A Conversation with Robert Langer: Pioneering Biomedical Scientist and Engineer

Prof. Robert Langer in his office at MIT. Reproduced with permission. Copyright 2005 Stu Rosner Photography.

I met with Prof. Robert Langer at his office at MIT last month. We discussed his approaches to science and the obstacles one faces in striking out in new directions.

PSW: You took a very unusual path for a chemical engineer and redefined what chemical engineers can do. When you started your career, how did you get advice and inspiration?

Robert Langer: When I got done with my chemical engineering degree, most of my colleagues went into the petrochemical industry and I didn't want to do that. I ended up getting a job in a surgery department with Judah Folkman. For me that was wonderful. It gave me an opportunity to learn a lot about medicine and gave me a lot of ideas. He was also a great person to give advice.

PSW: Did you have a background in biology at that time, or was that the starting point?

Robert Langer: I really had very little background in biology. I had taken a 10th grade class in biology. I did do my Ph.D. thesis in a biological area, "Enzymatic Regeneration of ATP,"[1] but I would not say that I had much of a background in biology.

PSW: When you train students now, do you have a particular cross-training regime for them, or are there particular areas you suggest, "Why don't you learn what you can in those areas?"

Robert Langer: I think it depends at what stage [of the student]. I still feel the most important thing for students to learn is the fundamentals, when they take classes and things like that. I think when they do research, you want them to learn how to attack a problem. I think those two things are *very* different. I would strongly emphasize classes in fundamentals, but in research, I think it is very important to have a lot of interdisciplinary training. Our lab does a lot of that.

PSW: How do you choose a particular problem?

Robert Langer: I think of things that I think will have a big impact on the world, either because of their basic nature or because of their applied nature. Either one is okay. The major thing is that I feel it will be able to do something that really can—hopefully, if we're successful—have a big impact.

PSW: How do you choose the people both for your laboratory and associated with those particular problems?

Robert Langer: For graduate students, of course MIT has their own procedures for admitting them, and that is good; that does a lot of filtering. I look for people who are highly motivated, who are somewhat independent, who really want to do work that will have high impact.

For postdocs, we get thousands of applications, and there, I look for people who have a strong publication record in good journals, often very good recommendations from people I know, went to good schools, things like that.

PSW: With particular backgrounds?

Robert Langer: It doesn't matter. I look for the best athlete.

PSW: When you first started working on controlled-release polymers, what was your specific inspiration?

Robert Langer: When I first started working in controlled-release polymers, it was to solve this problem of angiogenesis inhibition. I was working with Dr. Folkman as a postdoc and we were trying to isolate this molecule. It is actually the first molecule that could stop blood vessel growth in the body,[2] which was quite controversial at the time.

To hear Prof. Langer's advice to young scientists, please visit us at the audio page of http://www.acsnano.org/.

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The assay we wanted to develop was in the eye of a rabbit, to look at blood vessels.[3] What we wanted to do was to put a tumor in the eye, and if you put a tumor in the eye, over a month or two, blood vessels would form and they would grow, and you could actually quantitate the rate of their growth. The question was, "How could you develop an assay to see if you were stopping that vessel growth?" I wanted to have a slow-release polymer[4] that I could put in the eye that would: (A) not cause any harm to the eye (which wasn't easy), and (B) deliver large molecules (many of these inhibitors were macromolecules). That's how I got started.

PSW: When you visited us at Penn State, you gave a talk describing work on controlled release from a patch that was put in the brain to cure brain cancer. You went through what led up to that, your strategy, and your unsuccessful attempts at funding. Can you recount that for our readers?

Robert Langer: The paradigm for polymer development for most of the 20th century was more driven by clinicians who would take materials that existed in their house, but somehow resembled the organ or tissue they wanted to fix, and they'd use it in the body. A couple of examples: the material in the artificial heart was originally a lady's girdle material because it had a good flex life. One of the materials in breast implants was a mattress stuffing (for reasons you could probably think of). I started thinking, as a chemical engineer, maybe we should think about *design*. Maybe we should ask the question, "What do you really want in a biomaterial from an engineering standpoint, from a chemistry standpoint, from a biology standpoint?" Then, could we synthesize it from first principles? One of the applications later on that we thought about was brain cancer.

