angiogenesis research. However, from the standpoint of potential practical impact, something happened that I could not have anticipated. That was the advent of biotechnology and genetic engineering where, for the first time, it became possible to create large molecules such as peptides and proteins in a commercial way. But these molecules faced serious delivery challenges. Swallowing them did not work because they were too large and would be destroyed by enzymes or acid in the stomach or intestines. They were also too large to use in a patch. If you tried injecting them, they were quickly destroyed by enzymes. Delivering any of these molecules on a chronic basis would require a way to deliver them in an unaltered form, and yet protect them from harm.

When we started this work, the conventional wisdom in the field was that it could not be done. Scientists felt it was not possible to slowly release large molecules from biocompatible polymers.

In Vitro *Results*

Against this background, I began working in the laboratory to see if I could come up with a way to make tiny systems that could deliver molecules for long times. After two years of experimentation, I had found many different unsuccessful methods.

Finally, I discovered one way to make it work. My students and I took hydrophobic polymers like ethylene vinyl acetate copolymer or lactic glycolic acid copolymer and dissolved them in organic solvents, usually at low temperatures like −80°C. We added the proteins to them and slowly dried off the solvent. This is how we created small microspheres or even nanospheres (Figure 1).

We published in *Nature*[3] that you could use this approach to release molecules of almost any size, from 14,000 MW to a quarter of a million MW. These molecules could be released for more than 100 days *in vitro.* Although the release rates were not constant in those initial studies, we later developed ways to ensure constant rates. For example, we were able to achieve a constant release of albumin for over 50 days.

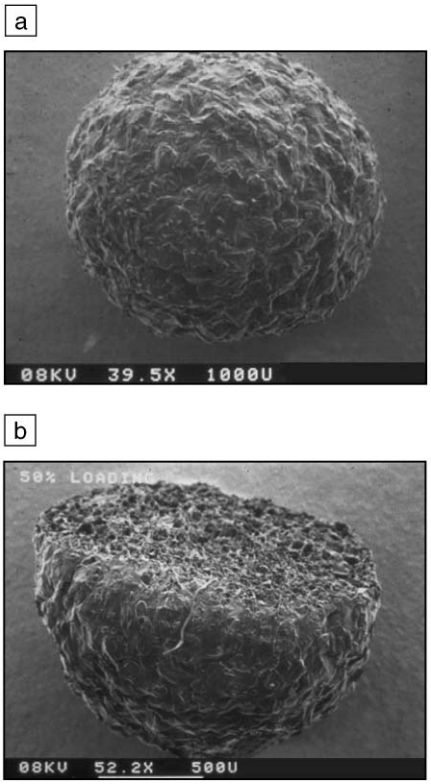


Figure 1. (a), (b) Polymer-based microspheres for drug delivery applications. The diameter of the microsphere in (a) is 1000 μm. (From Reference 6.)

At first, our concepts were not well accepted, and some of our colleagues were vocal in their lack of support. For example, as a postdoc, I had not realized that being a member of the scientific community meant giving a lot of talks. In 1976, I was asked for the first time to give a lecture—at the Midland Macromolecular Symposium in Midland, Michigan. I was 28 at the time, addressing distinguished elder polymer chemists and engineers. To make a good impression, I had practiced my talk diligently for weeks. After giving the lecture, which I felt I had delivered reasonably well, I hoped that these older scientists would want to encourage a young scientist like me. When I stepped off the podium, however, a group of them came up to me and said, "We do not believe anything you have just said." That was my introduction to the way in which scientists sometimes treat other scientists. It was not until three years later that different groups began to repeat what we were doing. Then the issue shifted from "This can't possibly occur!" to "How does this happen?"

To answer the question about how this happens, Rajan Bawa, one of my students, began to use the cryomicrotome, a low-temperature cutting instrument, to cut thin sections through one of the model polymers we used—ethylene vinyl acetate copolymer (Figure 2). We did a permeability study on a 5-μm section of one of these model polymers and found that if the

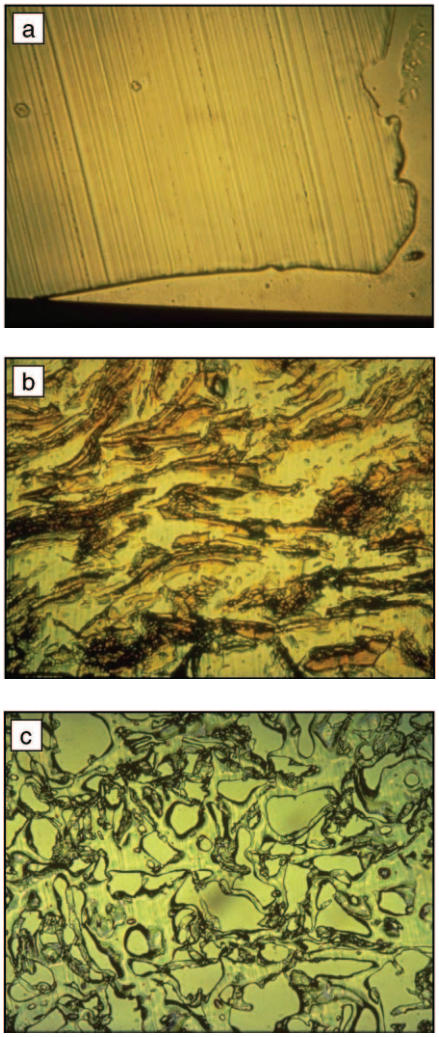


Figure 2. (a)–(c) A 5-μm-thick section of depleted polymer initially cast with bovine serum albumin. Pores in (c) are 3–100 μm. All micrographs are shown at the same magnification. See text for details.

molecules were 300 MW or greater, they were not able to diffuse from one side of the section to the other. To understand the mechanism of release better, we then put a reddish protein, myoglobin, in the polymer matrix. We observed a phase separation (Figure 2b). Next, we began the release process.

