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My Struggles and Dreams as a Chemical Engineer

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Abstract

My career has not been straightforward. Although I am a chemical engineer, and I'm proud of that, I took a path from chemistry and engineering to one that also involved experimental biology and medicine. This was very unusual many decades ago. In so doing, I met with rejection and ridicule early in my career. However, by going down that path, I was able to make discoveries and inventions that I hope have saved and improved lives, and I've been able to train a great number of people who are going down the road I began traveling over many years ago.

MY EARLY YEARS

I was born on August 29, 1948, in Albany, New York, and grew up there. My father, Robert, ran a small liquor store. He was very smart. I remember him doing complicated crossword puzzles very quickly. He worked very, very hard. But when he came home, he would play math games with me. My mother, Mary, was a homemaker. She took care of me and my sister, Kathy. My mother worried a lot, but she was one of the nicest people you could ever meet. I hope some of that rubbed off on me.

Among the gifts my parents got me when I was between the ages of 10 and 13 were Erector, microscope, and chemistry sets. I loved these sets. I would make robots and rocket launchers with the Erector set and watch shrimp hatch with the microscope. I set up a little laboratory with the chemistry set in the basement of our small house, where I would mix chemicals together and watch them turn different colors. I'd make rubber, polymers, and other materials.

I'd get other gifts as well, like baseball gloves, a basketball, and a football. I loved these too, and I played a lot of sports with my friends in the neighborhood. I think I had a pretty normal, happy childhood.

HIGH SCHOOL AND COLLEGE

From the time I was 12 to 17 years of age, I went to Milne High School in Albany, New York. I was very good in math and pretty good in science. However, courses like English and French were very challenging to me. Both my father and my guidance counselor said I should become an engineer because I was good in math and science, and that's what I did.

I applied to engineering schools and was fortunate to be accepted to Cornell University. In my freshman year, chemistry was my favorite subject by far, and it was the only course I did really well in, so I decided to major in chemical engineering. I did poorly grade-wise my first three terms at Cornell. One of the biggest issues I had in high school and college was paying attention in class. Today, I realize I had what is called ADHD (attention-deficit hyperactivity disorder), but at the time I thought there was something wrong with me. Nonetheless, to compensate for my inability to learn in class, I worked very hard at Cornell and memorized things like the organic chemistry texts, and I taught myself how to do homework problems. My grade point average the last five semesters was greater than a 4.0 (an A was 4.0—I had many A+s). I also got my first taste of teaching as a teaching assistant in a course on heat and mass transfer. I loved it and loved interacting with and teaching students just a year younger than myself. When I graduated from Cornell, I received several job offers to run chemical plants, but I didn't think I'd be very good at it, nor was it exciting to me, so I decided to apply to graduate school.

I applied to six graduate schools and chose to go to the Massachusetts Institute of Technology (MIT). While at MIT, I did two things. The first was my doctoral thesis on enzymatic regeneration of adenosine triphosphate. The goal was to explore enzymes for synthetic purposes, and an energy source—adenosine triphosphate—was required. On the positive side, my advisor, Clark Colton, was very thorough, and one of the postdoctoral fellows in the lab, Colin Gardner, taught me how to do very careful, reproducible research. But on the negative side, after the first year or two, I started to think that the research I was doing wasn't really important. I couldn't see how it would have great impact or change the world. That discouraged me about research. The second thing I did was to get involved in a lot of educational outreach, particularly teaching underprivileged children. During my first year at MIT, I did a lot of tutoring in poor communities. During my second year, some people wanted to start a school for poor high school students who had dropped out of the public schools. They asked me to help, and we started the Group School. I helped create and chaired the math and science departments. My big goal was to make math and science

interesting. I got MIT to fund a program to create a novel chemistry lab course where we would teach chemical principles using practical experiments—for example, making rubber illustrated a chemical reaction, and making ice cream illustrated freezing point lowering because you need to lower the freezing point of water to make ice cream into a solid. I also created math games to help make math interesting. The people at the school were very liberal, and students were not required to take math or science. I remember when I first came, only 5 of 42 students signed up for math. But one year later, 45 out of 50 did. This experience reinforced my love of teaching.

I finished graduate school with a doctorate in chemical engineering, and I didn't know what I wanted to do career wise. I graduated in 1974, and at that time there was a big gas shortage. The price of gas went way, way up, and you had to wait in line at the gas station for hours to fill up your car, at least in Boston, where I lived. Consequently, if you were a chemical engineer, you received a lot of job offers. In fact, many of my classmates in the 1970s joined oil companies. They had many openings, and that's really where the high-paying jobs in chemical engineering were at that time. I got 20 job offers from oil companies—4 from Exxon alone. I also got offers from Shell, Chevron, and others. One job interview made quite an impression on me. It was at Exxon in Baton Rouge. One of the engineers there asked, if I could increase the yield of a particular chemical by approximately 0.1%, wouldn't that be wonderful? He said that would be worth billions of dollars. I remember flying home to Boston that night, thinking to myself that I really didn't want to do that.

What did I want to do? Well, from my college experiences, I had this dream of using my background in chemistry and chemical engineering to improve people's lives. As mentioned, I had spent a lot of time starting a school for poor high school kids and developing new chemistry curricula. One day, I saw an advertisement for an assistant professor to develop chemistry curricula at City College in New York. I wrote them a letter applying for the job; they didn't write me back. But I liked that idea, so I found all the ads I could for an assistant professor position to develop chemistry curricula. I found approximately 40 such ads. I wrote to all of them, but I don't think any wrote back.

POSTDOCTORAL RESEARCH

Another way I thought I could help people was through health-related research, so I applied to a lot of hospitals and medical schools. None of them wrote back either. Then one day, one of the people, Barry Bunow, in the lab where I worked said I should write to a surgeon named Dr. Judah Folkman at Harvard and Boston's Children's Hospital. He said, "Sometimes he hires unusual people." Dr. Folkman was kind enough to offer me a job. I took what, at that time, seemed to all chemical engineers like a huge risk and began doing postdoctoral work in a hospital. It might seem more common today, but at that time few, if any, chemical engineers had done postgraduate work in a surgery lab. Dr. Folkman was trying to understand how blood vessels grow toward cancerous tumors in the body. He postulated that the tumors can grow because they produce a chemical substance that induces blood vessels to grow into them. That way, the tumor receives nutrients and can grow much larger. But if you could prevent nutrients from getting to the tumor, that might stop the tumor from growing. When I started working with him, this concept was only theoretical, and many people disagreed with Dr. Folkman. Moreover, this area of blood vessel growth was difficult to study. We realized that to solve this problem, we would need to isolate a blood vessel inhibitor, which is often in the form of a large molecule, but as has often been the case in the development of new medicines, discoveries were hampered because no bioassays existed. So we needed to develop a bioassay. We chose the cornea of a rabbit to study blood vessel growth, because there are normally no blood vessels in the cornea, and the chick

chorioallantoic membrane, which has very few blood vessels in certain areas. We put a tumor in these places in a way that would mimic what happens in humans. Over time, blood vessels grow toward the tumor. We wanted to stop those blood vessels from growing, but to do that, we needed a controlled-release system (e.g., composed of a polymer or lipids) that could protect and deliver the different molecules I was isolating. Because no such delivery system existed, I tried to develop one.

However, delivery of large molecules faced serious challenges. Swallowing them did not work because they were too large to be absorbed by the gastrointestinal tract, and they would also be destroyed by enzymes or acid in the stomach or intestines. They were also too large to use in a transdermal skin patch. If you tried injecting the molecules, they were quickly destroyed by enzymes. Delivering such 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 these large molecules from biocompatible materials, any more than a person could walk through a solid wall. Dr. Folkman contacted many experts, including Paul Flory, a Nobel laureate in chemistry for his work in polymers, and they told him it couldn't be done (1).

Against this background, I began working in the laboratory to see if I could make tiny particles that could deliver these molecules. Over two years of experimentation, I found hundreds of unsuccessful methods. Finally, I discovered one way to make it work. My students and I took water-repellant or lipophilic polymers and dissolved them in organic solvents, usually at extremely low temperatures like −80°C. We added the molecules to them and slowly dried off the solvent. This is how we created small microparticles or even nanoparticles. We published in *Nature* that you could use this approach to release molecules of almost any size (2, 3). These molecules could even be released for more than 100 days in test tubes. Although the release rates were not constant in those initial studies, we later developed mathematical models to design systems with certain shapes that could ensure constant release rates (4). At first, our concepts were not accepted, and many scientists ridiculed my work. For example, in 1976, as a very naïve postdoc, I was asked for the first time to give a major lecture—at the Midland Macromolecular Symposium. I was 27 years old, addressing distinguished elder chemists and engineers. I was very nervous about this talk, so starting two weeks in advance, I practiced it over and over into a tape recorder. Finally, the day came, and I was pleased that I hadn't forgotten too much of what I'd intended to say and didn't stammer too much. I thought that when I was done all these older, distinguished chemists and engineers in the audience would want to encourage me, this young guy. But instead, people gathered around me and stated, "We don't believe anything you've said. We know that you can't deliver these molecules." It wasn't until several years later that others began repeating what we did, and then the question shifted to, "How could this possibly happen?" In fact, I spent a good part of my early career at MIT understanding how these delivery systems functioned (5, 6) and trying to make them useful for different applications.