When we first proposed it, we sent the grant in to the NIH [National Institutes of Health] and they said we couldn't synthesize the polymers. I had a graduate student at the time, Howie Rosen. Howie later became president of ALZA Corp. [acquired in 2001 by Johnson & Johnson]; he's [now] a member of the National Academy of Engineering, but he was a graduate student with me then and he synthesized [the polymers].[5] Then, we sent [the proposal] back after we synthesized them, and the reviewer said, "Well, they'll react with whatever drug you put in." So, I had another couple of postdocs—Bob Linhardt, who is now the Senior Constellation Professor of Biocatalysis and Metabolic Engineering at the Rensselaer Polytechnic Institute and Kam Leong who is the James Duke Professor of the Departments of Biomedical Engineering and Surgery at Duke University—and they addressed that.[6,7] We sent it back in, and the reviewers said, "Well, the polymers are low molecular weight and they'll break up in the body. Still won't work, still shouldn't fund it." I had another couple of postdocs—particularly Avi Domb, who later would become Chairman [Lionel Jacobson Chair] of Medicinal Chemistry at Hebrew University and also Edith Mathiowitz was around the lab at that time helping on various things; now she's a Professor [of Medical Science and Engineering] at Brown University—they addressed that.[8–10] The next time we sent the grant in, the [reviewers] said [the NIH] still shouldn't fund it because, "You're putting new materials in people; they'll certainly be toxic." I had another graduate student, Cato Laurencin (Cato is now Dean, University of Connecticut School of Medicine; he was elected to the Institute of Medicine of the National Academy of Sciences a few years ago), and he showed that they were quite safe.[11]

Actually, I should point out that we built this on good science. One of the people who helped me figure out that these probably would be safe was Michael Marletta, who is now Chairman of the Department of Chemistry at the University of California, Berkeley. He was a colleague at MIT with me at the time, and we tried to lay a good foundation for this. But many of the reviewers still said we hadn't proven it. Anyway, Cato showed that they were safe. In 1998, the drug "didn't diffuse far enough." Then, people were concerned about manufacturing. They were concerned about everything, so they never wanted to fund us. But eventually, the FDA [Food and Drug Administration] approved it.

> **I think of things that I think will have a big impact on the world, either because of their basic nature or because of their applied nature. Either one is okay.**

It's helped tens of thousands, maybe hundreds of thousands of people around the world. Maybe even more importantly, it showed a couple of other scientific things: (1) you could create new materials and bring them to patients, and (2) that you could use what I'll call "localized polymer chemotherapy", which has become useful not only in cancer treatments but in interventional cardiology such as drug-eluting stents. That's become an enormous area, and I think there will be lots of other areas where it will be useful as well, and is being used by clinicians and scientists.

I think it's really hard. I think that when funding is tight, people look for why things won't work rather than what the benefits are if they do work. Second, with big ideas—generally, my experience is there is a lot of small-mindedness.

I still remember in 1978, I sent a grant in and I got turned down. Then, I sent it back in and they said "Well, the strength of this proposal is the preliminary results as judged by his 12 papers in this," and so then they funded it. But fast-forward to this morning, when I got a NIH study section review back and they said "this lab has been enormously productive, they've done all these great things, and the idea he proposes is really important, it could change a lot of things, but we want him to have a lot more preliminary results." Basically, I re-

ally felt it wasn't right to do the same old thing over and over again the fifth or sixth time. I hoped by this time I had built a good enough reputation. I guess I haven't! I guess the fact is that they probably want 12 more papers, and then maybe they'll consider it.

I think the nature of funding agencies, or rather reviewers, is unfortunately a lot of conservatism.

PSW: Do you see some way that that history would not be repeated? Do you see some solution in terms of funding for such work?

Robert Langer: There are a couple of things that would help: (1) more funding in general from the government, and (2) very clear instructions from study chairpersons or the NIH itself telling people that they really need to do this. But, I don't see it happening. I've been on these study sections myself and I think it is unlikely. I do think the review process (at least at the NIH) is good in the sense that you get feedback. I'm glad to know what they don't like. Sometimes a lot of agencies will give you grant reviews or you apply for a grant and you have no idea what they don't like. At least if I know that I have to do 12 papers, I'll go do 12 papers. Eventually, hopefully, we'll get it. That is what I've done throughout my career and I'm sure others have, too. I think it's human nature.

PSW: How do you bring your lab up to that point, and how do you advise younger principal investigators who don't have the laboratory operation that you do?