After the release had gone on for a year, we cut a thin section and found that what was left behind where the myoglobin had been were pores (Figure 2c). Since these pores had not existed before the addition of the protein, they clearly had been made by the formulation process. We then did a lot of imaging and even scanning microscopy studies and found that these pores were interconnected. They had a lot of very tight constrictions between them and were incredibly winding and tortuous, which accounts for the very long time it took for the protein to get through. I sometimes like to explain this long permeation process by comparing it to driving a car through Boston, which is often very tortuous. We then discovered that by adjusting these pore structures, we could actually make the systems last anywhere from a day to more than three years, or any time period in between.

In Vivo *Results*

One of my goals in doing laboratory work has been to move beyond just conducting the work and publishing the results to the point where I could apply that work to helping people. After our experiments worked successfully *in vitro,* we wanted to move to the next logical step, which was getting the drug release system to work in animals. For this experiment, I worked with one of my graduate students, Larry Brown.

The model system we chose first was diabetes. Our goal was to deliver insulin, which is a large molecule, to diabetic rats in order to lower their blood sugar. After making the rats diabetic, we made small plastic pellets, no bigger than aspirin tablets, containing insulin and implanted them into the rats. We found that the pellets could lower the rats' blood sugar from 400 mg/dl, which is diabetic, to 100 mg/dl, which is normal, for over 100 days. I will return to this concept later to explain how we may be able to adjust the dosage. My point here is that this experiment showed us that we could maintain biological activities for long time periods *in vivo.*

Our subsequent goal was to see if we could get this drug release process to work in humans. For the next 10 years, we experimented with various systems in the laboratory and published a lot of papers, but our work did not seem to be moving forward clinically. At that point, I realized that in order to achieve our goals, we needed to develop creative ways to work with pharmaceutical companies. Although initially these companies were only vaguely interested in our work, MIT eventually licensed patents to many of them. Also, by then I had come to believe that one solution was to start our own companies to develop these systems, and that was, in fact, what we did.

Today, products based on the drug delivery research done by us and others are used by many people. Examples include microspheres for treating advanced prostate cancer, endometriosis, precocious puberty, dwarfism, schizophrenia, alcoholism, and other diseases.

For all of these cases, the drug may come out at a constant rate or a decreasing rate. There is no way to increase the drug release rate or to regulate it after the release process starts. So, we are always thinking, how could we do better?

Drug Delivery Microchips

About 12 years ago, I was watching a television show on PBS about how the computer industry made chips, and I started thinking that chips might be a good way to carry out drug delivery. I called Michael J. Cima, who is one of my colleagues and a professor of materials science and engineering at MIT, and asked for his help in developing a way to test the idea. We solicited the help of a student, John Santini, who began developing a drug delivery chip first as a summer project and later for his PhD thesis. Santini was able to create a chip prototype with tiny wells into which drugs could be placed (Figure 3). These chips offered myriad delivery possibilities. The wells might contain different doses of the same drug, or a variety of different drugs—literally, a pharmacy on a chip. The wells were hermetically sealed and then covered with gold. We found a way to dissolve the gold by selectively applying one volt of electricity in the presence of a small amount of chloride ion. The concept was to store these drugs for literally any desired period and then trigger their release by selectively dissolving the gold on any of the wells. To our great benefit, the gold had no toxic effects. James M. Anderson, one of our collaborators and a professor in the Department of Pathology at Case Western Reserve University, has shown that you can dissolve 16,000 times the amount of gold we used without harming animals.

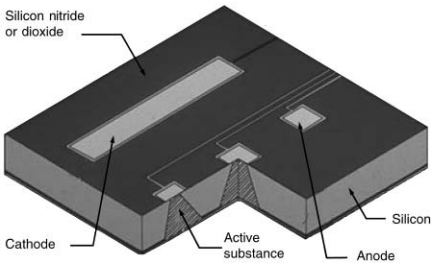


Figure 3. Prototype of a drug delivery microchip.

One of the first chips that Santini made was about the size of a U.S. dime. It had 34 wells on the top and 34 wells on the bottom, shown as white holes on the device in Figure 4a and the black holes on the device in Figure 4b, with each well capable of carrying a different drug or different doses of the same drug. This early chip is just one example of the many different types we have made. We have fabricated chips that are thin, like our early chip, chips that are thicker, and chips shaped like cylinders. We have made chips composed not only of silicon and gold, but also of many other materials. My former student Dr. Amy Grayson has made chips out of totally degradable materials, for example.

As I mentioned, the chips work by releasing the drugs that are stored in the wells. When we apply one volt selectively to a single gold-covered well, in about 10 seconds the gold begins to dissolve and the drug beneath it is released.

Santini experimented first with releasing the same drug in different amounts and at different times. He put varying levels of fluorescein in different wells and triggered the release at intervals: one and a half days, two and a half days, four and a half days, and five and a half days (Figure 5a).

Then, Santini tested the pharmacy-on-a-chip concept. He triggered the release of one drug from one well at 25 hours, a different drug from a different well at 37 hours, the same drug as that released at 25 hours but from a different well at 50 hours, and that same one as that released at 37 hours but from a different well at 60 hours (Figure 5b).