BECOMING A PROFESSOR

Shortly after that talk, I sought funding to support my research and wrote many grants. My first nine were rejected. They were reviewed by medical study sections who felt engineers had little ability to do experimental medical research. Also, when I was finishing my postdoctoral work, I applied for faculty positions in several chemical engineering departments. However, I could not get a faculty job because people felt, at that time, that what I was doing wasn't engineering. They thought it was more like biology. So I ended up joining what was then the Nutrition and Food Science Department at MIT. But the year after I got the position, the department chairman who

hired me left, and several senior faculty in the department decided to give me advice: I should start looking for another job. As my colleague at the time, Michael Marletta, recalled,

> One evening, I went to a faculty dinner at a Chinese restaurant with Bob Langer and some senior MIT professors. A senior scientist sat quizzing us while smoking a cigar. When the older scientist heard Langer's concepts for polymeric drug delivery, he blew a cloud of smoke in Langer's face and said, "You better start looking for another job." I thought I was in a Fellini movie. (7)

So there I was, getting my grants turned down and people not believing in my research, and it appeared I would not even get promoted to Associate Professor. Fortunately, within the next few years, scientists in the pharmaceutical industry and at different universities started using some of the principles and techniques I developed, and slowly things began to turn around.

MOVING OUR RESEARCH FORWARD

One of my goals in doing laboratory work has been to move beyond just conducting experiments and publishing the results to also applying that work to helping people. I worked with Dr. Folkman to use this delivery system in the bioassay mentioned earlier to find substances that could stop blood vessels from growing. I had isolated many different substances, and I tested all of them in 100 different studies. Every substance but one failed to stop the blood vessels from growing. For the one that did, we did more than 20 different experiments, and for the first time we saw that blood vessels growing toward a tumor could be halted. They actually formed a zone of inhibition around the area where the inhibitor had been placed. That never had happened before in thousands of control experiments. In 1976, we published a paper in *Science* showing for the first time that inhibitors of blood vessel growth did exist and providing bioassays that could be and were used to isolate future inhibitors (8). Today, many inhibitors of blood vessel growth have been isolated (9). Without this bioassay, the isolation of these inhibitors would likely not have been possible. As Judah Folkman (10) noted in his abstract for the 2006 Symposium Celebrating Thirty Years of Robert Langer's Science,

> Early research in tumor angiogenesis was propelled by the pioneering work of Robert Langer who discovered how proteins and other macromolecules could undergo sustained release from polymers that could be implanted into the avascular cornea of animals and into other tissues. This advance provided a general platform for the subsequent discovery and purification of angiogenesis regulatory molecules. It is difficult to imagine how such proteins could have been isolated and their angiogenic activity identified without Langer's contribution.

Similarly, as Cramer (11) has written, "The first proof that numerous angiogenic proteins stimulate new vessel formation arose from an elegant feat of chemical engineering by Robert Langer, who devised a polymer bead. The bead, when placed in the avascular cornea, slowly and continuously released these proteins to stimulate the formation of new vessels." The National Academy of Sciences' (12) Beyond Discovery Report, "Polymers and People," notes that "Robert Langer and Judah Folkman used this approach to isolate the first angiogenesis inhibitor." Many angiogenesis inhibitors, such as Avastin, have now been approved by regulatory authorities and are in widespread use. According to Carmeliet (13), they are expected to be used by 500 million patients worldwide.

TRANSLATING SCIENTIFIC DISCOVERY TO BENEFIT MANKIND IN BIOLOGY AND MEDICINE

The above controlled molecular release research has also significantly impacted developmental biology, starting with Silberstein & Daniel's (14) paper in *Developmental Biology*, in which they used

our delivery systems to study the development of mammary and salivary glands. Many other investigators have used our systems to release different substances to study developmental processes (see, for example, 15–20). Importantly, the principles established for the controlled movement of molecules have been essential to the development of numerous clinically used therapeutics. As former *Nature* editor Phil Ball (21, p. 241) wrote,

> It was widely believed at first that polymer delivery systems would not be equal to this task—the few polymeric materials that would allow large molecules to diffuse through them, such as polyacrylamide gels, gave too great a rate of discharge and could also damage tissues. But in 1976, Robert Langer and colleagues found that certain polymers, generally ones that were highly hydrophobic (water-repellent) such as copolymers of ethylene and vinyl acetate, could be mixed with powdered proteins and formed into microspheres that would release the proteins at a steady, slow rate, persisting sometimes for up to one hundred days. There seemed to be no limit to the size of the large molecules that could be released controllably in this way, nor to their nature: proteins, nucleic acids, and polysaccharides (sugar polymers) could all be used. . . . In 1989, a controlled-release system of this sort—microspheres made from a safe biocompatible copolymer of lactic and glycolic acid—was approved by the U.S. Food and Drug Administration for use with a large-molecule peptide drug that combats prostate cancer. This was the first polymeric controlled-release system for peptide-based drugs to find medical approval, and it now provides the most widely used treatment for advanced prostate cancer.

Patients worldwide use numerous controlled-release polymer systems that continuously release these peptides for up to 6 months from a single injection (Lupron Depot®, Zoladex®, and Decapeptyl®). Similar microspheres or other polymer systems containing bioactive molecules have led to new treatments for schizophrenia (Risperdal Consta®), alcoholism, opioid addiction (Vivitrol®), arthritis (Zilretta®), control of bleeding (Floseal®, Surgiflo®), pituitary dwarfism (Nutropin Depot®), type 2 diabetes (Bydureon®), and many other diseases (22). All drug-eluting stents are also based on this research (23).

In addition, this work has had a large impact on aquaculture. In the 1980s, I visited Israel and was invited to the Aquaculture Center in Eilat. There, I met Yonathan Zohar, who then came to my lab for a sabbatical. He used the drug-delivery systems we developed to release GnRHa (gonadotropin-releasing hormone agonist) to induce spawning and control reproduction in fish. These provided the industry with a means of inducing fish to spawn in captivity, thus opening the spawning bottleneck and enabling hatchery-based aquaculture. These GnRHa delivery systems are now used in fish hatcheries around the world to induce spawning and egg/juvenile production in scores of fish species, ranging from salmon to branzini (European seabass) to bluefin tuna. Over the years, Zohar's group has published many papers on the development and use of the technology (24–34). A small grant from BARD to Dr. Zohar and myself created more than $12 billion of value, and aquaculture is now a ∼$230 billion industry globally (34).

EXTENSIONS TO NANOMEDICINE

The original controlled-release materials we developed were small particles, in many cases microparticles. However, nanoparticles are often critical for delivering significant payloads of any drug into cells, particularly newer potential drugs such as small interfering RNA and messenger RNA (mRNA). Yet, once nanoparticles are injected into the body, they are destroyed almost immediately by macrophages and are unstable and often aggregate. These characteristics made their use essentially nonexistent. We defined seven key characteristics we wanted to build into nanoparticles to address these problems (35). We found that nanoparticles composed of a block copolymer of polyethylene glycol (PEG) and any other material, such as polylactic acid, and an added drug could circulate for hours in vivo, remain shelf stable for years, and not aggregate. Another issue with nanoparticles is that for nucleic acids, it is desirable that they have cations so that they can

complex negatively charged nucleic acids. However, charged nanoparticles can cause toxicity. Dan Pack, David Putnam, and I added molecules to nanoparticles that made them neutral at physiologic pH but charged inside the cells (36, 37). This approach (ionizable polymers or lipids) also enables endosomal escape inside cells. Many scientists and companies are now using these principles to practice nanomedicine. The US Food and Drug Administration (FDA) has approved a lipid nanoparticle with PEG and an ionizable lipid (Onpattro®) to treat the protein-misfolding disease transthyretin-related hereditary amyloidosis or transthyretin amyloidosis, abbreviated as ATTR amyloidosis. Another nanoparticle we helped develop (Inveltys®) has been approved to treat postoperative inflammation and pain following ocular surgery (38). Nanoparticles containing PEG and ionizable lipids have been essential for all mRNA therapeutics and vaccines (39).