Robert Langer: We work hard on our grants, and we send in a number of them, and every time I get the reviews back, I try to do a couple of things. If I get a grant, I try to do the very best job I can. We do publish lots of papers in high-quality journals. Every time I get [a grant approved], I do what I can to show the study section, show the NIH, that we're going to use their money carefully. I believe we do; almost every time I've gotten it, they've said we've done a very good job.

I think the second thing is, if they do make objections, we address those objections—whether it's experiments, more papers, more collaborators—whatever it is. When you're writing a grant, you're playing in somebody else's ballpark; you're not setting the rules. I listen to what they say and try to do the best I can.

I also do some other things. We have been fortunate that for some of our work, when it gets to a certain stage and it's really specialized (I can't predict in advance which ones it'll be), we have gotten substantial grants from companies from licenses to our patents. It's happened from time to time. We've gotten substantial grants from foundations, from various places. We do what we can to try to get funding.

I recommend that to all the young people: both having people go over and over their grants to get the best reviews possible before they send it in, and I recommend people patenting things.

I recommend people writing lots of grants. In fact, when I was a graduate student, I helped start a school for poor kids, and it was really hard to get money for that. What I learned is that there are a lot of places that you can find money, sometimes very unusual places. One part of the battle was finding where money was. The second part of the battle was once you found out where it was, writing a grant good enough to get it. But both parts are important, and I think a lot of times people aren't always aware that sometimes you can find money in unusual places. I recommend to everybody that they should look.

PSW: It sounds like persistence plays on top of that in a very important way.

Robert Langer: I'm very persistent. I don't give up and I tell everybody here not to give up!

PSW: Do you have a particular strategy for patents and commercialization? You have obviously been extremely successful!

Robert Langer: I do have a strategy in the sense that we put science first. We are going to publish whatever we do. But, I've found that a lot of publications, as we get ready to write them, also can be the body of a very good patent. I work with lawyers closely to come up with claims that will capture the essence of those papers and of our scientific discoveries or findings.

Between MIT and venture capitalists I know, we've licensed these things to companies. I've been very active in that. A lot of students who graduate from here get involved in these companies. A number of them have started up companies, and I've helped them do that. That has led to a great deal of commercialization, and again it goes back to what I said about impact. I think we can only do so much in the laboratory. If we want to get things to help people, we need to get companies to do that. A lot of the students who graduate from here become professors. I think 180−200 of my students, my trainees, are now professors. But probably an equal number have gotten involved in start-up companies, and other companies, and have been very active in taking technology, creating it, and bringing it to the public. The patents have been key. You couldn't raise the money without the patents.

PSW: Do you stay involved?

Robert Langer: I do. Not forever, but I've helped a lot in terms of getting a number of them started, being on the board, helping with the science. Even though I've had a lot of students, I'm still very close to pretty much all of them. I keep talking to them, and so I would say, yes.

PSW: Our students are like another family.

Robert Langer: They are! You're absolutely right; I view students that way. I consider it a big, extended family. It means a tremendous amount to me that they be happy and do well.

PSW: What are you most excited about in the lab now?

Robert Langer: I'm very excited about a couple of things. Nanotechnology is very high on our list. I'm particularly interested in new ways of treating cancer and other diseases. One of the really important things at the nanoscale

is being able to do targeted drug delivery of both conventional therapeutics as well as new therapeutics like siRNA [small interfering RNA][12−14] and DNA. I'm very excited about making nanoparticles such that we can target cancer cells and other cells [Figure 1].[15,16] That to me is one of the things I would certainly like to see at the nanoscale. We're working hard at doing it.[17−19]

PSW: Do you see some missing piece that would connect the dots?

Robert Langer: I think there are probably a lot of missing pieces. Some of it is just having a deep enough understanding of how to go about doing these things. Some of it is not having exactly the right tools.

We're doing some types of tool development, but it is more aimed at doing things at the nanoscale to follow cancer development. Michael Cima, Ralph Weissleder, and I, and others have some joint projects where we are using nanoparticles to help with imaging and diagnostics of cancer, cancer progression, and disease progression.[20]

One of the areas Ralph has developed is magnetic nanoparticles,[21] and Michael and I have been working on ways of putting them into microchips with little nanowells.[22] Theoretically, they can stay in the body indefinitely and monitor progression of the disease by differing MRI [magnetic resonance imaging] signals, depending on what they might bind to (or not bind to) and what is present in the body—a long-term readout.