The times and levels in these experiments were arbitrary, but they demonstrated the possibilities offered by the chip release system. Santini now heads MicroCHIPS Inc., a company that develops these chips, and his firm is continually advancing their capabilities. They are currently conducting animal trials on chips that can be controlled remotely using telemetry. After implanting the chip in the animal, researchers apply radio frequency in a specific way that can remotely open any of the chip wells, in a concept similar to a remote-controlled

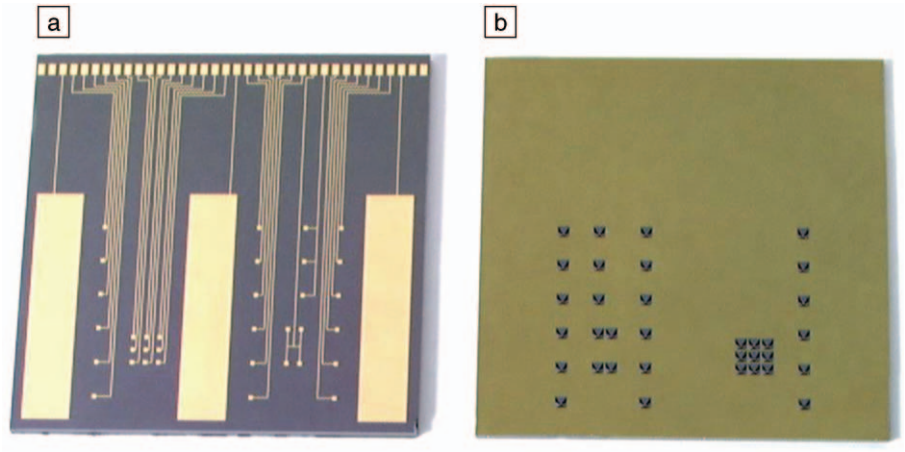


Figure 4. (a) Top and (b) bottom view of a drug delivery microchip. This chip is ~15 mm wide. (Courtesy of Paul Horwitz, Atlantic Photo Service.)

garage door. Santini's group has been able to remotely trigger drugs in animals many times over a six-month period, very reproducibly. They hope to be able to apply this concept to humans within the next few years. The triggering device, which might someday be embedded in something like a wristwatch or a Blackberry, could be programmed by the patient or the doctor and changed when necessary.

While that concept may be attainable in the not-too-distant future, it also suggests ideas that are more remote. For example, along with microprocessors and power sources, biosensors could be put on the chips to detect signals in the body, such as glucose levels, and provide feedback to tell the chip how much drug to deliver.

Medical Materials from Everyday Objects

These drug delivery systems are all built around the idea of engineering materials to do things they have never done before. That has been one of the primary pursuits of my research. Another facet of our work has been investigating how materials find their way into medicine, and creating newer, possibly better, materials. Being a chemical engineer, I had once thought that experienced chemical engineers or chemists were the driving force for bringing materials into medicine. But the closer I looked into that theory, the less I found it to be true. Rather, medical doctors were the ones who identified problems in their field and, urgently wanting to fix them, came up with materials solutions. They would search their surroundings—for example, their homes or local stores—to find objects that closely resembled the organ or tissue they wanted to fix. They would then adapt that material for use in the human body. While that practice has admittedly resulted in some solutions, it has also created problems.

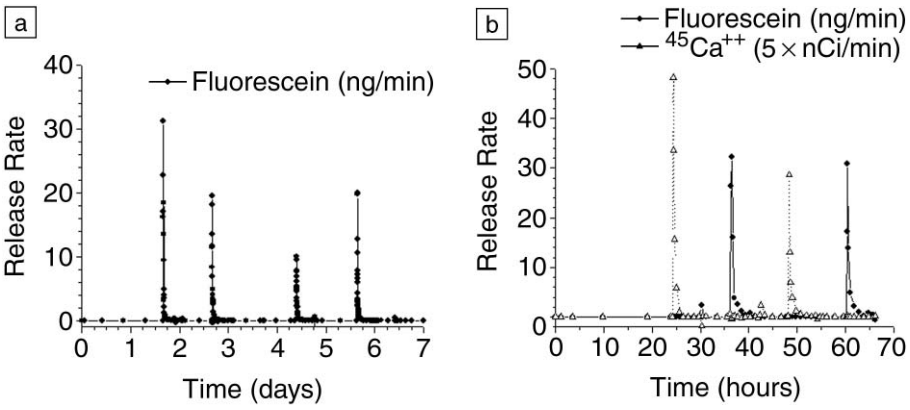


Figure 5. Controlled drug delivery from a microchip: (a) results from the controlled release of a single compound and (b) results from the controlled release of multiple compounds. (Reprinted by permission from Reference 7.)

For example, in 1967 at the National Institutes of Health, some clinicians and engineers wanted to make an artificial heart. They started by asking, what object has a good flex life, like a heart? The answer they came up with was a ladies' girdle. They then determined that since the girdle was made of a polyether urethane, they would make an artificial heart from that material. Today, 39 years later, we find that the artificial heart is still made of that same material—polyether urethane. Yet, when blood hits the surface of the artificial heart (the ladies' girdle material), it can form a clot. That clot can then go to the patient's brain and cause a stroke, which could result in death.

Similarly, dialysis tubing was originally made of sausage casing. The vascular graft, which is an artificial blood vessel, was developed by a Texas surgeon who searched for possible materials in a clothing store, based on what fabric would be easiest to sew. He chose Dacron. Of the two materials chosen for breast implants, one is a lubricant (silicone) and the other is a material used for stuffing mattresses (polyurethane).

Medical Materials Designed to Order

Against this background, we and others began thinking that we needed to find a model for solving medical problems other than to search for materials in everyday settings. As a chemical engineer, I believed that researchers could take an engineering design approach, asking the question, what do we really want in a biomaterial from an engineering standpoint, from a chemistry standpoint, and from a biology standpoint? Having answered that question, we could then synthesize the materials from first principles.

We started by studying a particular class of materials—synthetic degradable materials. Initially, the only family of polymers approved by the FDA was suture materials made from polyesters. They displayed bulk erosion, which meant that they started out as a solid, then got spongy, and then fell apart. Instead of distributing a drug uniformly, these polymers could break up or burst, releasing the drug into the patient with possibly fatal results if the drug were a toxic substance like insulin or an anticancer drug.