CONTROLLING THE MOVEMENT OF MOLECULES BY EXTERNAL FORCES

Even though by 1980 we could continuously release molecules of any size or charge, a problem central to the field of controlled-release technology is that all vehicles developed up until that time displayed drug-release rates that either were constant or decayed with time. There had been no way to change or modulate the release rate on demand once release had commenced. Furthermore, in many cases, constant or decreasing drug-release rates, as achieved with most drug-delivery systems, do not mimic the body's natural pattern of providing chemicals. For example, for drugs such as insulin, pulsatile delivery is desirable.

Magnetic Control of Molecular Release

The first approach involving external forces to control the movement of molecules within materials involved incorporating magnetic beads in an elastic polymer (40, 41). When an oscillating magnetic field was applied (e.g., as may someday be achieved in a wristwatch-like device), more molecules were released. This occurred reversibly and repeatedly over several months. The external magnetic field appears to cause alternative expansion and contraction of the drug-carrying pores. Key factors for achieving pulsatile release are magnetic bead strength, magnetic field strength, polymer elasticity, magnetic bead size, and polymer matrix structure (42).

Ultrasound Control of Molecular Release

We also discovered that ultrasound enhances transport of molecules entrapped within polymer systems. The enhancing effect of ultrasound on molecular release appears largely due to cavitation. Critical parameters in controlling molecular movement from polymers are ultrasound frequency, molecular mass of the incorporated drug, and polymer matrix structure (e.g., the size of pores in the polymer network) (43).

Electrical Control of Molecular Release

A third approach involves electrical control. In one case, we developed a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand (44). The release mechanism is based on the electrochemical dissolution of thin anode membranes covering micro-reservoirs filled with chemicals in solid, liquid, or gel form. Although it was used as a model compound in these initial studies, gold has been shown to be biocompatible (44). Subsequently, we also found platinum alloys to be useful and even demonstrated this approach could work in humans (45).

NEW MATERIALS

Another area I started thinking about involved new biomaterials. Working in a hospital, I realized that almost all materials used in medicine were derived from household objects, and their medical use was driven by clinicians who wanted to use them in medical areas based on their physical properties. For example, the polyether urethanes used in ladies' girdles are now used in artificial hearts because of their good flexural properties. The polyurethanes in mattress stuffings are used in breast implants. Yet, such an approach often leads to problems. Artificial hearts, for example, can cause clots to form when blood hits their surface—the ladies' girdle material—and these clots can cause strokes and death (46).

Against this background, I began thinking of ways of 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 what we want in a biomaterial from engineering, chemistry, and biology standpoints and then synthesizing the materials from first principles. As a proof of principle, we decided to synthesize a new family of biodegradable polymers for medical use. In particular, we wanted materials to display surface erosion to eliminate the possibility of dose dumping that could potentially occur with bulk eroding materials—the only such materials approved by regulatory authorities at the time of this endeavor in 1980. The first step was to decide on the mechanism of biodegradation. We selected hydrolysis, because excess water is present in people at all times, as opposed to enzymatic degradation, because enzyme levels can vary between patients as well as over time. Then we selected anhydrides as the bonds to connect to monomers due to their susceptibility to hydrolysis. To select the specific monomers—the building blocks of the polymer—I asked Mike Marletta what hydrophobic monomers (which would make polymers water repellant), from a list of substances we thought might make good polymers, would be safe in the human body. We then synthesized these polymers and discovered that by changing compositions we could make them last anywhere from days to years (47–49). Then with Henry Brem, who is now Chief of Neurosurgery at Johns Hopkins, we had the idea to use this polymer system to locally deliver drugs to treat brain cancer. However, I had to raise money for this project, so I wrote grants to the National Institutes of Health and other funding agencies. These grants were then repeatedly reviewed by Study Sections composed of other professors occurring over a decade and were rejected every time. However, in 1996, the FDA approved this treatment—the first time in more than 20 years that the FDA approved a new treatment for brain cancer, and the first time they approved polymer-based local chemotherapy (50).

The funding we obtained to support this research was from companies that licensed our polyanhydride patents. Twenty-eight years after their approval, these polymer systems are still used to treat brain cancer patients in more 30 countries. They have provided an entirely new paradigm in the drug-delivery field, paving the way for drug-eluting stents and other local delivery systems (23).

Sometimes it is difficult to predict where the materials we develop will have the greatest impact. Over the years, we have synthesized many new polymers. For example, we developed a new synthesis for poly(hydroxamic acid) (51). Interestingly, although our initial intent was to develop protective coatings for implantable medical devices, these polymers became widely used as a flocculent (Superfloc®) to decontaminate swimming pools and other areas. We also synthesized the first degradable shape-memory polymers (52, 53), the first degradable electrically conducting polymers (54), and materials that could change surface characteristics by throwing a simple switch (55). These materials allowed new potential uses in medicine and other areas, e.g., self-tying sutures for shape-memory polymers. Another approach to create biomaterials developed by David Lynn, now on the faculty of University of Wisconsin–Madison, and Dan Anderson,

now on the MIT faculty, when they were postdoctoral fellows in our laboratory at MIT involved synthesizing large polymer libraries. For example, by developing chemical and robotic methods that lent themselves to high-throughput parallel synthesis and screening approaches, we synthesized poly β-aminoesters. We synthesized thousands of such polymers and developed screening assays to identify useful polymers based on DNA binding, solubility, and cell transfection (56). This approach was extended to the synthesis and screening of thousands of lipids (57, 58) and is accelerating the rate at which nonviral vectors can be discovered. It has already led to many widely used gene therapy reagents (distributed by Sigma-Aldrich®, Clontech®, Stemgent®, and others). Interestingly—and again an example of how one can never anticipate all possible applications—some of these polymers have also become widely used as hair care products developed by Unilever/Living Proof, a company we started that also involved the actress Jennifer Aniston.

CONTROL OF MOLECULAR DELIVERY THROUGH PHYSIOLOGIC BARRIERS

We have also developed new approaches for delivering molecules through different physiologic barriers.

Controlled Delivery to the Lung

Local delivery to the lung has been used in the treatment of respiratory diseases such as asthma and more recently for protein therapies such as DNase for cystic fibrosis. The deep part of the lung also has potential advantages for systemic delivery of molecules, including a large surface area, thin tissue lining, and a limited number of proteases. Most current lung delivery systems deliver drugs in liquid form, and many incorporate chlorofluorocarbon propellants, which may be environmentally dangerous. In addition, many of these systems do not deliver the drug reproducibly or efficiently; generally, less than 10% of the drug is received by the lung from the device due, in part, to aerosol aggregation because the aerosols are so small (∼2 μm in diameter). In addition, repeated delivery every few hours is often necessary. For decades, scientists attempted to address the above issue by designing different inhalers that could break apart aerosol aggregates or have other features. However, in the early 1990s, David Edwards came to my lab and took a radically different approach: designing new aerosols by changing aerosol geometry. Prior work always involved designing small-diameter (∼2-mm diameter) nonporous aerosols. Our approach was to create large (5–20-μm), highly porous particles with extremely low densities. By lowering their density, we hypothesized that the particle aerodynamics would be altered, making it possible for unusually large particles to enter the lungs through an airstream. We further hypothesized that increasing aerosol particle size would lead to decreased particle aggregation, creating far greater inhalation efficiency, as well as decreased phagocytosis by alveolar macrophages. The decreased phagocytosis could result in sustained drug release. We then created such large and highly porous aerosols and found that more than 10 times the number of molecules could be delivered this way, compared with conventional aerosols and inhalers, and could last 10 times longer if desired (59). This capability enables simple, small inhalers that can deliver 70 mg of substance (before this, the delivery of 10 mg was difficult) in a single dose. These aerosols are leading to entirely new treatments for Parkinson's disease (Inbrija) and other diseases.

Controlled Delivery of Molecules Through the Skin

I was also interested in seeing if we could control the delivery of ionic molecules or large macromolecules through the skin. Transdermal delivery offers advantages compared with oral pills, in

that it avoids first-pass metabolism and enables long-term therapy. Compared to injections, it reduces pain and scarring risk. However, the skin has significant barrier properties; thus, only a few very-low-molecular-weight lipophilic molecules have been successfully delivered transdermally. We thought of several ways to control molecular movement through the skin. The first was ultrasound with Joseph Kost, who later became Dean of Engineering at Ben Gurion University. We had already shown that ultrasound could enhance molecular transport through polymers (43), so we wondered whether it would work on skin. In our first study, we discovered appropriate ultrasound conditions to deliver mannitol, insulin, and physostigmine transdermally (60). However, several groups tried to use ultrasound to transport other molecules through skin and told us it did not work (though they used different ultrasound conditions). So Samir Mitragotri, working with myself and Dan Blankschtein, investigated the possible mechanisms of ultrasound-enhanced permeation, including temperature effects, transport through hair follicles and sweat ducts, mixing effects, and acoustic cavitation. Acoustic cavitation was the dominant mechanism. By understanding this mechanism, we immediately realized we could get greater transport if we used very-low-ultrasound frequencies (61). We also did extensive research on the structural changes in the skin during ultrasound exposure and developed mathematical models to predict optimal delivery (62–64). As a result of these studies, SonoPrep became the first system to receive FDA approval using ultrasound. Ultrasound has also been used for glucose monitoring in humans (65) and to deliver methylprednisolone and cyclosporine in humans to treat alopecia. A second approach we examined to enhance molecular movement through the skin was electroporation, which Mark Prausnitz pioneered when he was in our lab (66–71). He used scanning fluorescence microscopy to image transport during electroporation and observed localized transport regions, through which molecules could diffuse more easily. We also found that skin electrical resistance dropped by up to 1,000-fold within microseconds. Electroporation-induced delivery of DNA vectors is now being used in human studies for the delivery of vaccines for treating Zika virus, Ebola virus, Middle East respiratory syndrome, HIV, and hepatitis B and is also being used in different cancer treatments (72). Our lab also analyzed how chemical enhancers affect skin permeability through a combination of experimental techniques and two-photon microscopy. We developed mathematical models for describing skin permeability, using a theory of charge, fluid mass, and transport through porous media under passive conditions, but also in the presence of the types of external forces, such as those discussed above, that can enhance penetration (62, 73, 74). Mitragotri (72) provided an analysis of some of our contributions to controlling molecular movement through the skin.

FUTURE DIRECTIONS FOR DRUG DELIVERY

Bill Gates came to visit me in 2012 because he wondered if we might be able to create new medicines for the developing world by extending some of the principles we developed. In particular, we worked to develop new approaches for vaccine delivery for very long-term oral delivery and for improving nutrition. Each is discussed below.

Controlling the Movement of Molecules to Improve Heath in the Developing World: Vaccines

One area is vaccines, because patients often do not return for second or subsequent injections. In 1979, we published the first paper illustrating a single-step method of vaccination (75). The Gates Foundation was particularly interested in the possibility of creating microparticles that release their contents in distinct, delayed bursts without any prior leaking. Again, we thought of using polymers to accomplish this. To address these issues, we developed a new

high-resolution microstructure fabrication technique to create microdevices with complex geometries using a variety of commercially safe materials, including lactide–glycolide copolymers (PGLA), the most widely used biodegradable polymers for human applications. This approach, termed StampEd Assembly of polymer Layers (SEAL), combines technology used for computer chip manufacturing with soft lithography and an aligned sintering process to produce small polymeric structures. We created several PLGA microparticles, each intended to pulse at a different predetermined, desired period of time to deliver timed pulses of antigens, so that essentially any vaccine could be delivered on whatever schedule was desirable in a single injection (76).

Long-Term Oral Delivery and Oral Delivery of Macromolecules

The Gates Foundation believes that numerous diseases, such as malaria, could be treated in the developing world if the drugs could last enough to treat them. However, patient compliance is a major issue. The Gates Foundation asked if we could make oral systems that could last one or two weeks or a month. To address this problem, Gio Traverso, then a fellow in our lab, and now a professor at MIT and Harvard, and other members of our lab designed a polymer drug-delivery system with shape-memory properties such that it can be folded and placed inside a vitamin capsule; when the capsule dissolves in the stomach, the polymer system escapes and assumes a shape large enough that it cannot pass through the pylorus but open enough to allow food to pass through (77) (**Figure 1**). This system is now in multiple human clinical trials, including in the use of ivermectin to prevent malaria. We have also used these systems to release three different drugs at once for HIV treatment (78). In addition, Dr. Traverso, Alex Abramson, and our team designed a pill containing a needle that can be made almost entirely of a pharmaceutical and injected into the stomach or intestine after swallowing. To ensure the pill is always pointing in the correct direction to enable appropriate injection, we made it self-orienting by designing it to mimic the leopard tortoise. Insulin, antibodies, and even mRNA have been shown to be available orally in animal studies (79–81).

Controlled Delivery of Nutrients

Another area where we have applied our approaches is human nutrition in the developing world, where micronutrient deficiencies are prevalent. They impact nearly two billion people and cause up to two million childhood deaths per year, as well as numerous disabilities and diseases and impaired growth in children. In particular, many populations in developing countries consume

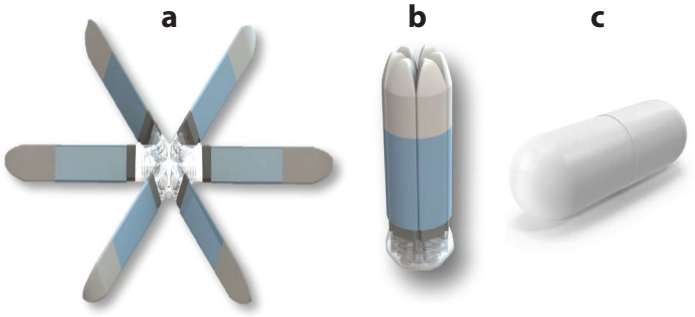

Figure 1

(*a*) Star-shaped system containing the drug in the spokes. It can be (*b*) folded up and (*c*) placed in a capsule. Image courtesy of Jessica Ballinger/Lyndra (2015).

staple foods that often require extensive cooking, which introduces heat, moisture, and oxidation challenges, leading to degradation and chemical changes of vitamins and minerals. As such, the development of technologies that address these stability challenges can potentially have an enormous impact on global health. To address these issues, we hypothesized that an encapsulation system employing an appropriate pH-sensitive polymer could potentially remain stable in boiling water for hours yet dissolve rapidly in acidic stomach conditions. We examined more than 50 polymers and discovered a material with a unique combination of (*a*) stability in boiling water for hours, yet rapid dissolution in gastric acid at body temperature; (*b*) proven safety in humans; and (*c*) the ability to effectively encapsulate nutrients with a wide range of chemical and physical characteristics (82). We studied our system with 11 different micronutrients and found that this microparticle platform enabled the individual encapsulation of iron; iodine; zinc; and vitamins A, B2, niacin, biotin, folic acid, B12, C, and D. In vivo studies in mice confirmed rapid micronutrient release in the stomach and absorption in the intestines. Specifically, encapsulated vitamin A exhibited statistically indistinguishable differences in absorption as compared with free vitamin A in animal models and humans, highlighting that encapsulation did not influence absorption (83). Two separate human studies with iron were performed, and iron bioavailability was statistically the same as in the use of nonencapsulated iron (84). The Joint Food and Agriculture Organization of the United Nations and the World Health Organization Expert Committee on Food Additives responded positively to our encapsulation material for food fortification at their eighty-sixth annual meeting, when we submitted our application for approval, paving the way toward potentially reducing or eliminating micronutrient malnutrition.

ENZYME APPLICATIONS

Although in most cases we were interested in delivering molecules, in some cases, I thought it would be desirable to remove specific molecules. Examples are heparin (see below), which can cause serious bleeding complications; bilirubin, which causes jaundice (84); low-density lipoprotein cholesterol, which can cause heart disease (85–87); and β_2-microglobulin, which can cause potentially fatal amyloid deposits (88).

Heparin represents an important example. It is widely used as an anticoagulant to treat and prevent deep vein thrombosis, pulmonary embolisms, and thromboembolisms. However, it can cause serious complications. The common way to neutralize heparin is by using protamine, which has a charge opposite to that of heparin. However, protamine causes complications. It occurred to me that an enzyme that could specifically degrade heparin—heparinase—might be used to selectively remove heparin. With Charles Cooney, Bob Linhardt, and others, we developed ways to produce heparinase by fermentation (89), purified it to homogeneity (90), cloned it (91), and showed that immobilized heparinase could remove heparin in vivo (92).

One recurring theme of my career is that doing chemical research enables applications that we would not always envision initially. This was no exception. In this case, two of my postdocs, Ram Sasisekharan and Ganesh Venkataraman, began using heparinases along with mass spectroscopy and computer modeling to develop the first way to sequence heparin and other complex polysaccharides (93). In 2008, Ram and I were contacted by the FDA (I had previously been chair of the FDA's Science Board—their highest advisory board), because hundreds of people in more than 20 countries had died due to contaminated heparin. Using heparinase and these sequencing techniques, and working with the FDA and Centers for Disease Control, we uncovered the contaminant—an oversulfated chondroitin sulfate (94)—which enabled new guidelines (95, 96). After that, there were no more deaths.