Looking at this problem from an engineering standpoint, we and others thought that it would be desirable to have surface erosion instead of bulk erosion. We wanted to structure the polymer so that it would become increasingly thinner, avoiding a catastrophic breakup and drug dumping. Starting from scratch, we first thought

about what catalyst we wanted to use to cause the polymer to degrade. We determined that an enzyme would not work optimally because everyone has different enzyme levels, which means that the process might not be reproduced from person to person. We realized then that excess water is something everyone possesses, and decided to use water as our catalyst. Next we looked at the problem from a chemistry viewpoint. Using water as a catalyst, how could we create the conditions for surface erosion? We would want to make the monomers hydrophobic to keep the water out, while guaranteeing that the polymer would still dissolve fast enough. A solution would be to have the bonds connecting those monomers be water-labile. A lot of chemical calculations later, we estimated that the anhydride bond would be the right one.

Our next step was to choose the right monomer. Here, we took a biological approach and sought advice from chemists and toxicologists. Michael A. Marletta, an outstanding chemist who now heads the Chemistry Department at the University of California, Berkeley, but who was then a professor at MIT, helped us determine what monomers would be safe. We chose carboxyphenoxy propane, which is a copolymer, and sebacic acid, and tried to make polymers out of these substances (Structure **1**).

The results were gratifying. Not only did we achieve the surface erosion we were seeking, but we also acquired the ability to control the degradation rate. For example, by using varying amounts of sebacic acid—say, from 0%, to 15%, to 55%, to 79%—we attained degradation rates that ranged from two weeks to three or four years. The result was that we could simply dial in the monomer ratio and target the material for different degradation time periods.

Polymer-Based Local Chemotherapy

Based on this success, we thought we might be able to facilitate other medical applications. An interesting example of our subsequent efforts was the brain cancer work we did with neurosurgeon Henry Brem. Dr. Brem visited my laboratory in 1985 when he was a young doctor just starting his medical career at the Johns Hopkins University. At that time, he was looking for a way to treat brain cancer in its worst form—glioblastoma multiforme. This disease is uniformly fatal; regardless of the type of treatment patients receive, they normally die within a year.

In addition to that, the chemotherapy drugs normally used to treat this cancer are extremely toxic. One of these drugs is BCNU, or 1,3-bis(2-chlorethyl)-1-nitrosourea. In brain chemotherapy, the drug is administered to the patient intravenously and travels throughout the entire body, with devastating side effects to the liver, the kidney, and the spleen.

To avoid these side effects, Dr. Brem and I developed a concept that we call local chemotherapy. In this case, the idea is built around allowing a neurosurgeon to operate on the patient to remove as much of the tumor as possible, which is the standard procedure; then, prior to closing the patient, the surgeons lines the surgical cavity with a polymer containing BCNU. Normally, BCNU has a lifetime of only 12 minutes. Our goal was to extend this lifetime by placing the drug in a polymer that would prevent it from being destroyed right away. What Dr. Brem and other neurosurgeons at Johns Hopkins wanted was a degradable polymer that would not accumulate in the brain, one that had the surface erosion characteristics that would prevent a sudden drug release, and one that, based on their animal studies, would last for a month. Because we could target different drug release time frames by changing the copolymer composition, we were able to develop a drug delivery system that would protect the BCNU from degradation and not accumulate in the brain. The resulting system allowed doctors to produce high concentrations of the drug in the brain, where they wanted it to be, and low concentrations in the rest of the body, where it would cause harm.

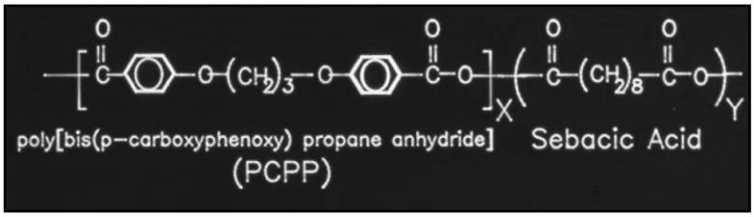
This polymer drug delivery system received a cool reception when we tried to get funding to support its development. Like other professors who do research, we need to raise money to support our projects. In my case, I usually write grants to the National Institutes of Health. These grants are then reviewed by my colleagues, who are also professors.

When I wrote grant requests for this research, the response was quite negative. As an example, our first grant in 1981 was reviewed by a lot of chemists, who asserted that we would never be able to synthesize the polymers. However, Howie Rosen, one of my graduate students at the time, did manage to synthesize the polymers for his graduate thesis. Rosen ultimately became president of the ALZA Corp., now a significant part of Johnson & Johnson, and vice president of Gilead Sciences, also a very successful company. He was recently elected to the National Academy of Engineering.

After Rosen had accomplished the polymer synthesis, we sent the grant back for another review, and received this reply: *The grant should still not be funded because the polymers will react with whatever drug you put in.* Again, with the help of several resourceful postdocs—Kam Leong, now a professor at Duke University, and Robert J. Linhardt, who is Constellation Chair and Professor in the Chemistry and Chemical Biology Department at Rensselaer Polytechnic Institute—we were able to work out ways to prevent this reaction.

Then we returned the grant for another review, which came back with the comment that although the work was better, the polymers were fragile and would be likely to break because of their low molecular weight, which was 7000. This time, two other postdocs in our laboratory skillfully moved the project forward. Avi Domb, who is chair of medicinal chemistry at Hebrew University, found the right catalysts, reaction times, and temperature conditions to increase the molecular weight of the polymers to a quarter of a million, at which point they were definitely not fragile any more. Edith Mathiowitz, who is now a professor of medical science and engineering in the Artificial Organs Laboratory at Brown University, was also very helpful.