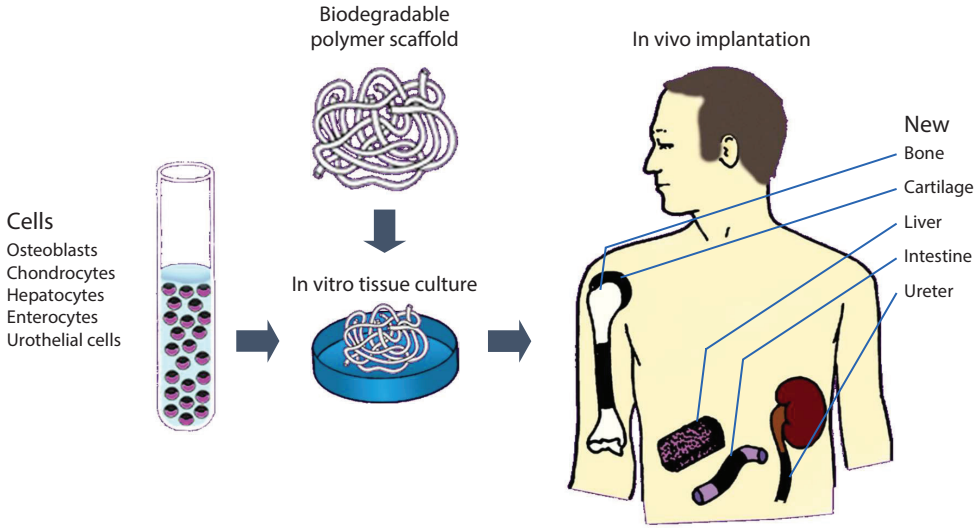

Figure 2

Schematic diagram of tissue engineering. Figure adapted with permission from Reference 116.

TISSUE ENGINEERING

In the early 1980s, Jay Vacanti, who was head of the liver transplant program at Boston Children's Hospital, asked me if we could create a new liver. Prior to this, several research groups had worked on developing two-dimensional systems to create certain tissues. We started to use two-dimensional cell/materials systems as well. However, after much work trying to grow liver cells on two-dimensional structures (e.g., discs, Petri dishes) to test our prototypes, we realized that we could not get enough cells per unit volume to create tissue with enough liver function. One day on Cape Cod, Jay saw some seaweed. He called me and said, "Bob, could you make a polymer system that was three-dimensional, like seaweed, and, if so, could that solve the surface-to-volume problem?" So we did (see **Figure 2**). Through many experiments, we saw this approach could address the surface-to-volume issue. We thought we could take isolated, dissociated cells from patients themselves or from a close relative. These cells could include, for example, bone, cartilage, liver, intestinal, and urothelial cells. Today, they can also include stem cells that could be made to differentiate into a desired cell type. If the cells are injected at random, very little happens. However, the cells can be "smart." If you put these cells close enough together, they can organize themselves and create structures. We wondered if we could make different tissues by putting dissociated cells on a polymer template, in three dimensions, with the right media. We would grow them outside the body, on the correct materials, and then ultimately return them to the body to make whatever tissue we wanted. We would either use existing FDA-approved polymers like PGLA or synthesize new ones. For example, Denise Barrera, who worked in our laboratory, developed polymers in which one could attach amino acid sequences that would be specific for certain cell types (97). Wang et al. (98) also synthesized new materials, such as polyglycerol sebacic acid with adjustable elasticity (these were later approved by regulatory authorities). Tony Mikos, David Mooney, and Prasad Shastri then developed a variety of methods to convert different polymers into fibers or other three-dimensional structures that can be used as substrates for cells to create a new tissue (99–103). These cell/polymer systems were implanted in animals or humans. New blood vessels would grow toward the polymer system in response to

polymer scaffold degradation. This process would lead to the creation of permanent, new tissue that could function as a living tissue replacement. The cells could then go on to form vascularized living tissue after implantation (104). This discovery has been credited by the National Academy of Sciences (12) as "giving rise to the field of tissue engineering" and by *Nature* as "founding the field of tissue engineering" (105). To move this area forward, we built upon these initial findings in several ways. For example, Gordana Vunjak-Novaković and others developed flow bioreactors to improve mass transfer as well as provide mechanical signals to the developing tissue. To create new blood vessels, Laura Niklason hypothesized that the failure of others to create safe and effective small-diameter blood vessels was due to the fact that in earlier studies, blood vessel cells (smooth muscle cells, endothelial cells) were generally grown in static tissue culture. Yet, in humans, these cells are connected to a pulsatile pump—the heart. Hence, she created bioreactors that created pulsatile radial stress cells (165 beats/min) to simulate the heart to grow the cells. The polymer scaffolds led to the first safe and effective way to create small-diameter blood vessels (106), which are now being used in humans. [In this case, Niklason grew the cells in bioreactors and then decelluralized the scaffolds once the scaffolds were strong enough to put into patients (107).] In addition, we developed ways to use neuronal stem cells on a specialized polymer scaffold to aid in spinal cord repair (108). We developed approaches using stem cells to create muscle (109), created materials to make heart tissue (110), and synthesized the first surfaces for growing stem or induced pluripotent stem cells in a completely xeno-free, serum-free environment (111). This work has also led to the creation of skin in humans that is now approved for burn victims and patients with diabetic skin ulcers (e.g., distributed by Organogenesis). Already more than a million patients have received tissue-engineered human skin (for burns or diabetic skin ulcers) (e.g., Dermagraft® uses the exact polymer we originally used, polylactic glycolic acid, in this case with neonatal fibroblasts) (112). Since 1986, we and our colleagues have demonstrated the formation of more than 20 different tissues of the body in animal models, as well as several tissues in humans. In addition, our former students and others are now creating organs or chips to reduce animal and human testing (from companies like TARA Biosystems and Emulate). Some groups are even using tissue engineering to create meat (e.g., Aleph Farms) and leather (e.g., Modern Meadow).

CREATING COMPANIES AND PRODUCTS

I also wanted the inventions and materials we developed to help patients. This is difficult because it takes a great deal of money to develop medical products. So I began writing patents on our work. Today, we have licensed and sublicensed those patents to more than 400 companies, and I even helped start several companies with my students. I should add that when I wrote these patents and helped start these companies, many scientists looked down upon it. They thought it wasn't a very good thing for a professor to do. But today, these companies have made numerous products that treat patients with cancer, heart diseases, COVID, and many other sicknesses. These companies have also created many thousands of jobs throughout the world.

Let me give a few examples. First, to expand on what I mentioned earlier, we developed polymer systems that could slowly and continuously release large molecules. One of the challenges was getting a patent. We filed a patent in 1976, and the Patent Office turned it down. In fact, they turned it down five times between 1976 and 1981. The lawyer told me I should just give up, but I've never given up easily, and I started to think about new ways in which we could get this patent allowed. The patent examiner said that what we had done was obvious, but I knew that wasn't true because, as I mentioned, scientists said it was impossible. So, I scoured the literature and discovered that a paper published by five famous chemists and chemical engineers in 1979 referred to our work by saying,

> Generally the agent to be released is a relatively small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g., proteins, could be released by such a technique because of their extremely small permeation rates through polymers. However, Folkman and Langer have reported some surprising results that clearly demonstrate the opposite. (113, p. 105)

I showed this to our lawyer, and he showed it to the patent examiner, who said, "I will allow this patent if Dr. Langer can get affidavits from the five chemists and engineers saying they really wrote this." All five scientists were kind enough to sign the affidavits, and we got this very broad patent. We then licensed it to two very large companies, one in animal and one in human health. Both companies gave us grant money and promised to do experiments to develop our invention. However, these companies were very large; they did a few experiments, and when they didn't work optimally, they gave up. So a few years later, Alex Klibanov said, "Bob, why don't we start a company ourselves?" I was able to get these patents back, and we started a company called Enzytech, which later merged to become Alkermes. Alkermes has made long-acting injectable microspheres that have helped millions of patients suffering from type 2 diabetes, schizophrenia, alcoholism, opioid addiction, and pituitary dwarfism.

In a second example, in 2001, I started Momenta Pharmaceuticals (114) with Ram and Ganesh. The technology in this case involved the use of enzymes called heparinases for polysaccharide sequencing, which I mentioned previously. Momenta used this polysaccharide sequencing approach to create the first FDA-approved generic, low-molecular-weight heparin, which is an anticoagulant. It was the largest syringe launch in history. A second product that received approval was Copaxone®. In 2020, Johnson & Johnson acquired Momenta for $6.5 billion USD. Probably the most well-known example is Moderna. Noubar Afeyan, Ken Chien, Derrick Rossi, and I decided to start a company to make mRNA therapeutics. If mRNA was injected into patients, it would be destroyed, so we encapsulated mRNA in nanoparticles based in part on some of the research I discussed earlier. Moderna was widely criticized by scientists, stock analysts, and the news media. For example, *The Boston Globe* wrote an article saying "This is not how you do science," with my picture underneath. However, all of them were wrong, and Moderna produced a COVID-19 vaccine that saved millions of lives. Many other new medical treatments for cancer and other diseases are in late-stage clinical trials. Polaris Ventures estimates that billions of people are or will be helped by products created by companies I helped start (115).

The above companies are examples of how we have been able to move discoveries from the lab to patients. We've helped launched approximately 40 companies. These companies are creating new aerosols to treat diseases like Parkinson's, doing new types of genetic therapy for treating diseases like cancer or heart disease, and even developing new hair and skin care products (Unilever/Living Proof). Polaris Ventures estimates that billions of people are or will be helped by products created by these companies (115).

TEACHING AND MY STUDENTS

I have also really enjoyed giving lectures, teaching classes, and helping students. One of the things I learned from helping start the Group School was the importance of making classes fun (if possible) and relevant. When I was in the nutrition department, I was in charge of several laboratory classes. When I subsequently joined the chemical engineering department, I taught thermodynamics and an integrated chemical engineering course. In addition, I also taught and developed a course in pharmacological engineering for several years. Finally, I created a summer course in drug-delivery systems that I taught with Nick Peppas and several others for 40 years. We also gave the course in Europe several times. It's been a thrill to see how well the thousands of people in both the MIT courses and the MIT summer course have done. I'm also so proud of the students and postdocs

who worked in our laboratory. When I turned 70, they had a celebration, and more than 700 people came. Today, more than 400 of our trainees are professors, more than 500 have worked in industry or started companies, and another 100 or so have worked in government or other jobs. Forty-eight have been elected to the National Academy of Inventors, 23 to the National Academy of Medicine, 23 to the National Academy of Engineering, three to the National Academy of Sciences, and 40 to the Technology Review 35.

MY FAMILY AND LIFE TODAY

I want to mention my personal life. I've been married for more than 35 years to a wonderful, beautiful, and kind woman—my wife, Laura. I met Laura because she was the roommate of one of my postdocs and I'd seen her running on the track where I also ran for exercise. I thought she was very beautiful, stimulating, smart, and nice. Laura has a bachelor's degree from Harvard and a PhD in Neuroscience from MIT. Being married to someone with a scientific background has the added benefit that she knows the pressures I feel and the rewards I get from science, and being able to share that with her has been wonderful. Laura is my best friend as well as my wife. I've also been very lucky because Laura is a very straightforward person. I always know exactly where I stand. I should add that several years ago, my postdocs and students had a symposium for me, and one of them, Edith Mathiowitz, made a graph of my productivity. She asked everyone a question: Why is there a big inflection point in 1986? Her answer? That's when Bob met Laura. We also have three wonderful children, Michael, Susan, and Sam (**Figure 3**).

I feel incredibly fortunate that I've had such a wonderful staff at MIT and such super students, postdocs, and collaborators. I view my students and postdocs as an extended family, and I am so very proud of them. I would not be where I am today (**Figure 4**) without having had so much support and help from so many people.

Figure 3

The Langer family: (*from left*) Sam, Susan, Bob, Laura, and Michael Langer.

Figure 4

Dr. Langer receiving (*a*) the National Medal of Science from President George W. Bush in 2006, (*b*) the National Medal of Technology and Innovation from President Obama in 2011, and (*c*) the Queen Elizabeth Prize for Engineering from Queen Elizabeth II in 2015.

DISCLOSURE STATEMENT

The author believes that his affiliations, memberships, funding, or financial holdings do not affect the objectivity of this review. Nonetheless, for a list of entities with which R.L. is involved, compensated, or uncompensated, see **https://www.dropbox.com/scl/fi/xjq5dbrj8pufx53035zdf/RL-COI-2024.pdf?rlkey=fwv336uoepiaiyg4e7jz5t4zo&dl=0**.

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LITERATURE CITED

1. Cooke R. 2001. *Dr. Folkman's War: Angiogenesis and the Struggle to Defeat Cancer*. New York: Random House
2. Langer R, Folkman J. 1976. Polymers for the sustained release of proteins and other macromolecules. *Nature* 263:797–800

3. Rhine WD, Hsieh DST, Langer R. 1980. Polymers for sustained macromolecule release: procedures to fabricate reproducible delivery systems and control release kinetics. *J. Pharm. Sci.* 69:265–70
4. Hsieh DS, Rhine WD, Langer R. 1983. Zero-order controlled-release polymer matrices for micro- and macromolecules. *J. Pharm. Sci.* 72:17–22
5. Hsu TT, Langer R. 1985. Polymers for the controlled release of macromolecules: effect of molecular weight of ethylene-vinyl acetate copolymer. *J. Biomed. Mater. Res.* 19:445–60
6. Bawa R, Siegel RA, Marasca B, Karel M, Langer R. 1985. An explanation for the controlled release of macromolecules from polymers. *J. Control. Release* l:259–67
7. Lash A. 2014. Langer, Led Zeppelin, and hookups: three days behind the BIO Scenes. *Exome.com*, June 27
8. Langer R, Brem H, Falterman K, Klein M, Folkman J. 1976. Isolations of a cartilage factor that inhibits tumor neovascularization. *Science* 193:70–72
9. Cao Y, Langer R, Ferrara N. 2023. Targeting angiogenesis in oncology, ophthalmology and beyond. *Nat. Rev. Drug Discov.* 22:476–95
10. Folkman J. 2006. *Angiogenesis as an organizing principle in biology: the Langer contribution*. Presented at the Symposium: Celebrating Thirty Years of Robert Langer's Science, chair J Kohn, July 14–16, Cambridge, MA
11. Cramer D. 1998. Applied vascular biology: can angiogenesis inhibitors help control malignant growth. *Ann. Intern. Med.* 129:841–43
12. Natl. Acad. Sci. 1999. *Polymers and people*. Beyond Discov. Rep., Natl. Acad. Sci. **http://www.nasonline.org/publications/beyond-discovery**
13. Carmeliet P. 2005. Angiogenesis in life, disease, and medicine. *Nature* 438:932–36
14. Silberstein GB, Daniel CW. 1982. Elvax 40P implants: sustained, local release of bioactive molecules influencing mammary ductal development. *Dev. Biol.* 93:272–78
15. Park CM, Hollenberg MJ. 1993. Growth factor-induced retinal regeneration in vivo. *Int. Rev. Cytol.* 146:49–74
16. Reh TA, Constantine-Pato M. 1985. Eye-specific segregation requires neural activity in three-eyed *Rana pipiens*. *J. Neurosci.* 5:1132–43
17. Cline HT, Debski EA, Constantine-Paton M. 1987. *N*-methyl-D-aspartate receptor antagonist desegregates eye specific stripes. *PNAS* 84:4342–45
18. Simon DK, Prusky GT, O'Leary DD, Constantine-Paton M. 1992. *N*-methyl-D-aspartate receptor antagonists disrupt the formation of mammalian neural map. *PNAS* 89:10593–97
19. Ling JJ, Yu J, Robertson RT. 1995. Sustained inhibition of acetylcholinesterase activity does not disrupt early geniculocortical ingrowth to developing rat visual cortex. *Dev. Brain Res.* 86:354–35
20. Kalb R, Hockfield S. 1990. Induction of a neuronal proteoglycan by the NMDA receptor in the developing spinal cord. *Science* 250:294–96
21. Ball P. 1999. *Made to Measure: New Materials for the 21st Century*. Princeton, NJ: Princeton Univ. Press
22. Langer R. 2019. Controlling the movement of molecules. *Q. Rev. Biophys.* 52:E5
23. Natl. Inst. Health. 2004. *Overview of research activities*. Publ. No. 04–5488, Natl. Inst. Health, Bethesda, MD
24. Mylonas CC, Zohar Y, Richardson BM, Minkinnen SP. 1995. Induced spawning of American shad (*Alosa sapidissima*) using sustained administration of gonadotropin-releasing hormone analog (GnRHa). *J. World Aquacult. Soc.* 26:39–50
25. Mylonas CC, Gissis A, Magnus Y, Zohar Y. 1997. Hormonal changes in male white bass (*Morone chrysops*) and evaluation of milt quality after treatment with a sustained-release GnRHa delivery system. *Aquaculture* 153:301–13
26. Mylonas CC, Bridges CR, Gordin H, Belmonte Ríos A, García A, et al. 2007. Preparation and administration of gonadotropin-releasing hormone agonist (GnRHa) implants for the artificial control of reproductive maturation in captive-reared Atlantic bluefin tuna (*Thunnus thynnus*). *Rev. Fish. Sci.* 15:183–210
27. Sorbera LA, Mylonas CC, Zanuy S, Carrillo M, Zohar Y. 1996. Sustained administration of GnRHa increases sperm volume without altering sperm counts in the seabass (*Dicentrarchus labrax*). *J. Exp. Zool.* 276:361–68