After the grant had gone back for another evaluation, the reviewers said that despite the merit of the research, it could not be funded because new polymers were not safe to test on people. Another graduate student, Cato T. Laurencin, then was able to show that the polymers are safe, supporting Marletta's theories. Laurencin is now University Professor and Chair of Orthopedic Surgery at the University of Virginia and last year was elected to the



*Structure **1**.*

Institute of Medicine of the National Academy of Sciences.

These kinds of negative reviews continued until 1996, when the FDA finally approved this treatment—the first time in more than 20 years that the agency had approved a new treatment for brain cancer, and their first time ever to approve the concept of polymer-based local chemotherapy. This could not have been achieved without the help of our excellent graduate students and postdocs, of whom I am extremely proud.

I would like to describe in broad terms the brain cancer surgery during which this drug delivery system is implanted. During this operation, our BCNU-containing wafers, which are about the size of a dime, are inserted into a human brain (Figure 6). Seven or eight wafers are usually inserted before the surgeon closes the brain.

The final phase of clinical testing for this procedure, which for human patients is called the phase three trial, monitored the survival rates for patients treated with the drug release system and for a control group, which represented the best conventional treatments. At the end of a year, 63% in the treated group had survived, while only 19% in the control group had survived. At the end of two years, 31% in the treated group had survived versus 6% in the control group (Figure 7). The BCNU drug delivery system was approved by the FDA and has been in use for some years now for recurrent glioblastoma. Three years ago, it was also approved for primary glioblastoma. Today, the system is one of the common ways of treating this disease. We are still working with the Johns Hopkins group to find better drugs to use with the system.

The principle of polymer-based local chemotherapy is continually expanding. Since 1996, when we received FDA approval for the brain cancer drug delivery system, other groups have used this concept to develop similar systems. A drug release system for spinal cancer has been approved, and clinical trials are taking place for other kinds of cancer.

Yet, the area where polymer-based local chemotherapy has had the greatest impact is not in cancer at all, but in interventional cardiology. Another of my former graduate students, Elazer R. Edelman, who is now a professor in the Harvard–MIT Division of Health Sciences and Technology, has done some outstanding work in this field. One of the standard treatments for heart disease is to insert a stent into the blood vessel. Stents are wire mesh tubes that look something like Chinese finger puzzles. During insertion, the stents often injure the blood vessel, causing the smooth muscle cells to proliferate wildly. About 50% of the time, within just six months after stent placement, these muscle cells proliferate enough to cause a problem called restenosis—a blockage of the blood vessel that can lead to patient death. Even in the best-case scenario, the surgeon has to reoperate.

To solve this problem, scientists at Boston Scientific, Johnson & Johnson, Medtronic, and other places coated the stents with polymers and used these in conjunction with anticancer drugs such as Taxol. From a medical standpoint, the results have been remarkable. The rate of restenosis has fallen from 40% to about 3%. From a market standpoint, these coated stents have had an equally enormous impact. Although this device was only approved in 2003, sales in 2005 were already about $5 billion. Efforts to improve the stents are ongoing.

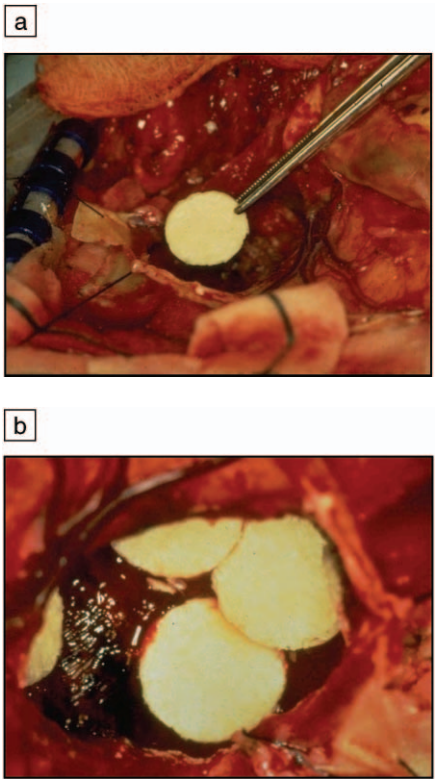


Figure 6. Polymer-based local chemotherapy. (a) Photograph of a wafer containing chemotherapeutic drug BCNU being surgically inserted into a human brain. (b) Seven or eight wafers are inserted in the surgical site before the surgeon closes the brain.

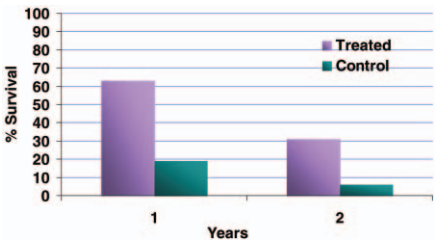


Figure 7. Results of phase three clinical trials of the local chemotherapy wafers in Figure 6, showing the survival rates for patients treated with the drug release system and a control group that represented the best conventional treatments. At the end of a year, 63% in the treated group had survived, while only 19% in the control group had survived. At the end of two years, 31% in the treated group had survived, versus 6% in the control group.

Tissue Engineering

I would now like to describe another area, the delivery of mammalian cells through materials, which our group has been working on for some time. My motivation for working on this project goes back more than 20 years to work we did with Boston surgeon Joseph P. "Jay" Vacanti, who is now chief of pediatric surgery at Massachusetts General Hospital and the John Homans Professor of Surgery at Harvard Medical School. Among his patients were small children dying of liver failure whose lives depended on someone else dying and donating a liver for transplant. Not enough transplants, however, were available to treat these patients. The problem, of course, was not limited to liver disease, but extended to paralysis and to advanced diseases of nearly any organ or tissue.

Twenty years ago, Vacanti and I came up with an idea for tissue engineering. This concept involves taking isolated dissociated cells from patients themselves or from a close relative. These cells include, for example, bone cells, cartilage cells, liver cells, intestinal cells, and urothelial cells. Today, they could also include stem cells. If these cells are injected at random, very little happens. It turns out that the cells are "smart," however, and if you put these cells close enough together, they can organize themselves and create structures. A group at UC–Berkeley has shown that if you take mammary epithelial cells and put them close enough together *in vitro,* they can form acinae and make milk.

We wondered if we could make tissues by taking cells and putting them on a polymer template, in three dimensions, with the right media. We would want to grow them outside the body, on the right materials, and then ultimately return them to the body to make whatever tissue we wanted (Figure 8). We would either

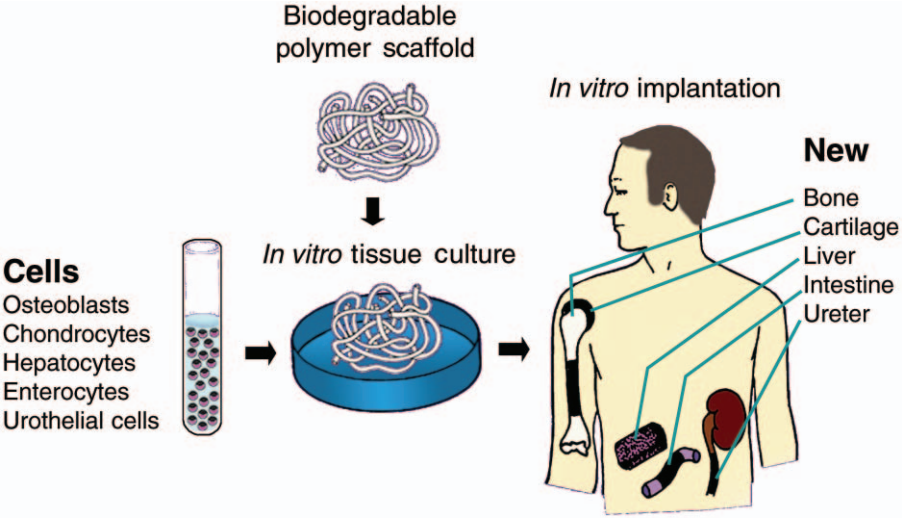


Figure 8. Schematic diagram of tissue engineering. Osteoblasts (bone cells), chondrocytes (cartilage cells), hepatocytes (liver cells), enterocytes (intestinal cells), and urothelial cells are depicted.

utilize existing FDA-approved polymers like lactic glycolic acid copolymer, or synthesize brand new ones. For example, Denise Barrera, who was in our laboratory then and who now works for 3M, developed polymers that could attach amino acid sequences that would be specific for certain cell types. We would then convert them into fibers that can be used as substrates for cells to create new blood vessels or other tissues.

Let me now speculate about where this field might be in, say, 30 years. A good example would be plastic surgery. Imagine a patient visiting a plastic surgeon and asking for a new nose. I believe that in 30 or 40 years, patients might be able to go to a computer screen to select whatever nose they like, or create their own "designer" noses.

V. Prasad Shastri, one of my former postdocs and now an assistant professor of biomedical engineering at Vanderbilt University, worked out a way to do that using a novel fabrication process that could someday be adapted to computer-aided design techniques. Shastri was able to fabricate a "regular" nose by using a polymer, lactic glycolic acid, and forming it in the shape of a nose that was 97% porous (Figure 9). Pieces of the polymer could then be added or reshaped to create other kinds (or shapes) of noses that patients might desire. The donor cells for the nose could, for example, be taken from the patient's ear through a minimally invasive surgery procedure called arthroscopy. The cells would be placed on a scaffold and grown in a culture until the nose was fully formed. We are now doing this procedure, but not on noses. Later, I will describe several different tissues that our group and others are growing in this manner.

Shape-Changing Devices for Minimally Invasive Surgery

I want to shift gears just a little and discuss the concept of minimally invasive surgery. Surgery often involves the insertion of bulky medical devices into the human body, an unpleasant experience. In the nose example I just mentioned, a patient might wonder if that would involve an operation to insert the new nose. An advanced area of medicine, called minimally invasive surgery, has eliminated some of the medical and emotional trauma associated with certain operations. Twenty years ago, prior to the development of this type of surgery, having a gall bladder removed was a major operation that involved a large incision, a week's recovery in the hospital, and two or three months of recuperation at home. Today, a minimally invasive gall bladder operation consists of making a tiny incision, inserting medical instruments, pulling the gall bladder out through that tiny hole, and doing the entire surgery via a TV screen. The patient is out of the hospital in less than a day and back to work in less than a week.

The success of this type of procedure gave me an idea: what if bulky medical devices could be inserted through these tiny holes? That might sound like science fiction, but with the help of materials, I hope it will become a reality. Since the devices that might be inserted into the body are usually polymer-based, we thought about making devices from polymers that would originally be very thin, like a string, outside the body, but convert to different bulkier shapes once inside the body. Working with Andreas Lendlein, one of my postdocs at the time and who has subsequently headed large groups in Germany—first at Aachen and now at Potsdam University—we came up with several ways to do this. We published one method in *Science*,[4] the other in *Nature*.[5]