28. Fukaya M, Ueda H, Sato A, Kaeriyama M, Ando H, et al. 1998. Acceleration of gonadal maturation in anadromous maturing sockeye salmon by gonadotropin-releasing hormone analog implantation. *Fish. Sci.* 64:948–51
29. Mylonas C, Zohar Y. 1998. New techniques for the control of gamete maturation in marine fishes as tools in broodstock management. *Cah. Options Med.* 34:193–213
30. Zohar Y, Mylonas CC. 2001. Endocrine manipulations of spawning in farmed fish: from hormones to genes. *Aquaculture* 197:99–136
31. Holland MCH, Hassin S, Zohar Y. 2003. The effects of long-term testosterone, gonadotropin-releasing hormone agonist and pimozide treatments on testicular development and luteinizing hormone levels in juvenile and early maturing striped bass, *Morone saxatilis*. *Gen. Comp. Endocrinol.* 129:178–87
32. Marino G, Panini E, Longobardi A, Mandich A, Fionia MG, et al. 2003. Induction of ovulation in captive-reared dusky grouper, *Epinephelus marginatus* (Lowe, 1834), with a sustained release GnRHa implant. *Aquaculture* 326:1–18
33. Taranger GL, Vikingstad E, Klenke U, Mayer I, Stefansson SO, et al. 2004. Effects of photoperiod, temperature and GnRHa treatment on the reproductive physiology of Atlantic salmon (*Salmo salar* L.) broodstock. *Fish Physiol. Biochem.* 28:403–6
34. BARD. 2019. *Full life-cycle hatchery-based aquaculture.* Case Study 7, BARD, Rishon LeZion, Isr. **https://www.bard-isus.com/bard40/docs/case7.pdf**
35. Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchillin V, Langer R. 1994. Biodegradable long-circulating polymeric nanospheres. *Science* 263:1600–3
36. Pack DW, Putnam D, Langer R. 2000. Design of imidazole-containing endosomolytic biopolymers for gene delivery. *Biotechnol. Bioeng.* 67:217–23
37. Putnam D, Gentry CA, Pack DW, Langer R. 2001. Polymer-based gene delivery with low cytotoxicity by a unique balance of side chain termini. *PNAS* 98(3):1200–5
38. Linnehan R. 2018. FDA approves Inveltys for treatment of inflammation, pain after ocular surgery. *healio.com*, Aug. 23. **https://www.healio.com/news/ophthalmology/20180823/fda-approves-inveltys-for-treatment-of-inflammation-pain-after-ocular-surgery**
39. Liu C, Shi Q, Huang X, Huang X, Koo S, et al. 2023. mRNA-based cancer therapeutics. *Nat. Rev. Cancer* 23:526–43
40. Langer R, Hsieh DST, Rhine W, Folkman J. 1980. Control of release kinetics of macromolecules from polymers. *J. Membr. Sci.* 7:333–50
41. Hsieh DS, Langer R, Folkman J. 1981. Magnetic modulation of release of macromolecules from polymers. *PNAS* 78:1863–67
42. Edelman E, Kost J, Bobeck H, Langer R. 1985. Regulation of drug release from porous polymer matrices by oscillating magnetic fields. *J. Biomed. Mater. Res.* 19:67–83
43. Kost J, Leong K, Langer R. 1989. Ultrasound-enhanced polymer degradation and release of incorporated substances. *PNAS* 86:7663–66
44. Santini JT Jr., Cima MJ, Langer R. 1999. A controlled-release microchip. *Nature* 397:335–38
45. Farra R, Sheppard NF Jr., McCabe L, Neer RM, Anderson JM, et al. 2012. First-in-human testing of a wirelessly controlled drug delivery microchip. *Sci. Transl. Med.* 4:122ra21
46. Peppas NA, Langer R. 1994. New challenges in biomaterials. *Science* 263:1715–20
47. Rosen HB, Chang J, Wnek GE, Linhardt RJ, Langer R. 1983. Bioerodible polyanhydrides for controlled drug delivery. *Biomaterials* 4:131–33
48. Leong KW, Brott BC, Langer R. 1985. Bioerodible polyanhydrides as drugcarrier matrices: I. Characterization, degradation and release characteristics. *J. Biomed. Mater. Res.* 19:941–55
49. Leong KW, D'Amore PD, Marletta M, Langer R. 1986. Bioerodible polyanhydrides as drug-carrier matrices II: biocompatibility and chemical reactivity. *J. Biomed. Mater. Res.* 20:51–64
50. Brem H, Langer R. 1996. Polymer-based drug delivery to the brain. *Sci. Am.* 3:52–61
51. Domb AJ, Cravalho EG, Langer R. 1988. The synthesis of poly(hydroxamic) from poly(acrylamide). *J. Polym. Sci.* 26:2623–30
52. Lendlein A, Langer R. 2002. Biodegradable, elastic shape-memory polymers for potential biomedical applications. *Science* 296:1673–76

53. Lendlein A, Jiang H, Jünger O, Langer R. 2005. Light-induced shape-memory polymers. *Nature* 434:879–82
54. Zelikin AN, Lynn DM, Farhadi J, Martin I, Shastri V, Langer R. 2002. Erodible conducting polymers for potential biomedical applications. *Angew. Chem.* 41:141–44
55. Lahann J, Mitragotri S, Tran T-N, Kaido H, Sundaran J, et al. 2003. A reversibly switching surface. *Science* 299:371–74
56. Lynn DM, Langer R. 2000. Degradable poly(β-amino esters): synthesis, characterization, and self-assembly with plasmid DNA. *J. Am. Chem. Soc.* 122:10761–68
57. Akinc A, Zumbuehl A, Goldberg M, Leshchiner ES, Busini V, et al. 2008. A combinatorial library of lipid-like materials for delivery of RNAi therapeutics. *Nat. Biotechnol.* 26:561–69
58. Dahlman JE, Barnes C, Khan OF, Thirio A, Jhunjunwala S, et al. 2014. *In vivo* endothelial siRNA delivery using polymeric nanoparticles with low molecular weight. *Nat. Nanotechnol.* 9:648–55
59. Edwards DA, Hanes J, Caponetti G, Hrkach J, Ben-Jebria A, et al. 1997. Large porous particles for pulmonary drug delivery. *Science* 276:1868–71
60. Levy D, Kost J, Meshulam Y, Langer R. 1989. Effect of ultrasound on transdermal drug delivery to rats and guinea pigs. *J. Clin. Investig.* 83:2074–78
61. Mitragotri S, Blankschtein D, Langer R. 1995. Ultrasound-mediated transdermal protein delivery. *Science* 269:850–53
62. Johnson ME, Blankschtein D, Langer R. 1997. Evaluation of solute permeation through the stratum corneum: lateral bilayer diffusion as the primary transport mechanism. *J. Pharm. Sci.* 86:1162–72
63. Tang H, Mitragotri S, Blankschtein D, Langer R. 2001. Theoretical description of transdermal transport of hydrophilic permeants: application to low-frequency sonophoresis. *J. Pharm. Sci.* 90:545–68
64. Polat BE, Deen WM, Langer R, Blankschtein D. 2012. A physical mechanism to explain the delivery of chemical penetration enhancers into skin during transdermal sonophoresis: insight into the observed synergism. *J. Control. Release* 158:250–60
65. Kost J, Mitragotri S, Gabbay R, Pishko M, Langer R. 2000. Noninvasive blood glucose measurement using ultrasound. *Nat. Med.* 6:347–50
66. Prausnitz MR, Bose VG, Langer R, Weaver JC. 1993. Electroporation of mammalian skin: a new mechanism to enhance transdermal drug delivery. *PNAS* 90:10504–8
67. Prausnitz MR, Seddick DS, Kon AA, Bose VG, Frankenburg S, et al. 1993. Methods for *in vivo* tissue electroporation using surface electrodes. *Drug Deliv.* 1:125–31
68. Prausnitz MR, Pliquett U, Langer R, Weaver JC. 1994. Rapid temporal control of transdermal drug delivery by electroporation. *Pharm. Res.* 11:1834–37
69. Prausnitz MR, Corbett JD, Gimm JA, Golan DE, Langer R, Weaver JC. 1995. Millisecond measurement of transport during and after an electroporation pulse. *Biophys. J.* 68:1864–70
70. Prausnitz MR, Gimm JA, Guy RH, Langer R, Weaver JC, Cullander C. 1996. Imaging regions of transport across human stratum corneum during high voltage and low-voltage exposures. *J. Pharm. Sci.* 85:1363–70
71. Prausnitz MR, Lee CS, Liu CH, Pang JC, Singh T-P, et al. 1996. Transdermal transport efficiency during skin electroporation and iontophoresis. *J. Control. Release* 38:205–17
72. Mitragotri S. 2013. Engineering approaches to transdermal drug delivery: a tribute to contributions of Prof. Robert Langer. *Skin Pharmacol. Physiol.* 26:263–76
73. Edwards D, Langer R. 1994. A linear theory of transdermal transport phenomena. *J. Pharm. Sci.* 83:1315–34
74. Johnson ME, Berk DA, Blankschtein D, Golan DE, Jain RK, Langer RS. 1996. Lateral diffusion of small compounds in human stratum corneum and model lipid bilayer systems. *Biophys. J.* 71:2656–68
75. Preis I, Langer RS. 1979. A single-step immunization by sustained antigen release. *J. Immunol. Methods* 28:193–97
76. McHugh KJ, Nguyen TD, Linehan AR, Yang D, Behrens AM. 2017. Fabrication of fillable microparticles and other complex 3D microstructures. *Science* 357:1138–42
77. Bellinger AM, Jafari M, Grant TM, Zhang S, Slater HC, et al. 2016. Oral, ultra-long-lasting drug delivery: application toward malaria elimination goals. *Sci. Transl. Med.* 4:365ra157