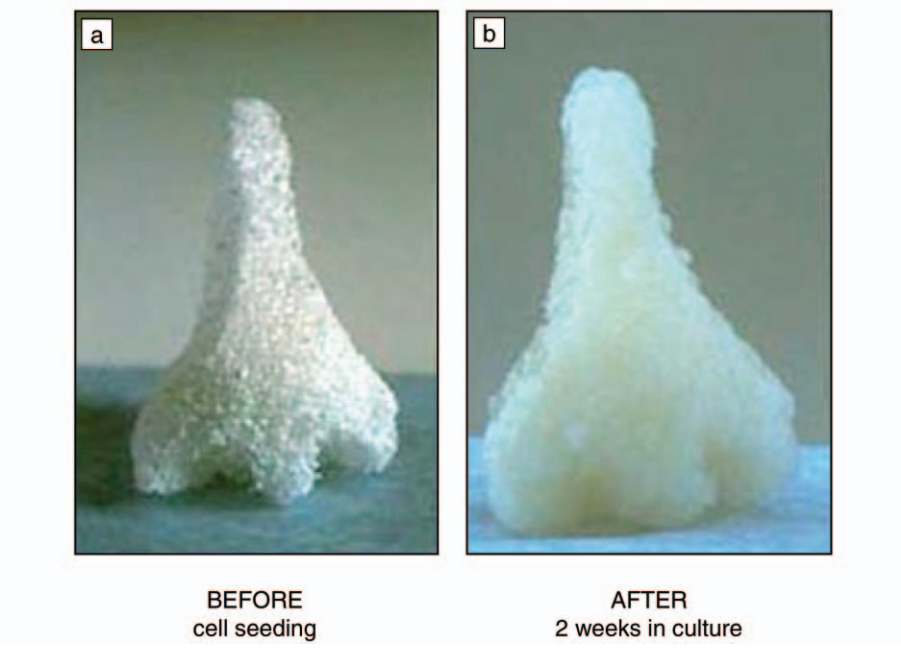


Figure 9. Cartilage tissue engineering: polymer scaffold for a human nose (courtesy of V.P. Shastri).

Our project was based on using different stimuli to trigger the shape change. First, we used temperature as a trigger, developing a polymer that at room temperature would have one shape, like a string, then at body temperature would convert to a different shape—whatever-shaped medical device was desired. We then experimented with light as a trigger, changing the material from one shape to another at different wavelengths.

To provide a specific illustration of how this works, I would like to describe some work done by Lendlein and myself. In fact, there is now an innovative company in Germany called Mnemoscience, which is developing these applications. First, Lendlein created a device programmed in such a way that at room temperature it has the shape of a string, but when dropped into body-temperature water, it changes into a coil like a stent.

Another example, one that has interesting applications for surgery, is a self-tying suture. An ordinary suture works well in the case of an arm wound, for instance, where the doctor can easily tie a surgical knot. If that wound is in the lung or stomach, however, and minimally invasive surgery is needed, tying the knot becomes much more complicated. We believed that a solution would be to develop a suture that would tie itself into a knot with a change in temperature. At room temperature, the suture could be introduced in a loose loop like a lasso, but when it reached body temperature, the suture would tighten. This concept was demonstrated by dropping the loosely tied suture into body-temperature water, which causes it to tighten. Because many different kinds of shape changes can be created along these lines, this concept could have a profound effect on minimally invasive surgery and tissue engineering, among other areas.

Replacement Cartilage

To conclude this talk, I would like to present three examples of tissue engineering using the principles I have discussed. The first one is a form of replacement cartilage that we developed in cooperation with Charles A. Vacanti, who now heads the Department of Anesthesiology, Perioperative, and Pain Medicine at Brigham and Women's Hospital. Every year, about one million people need to replace cartilage in their bodies. Vacanti did some experiments with nude (hairless) mice, using their own cells on a scaffold to develop new cartilage that would resist rejection. For example, he reconstructed the skull of one mouse and the cheek of another. If you opened up the animals to see the results, you would see pure-white glistening cartilage, with histologically the same characteristics as the original cartilage. Since this replacement cartilage is not as mechanically strong as the original, however, we still have work to do before we could provide, for example, new cartilage for a human arthritic knee.

However, the development of artificial cartilage for such areas as cosmetic defects may be closer to becoming a reality. Vacanti sees patients who, for example, do not have ears. Linda Griffith, one of my former postdocs and now a professor of mechanical and biological engineering at MIT, has created an artificial human ear by making a scaffold in the form of an ear with polymer fibers, cartilage cells, and a matrix. Vacanti has not yet put this ear on human patients, but he has tried it on rabbits to test its safety.

Replacement cartilage has been tried on humans, however, in other forms. Jay Vacanti first used it on a 12-year-old boy who had no ribs covering his heart. This boy, like many his age, liked to play baseball, but he would have been at grave risk from something as ordinary as being hit in the chest by a stray ball. Vacanti operated on him and gave him a new chest created on a polymer scaffold using the boy's own cells.

Replacement Skin

A second example is the development of new skin for burn victims. This research was done by Smith & Nephew, which licensed our MIT patents. Let us consider an actual patient, a two-year-old boy who was badly burned. The clinicians took a polymer scaffold with neonatal skin fibroblasts and inserted it into the child at the time of injury. Three weeks later, new skin had started to form. Six months later, the burned areas were nearly invisible. This treatment was approved by the FDA for patients with skin ulcers and burns.

Spinal Cord Repair

A final example is spinal cord repair. We are still at an early stage in developing a solution for this major problem. Erin Lavik, who is now an assistant professor at Yale University, led this work in our lab. Lavik made a polymer scaffold that mimicked the human spinal cord. The outer portion was oriented to provide axonal guidance, while the inner portion had large pores seeded with neural stem cells, which are similar to brain stem cells (Figure 10).

We then worked with neurosurgeon Ted Tang and stem cell specialist Evan Snyder to test this device in animals. Paraplegic mice that had difficulty moving their back legs were tested. We divided the mice into four groups: a treatment group that had the polymer stem cell scaffold inserted, and three control groups: ones that were given a sham operation, ones implanted with stem cells only, and ones with the polymer only. We then followed the mice for a year, doing numerous studies.

At 100 days following the operation, we found that in the control groups, the mean—about 40 animals—dragged their legs, and their paws were splayed in an awkward fashion. This is typical. In contrast, in the mice that were implanted with a polymer scaffold containing stem cells, we see results that are dramatically different from those of the control group. These mice can now bear their own weight and walk. Their paws are splayed in a much more normal fashion. This treatment as it now stands, however, is by no means a cure for humans, and a lot of work remains to be done. Nonetheless, it shows that promising results can be obtained. Hopefully,

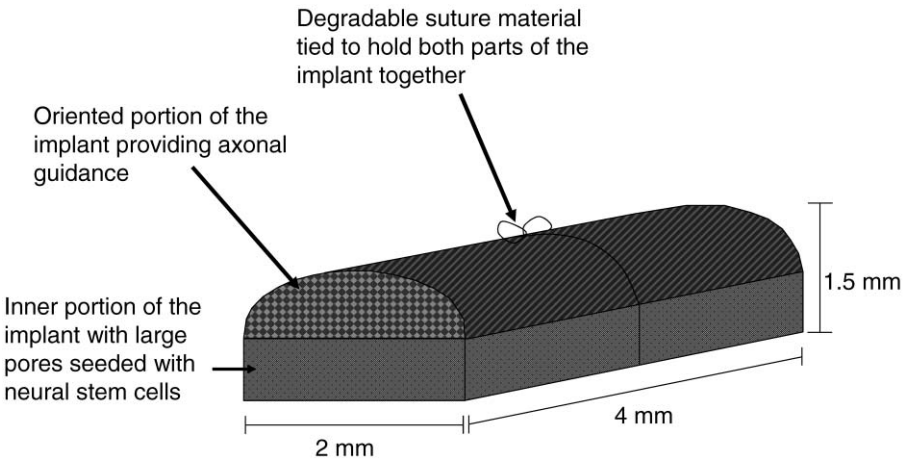


Figure 10. Schematic illustration of a polymer scaffold for spinal cord repair.

with further research, we and others will be able to develop improved solutions.

Conclusion

Throughout all of this research—with its challenges, setbacks, and successes—I have remained incredibly excited about the medical potential of materials. I believe that we are only at the tip of the iceberg in exploring and developing materials for all types of medical applications. It's my hope that scientists throughout the world will more fully embrace materials science as a resource for creating technologies that can profoundly relieve suffering and prolong life.

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References

1. R. Langer, *Nature* **392** (Supp.) (1998) p. 5.
2. J. Lazarou, B.H. Pomeranz, and P.N. Corey, *JAMA* **279** (1998) p. 1200.
3. R. Langer and J. Folkman, *Nature* **263** (1976) p. 797.
4. A. Lendlein and R. Langer, *Science* **296** (2002) p. 1673.
5. A. Lendlein, H. Jiang, O. Junger, and R. Langer, *Nature* **434** (2005) p. 879.
6. M.V. Sefton, L.R. Brown, and R.S. Langer, *J. Pharm. Sci* **73** (1984) p. 1859.
7. J.T. Santini Jr., M.J. Cima, and R. Langer, *Nature* **397** (1990) p. 335.

Robert Langer *is one of 14 Institute Professors (the highest honor awarded to a faculty member) at the Massachusetts Institute of Technology (MIT). Langer has written more than 870 articles and has more than 500 issued or pending patents worldwide that have been licensed or sublicensed to over 150 pharmaceutical, chemical, biotechnology, and medical device companies. Langer's contributions, discoveries, and inventions have been recognized with numerous honors and awards, including the Charles Stark Draper Prize (2002), considered the equivalent of the Nobel Prize for engineers and the world's most prestigious engineering prize, from the National Academy of Engineering; the Gairdner Foundation International Award (1996), which Langer is the only engineer to have received; the Dickson Prize for Science (2002); the Heinz Award for Technology, Economy, and Employment (2003); the Harvey Prize (2003); the John Fritz Award (2003), given previously to inventors such as Thomas Edison and Orville Wright; and the General Motors Kettering Prize for Cancer Research (2004). Langer also shared the 2005 Dan David Prize of $1 million, from which he donated several scholarships of $15,000 each to outstanding doctoral students around the world. He also received the Albany Medical Center Prize in Medicine and Biomedical Research (2005), the largest prize in the United States for medical research, and was elected to the National Inventors Hall of Fame in 2006. In 1998, Langer received the Lemelson–MIT Prize, the world's largest prize for invention, for being "one of history's most prolific inventors in medicine." In 1989, Langer was elected to the Institute of Medicine of the National Academy of Sciences, and in 1992 he was elected to both the National Academy of Engineering and the National Academy of Sciences. He is one of very few people ever elected to all three U.S. National Academies, and the youngest in history (at age 43) to receive this distinction.*

Langer served as a member of the U.S. Food and Drug Administration's Science Board, the FDA's highest advisory board, from 1995 to 2002, and as its chair from 1999 to 2002. He has also served, at various times, on more than 15 boards of directors and 30 scientific advisory boards of such companies as Wyeth, Alkermes, Mitsubishi Pharmaceuticals, Warner-Lambert, and Momenta Pharmaceuticals. Langer has received honorary doctorates from the ETH (Switzerland), the Technion (Israel), the Hebrew University of Jerusalem (Israel), the Université Catholique de Louvain (Belgium), the University of Liverpool (England), the University of Nottingham (England), Albany Medical College, the Pennsylvania State University, Northwestern University, Yale University, and Uppsala University (Sweden).

Upon receiving his ScD degree in chemical engineering from the Massachusetts Institute of Technology in 1974, Langer became a research associate at Children's Hospital Medical Center of the Harvard Medical School in Boston—a position he still holds. From 1988 to the present, his professional appointments have included the Whitaker College of Health Sciences, Technology, and Management; the Harvard–MIT Division of Health Sciences and Technology; and his current position at MIT.

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