78. Kirtane AR, Abouzid O, Minahan D, Bensel T, Hill AL, et al. 2018. Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy. *Nat. Commun.* 9:2
79. Abramson A, Caffarel-Salvador E, Khang M, Dellal D, Silverstein D, et al. 2019. An ingestible self-orienting systems for oral delivery of macromolecules. *Science* 363:611–15
80. Abramson A, Frederiksen MR, Vegge A, Jense B, Poulsen M, et al. 2021. Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors. *Nat. Biotechnol.* 40:103–9
81. Abramson A, Kirtane A, Shi Y, Zhong G, Collins JE, et al. 2022. Oral mRNA delivery using capsule-mediated gastrointestinal tissue injections. *Matter* 5(3):975–87
82. Anselmo AC, Xu X, Buerkli S, Zeng Y, Tang W, et al. 2019. A heat-stable microparticle platform for oral micronutrient delivery. *Sci. Transl. Med.* 11(518):eaaw3680
83. Tang W, Zhuang J, Anselmo AC, Xu X, Duan A, et al. 2022. Enhanced stability and clinical absorption of a new form of encapsulated vitamin A for food fortification. *PNAS* 119(51):e2211534119
84. Lavin A, Sung C, Klibanov AM, Langer R. 1985. Enzymatic removal of bilirubin from blood: a potential treatment for neonatal jaundice. *Science* 230:543–46
85. Labeque R, Mullon CJ, Ferreira JP, Lees RS, Langer R. 1993. Enzymatic modification of plasma low density lipoproteins in rabbits: a potential treatment for hypercholesterolemia. *PNAS* 90:3476–80
86. Shefer S, Breslau J, Langer R. 1995. Computer simulation of LDL removal in the presence of a bioreactor containing phospholipase A2. *Biotechnol. Prog.* 11:133–39
87. Frank-Kamenetsky M, Grefhorst A, Anderson A, Racie T, Bramlage B, et al. 2008. Therapeutic RNAi targeting PCSK9 acutely lowers plasma cholesterol in rodents and LDL cholesterol in nonhuman primates, *PNAS* 105:11915–20
88. Ameer G, Grovender E, Ploegh H, Ting D, Owen W, et al. 2001. A novel immunoadsorption device for removing β_2-microglobulin from whole blood. *Kidney Int.* 59:1544–50
89. Galliher PM, Cooney CL, Langer R, Linhardt R. 1981. Heparinase production by *Flavobacterium heparinum*. *Appl. Environ. Microbiol.* 41:360–65
90. Yang VC, Linhardt RJ, Bernstein H, Cooney CL, Langer R. 1985. Purification and characterization of heparinase from *Flavobacterium heparinum*. *J. Biol. Chem.* 260:1849–57
91. Sasisekharan R, Bulmer M, Moremen KW, Cooney CL, Langer R. 1993. Cloning and expression of heparinase I gene from *Flavobacterium heparinum*. *PNAS* 90:3660–64
92. Langer R, Linhardt RJ, Galliher PM, Flanagan MM, Cooney CL, Klein MD. 1982. A system for heparin removal. In *Biomaterials: Interfacial Phenomena and Applications*, ed. S Cooper, A Hoffman, N Peppas, B Rattner, pp. 493–509. Adv. Chem. Ser. Washington, DC: Am. Chem. Soc.
93. Venkataraman G, Shriver Z, Raman R, Sasisekharan R. 1999. Sequencing complex polysaccharides. *Science* 286(5439):537–42
94. Guerrini M, Beccati D, Shriver Z, Naggi A, Viswanathan K, et al. 2008. Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events. *Nat. Biotechnol.* 26:669–75
95. Kishimoto T, Viswanathan K, Ganguly T, Elankumaran S, Smith S, et al. 2008. Contaminated heparin associated with adverse clinical events and activation of the contact system. *New Engl. J. Med.* 358:2457–67
96. Blossom DB, Kallen AJ, Patel PR, Elward A, Robinson L, et al. 2008. Outbreak of adverse reactions associated with contaminated heparin. *New Engl. J. Med.* 359:2674–84
97. Barrera DA, Zylstra E, Lansbury PT Jr., Langer R. 1993. Synthesis and RGD peptide modification of a new biodegradable copolymer system: poly(lactic acid-*co*-lysine). *J. Am. Chem. Soc.* 115:11010–11
98. Wang Y, Ameer GA, Sheppard BJ, Langer R. 2002. A tough biodegradable elastomer. *Nat. Biotechnol.* 20:602–6
99. Shastri VP, Martin I, Langer R. 2002. Macroporous polymer foams by hydrocarbon templating. *PNAS* 97:1970–75
100. Mikos AG, Bao Y, Cima LG, Ingber DE, Vacanti JP, Langer R. 1993. Preparation of poly(glycolic acid) bonded fiber structures for cell attachment and transplantation. *J. Biomed. Mater. Res.* 27:183–89
101. Mikos A, Sarakinos G, Lyman MD, Ingber DE, Vacanti JO, Langer R. et al. 1993. Prevascularization of biodegradable polymer scaffolds for hepatocyte transplantation. *Biotechnol. Bioeng.* 42:716–23

102. Mikos AG, Thornsen AJ, Czerwonka LA, Bao Y, Langer R, et al. 1994. Preparation and characterization of poly(L-lactic acid) foams. *Polymer* 35:1068–77
103. Mooney DJ, Mazzoni CL, Breuer C, McNamara K, Hern D, et al. 1996. Stabilized polyglycolic acid fibre-based devices for tissue engineering. *Biomaterials* 17:115–24
104. Vacanti JP, Morse MA, Saltzman WM, Domb AJ, Perez-Atayde A, Langer R. 1988. Selective cell transplantation using bioabsorbable artificial polymers as matrices. *J. Pediatr. Surg.* 23:3–9
105. Pearson H. 2009. Profile: being Bob Langer. *Nature* 458:22–24
106. Niklason LE, Gao J, Abbott WM, Hirschi KK, Houser S, et al. 1999. Functional arteries grown in vitro. *Science* 284:489–93
107. Lawson JH, Glickman MH, Ilzecki M, Jakimowicz T, Jaroszynski A, et al. 2016. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. *Lancet* 387(10032):2026–34
108. Teng YD, Lavik EB, Qu X, Park KI, Ourednik J, et al. 2002. Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. *PNAS* 99:3024–29
109. Levenberg S, Rouwkema J, Macdonald M, Garfein ES, Kohane DS, et al. 2005. Engineering vascularized skeletal muscle tissue. *Nat. Biotechnol.* 23:879–84
110. Engelmayr GC Jr., Cheng M, Bettinger CJ, Borenstein JT, Langer R, Freed LE. 2008. Accordian-like honeycombs for tissue engineering cardiac anisotropy. *Nat. Mater.* 7:1003–10
111. Mei Y, Saha K, Bogatyrev SR, Yang J, Hook AL, et al. 2010. Combinatorial development of biomaterials for clonal growth of human pluripotent stem cells. *Nat. Mater.* 9:768–78
112. Hansbrough JF, Doré C, Hansbrough WB. 1992. Clinical trials of a living dermal tissue replacement placed beneath meshed, split-thickness skin grafts on excised burn wounds. *J. Burn Care Rehabil.* 13:519–29
113. Stannett VT, Koros WJ, Paul DR, Lonsdale HK, Baker RW. 1979. Recent advances in membrane and science technology. *Adv. Polym. Sci.* 32:69–121
114. Langer R. 2013. A personal account of translating discoveries in an academic lab. *Nat. Biotechnol.* 31:487–89
115. Prokesh S. 2017. The Edison of medicine. *Harvard Business Review*, March–April. **https://hbr.org/2017/03/the-edison-of-medicine**
116. Langer R, Vacanti J. 1993. Tissue engineering. *Science* 260:920–26