PSW: How stable are those?

Robert Langer: They're reasonably stable, but that's one of the areas that we're working on—making them more stable over time.

PSW: What do you see coming up in the next decade in your lab?

Robert Langer: Another area that we are very excited about, in addition to nanotechnology, is this whole area of regenerative medicine and tissue engineering.[23−25] We're doing a lot of work on that. In our case, it has to do with how materials can affect the behavior of cells—stem cells and other cells. Can we combine cells and materials to make new tissues and organs? This is something we have worked on for a number of years, but my hope is that in the next decade, we will make even more progress, and that we'll see even more tissues and organs that will be at a point where they are ready for clinical use (or near-clinical use).

PSW: Is there some path to creating the complex, hierarchical structures that would be in vascularized organs?

Robert Langer: That's a very good question. There are a couple of strategies to create vascularization, but one strategy that we've been working on with Draper Labs and Jeff Borenstein is the idea of microfabrication and nanofabrication, building in a microvasculature.[26] We've published a few papers on that and I think there's more to do.

> One of the really important things at the nanoscale is being able to do targeted drug delivery of both conventional therapeutics as well as new therapeutics like siRNA.

Another approach is to put a growth factor in a controlled-release microsphere/nanosphere that can release a molecule like VEGF [vascular endothelial growth factor] or basic FGFs [fibroblast growth factors] and induce blood vessels to grow into the region. We've been looking at both of these kinds of approaches.

PSW: Is there a way to structure those in the sense of laying out what ultimate pattern one wants?

Robert Langer: Yes, and again, this is where the Draper Labs is very help-

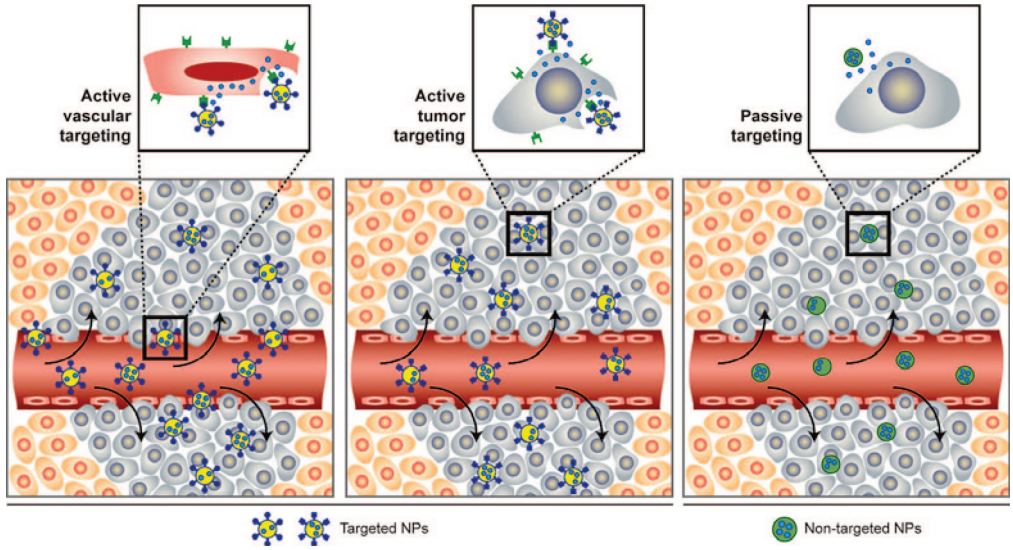

Figure 1. In a recent Perspective, Omid Farokhzad and Robert Langer discussed the impact of nanotechnology on drug delivery.[16] Reproduced from ref 16. Copyright 2009 American Chemical Society.

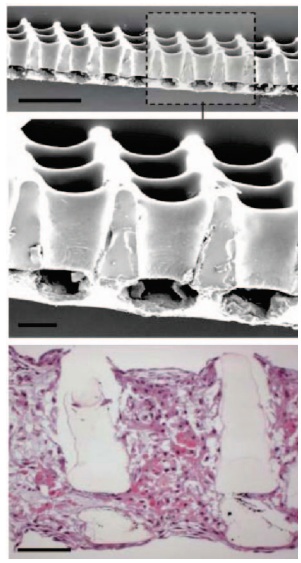

Figure 2. Interconnected three-dimensional networks of pores offer scaffolding for heart cell cultivation. Scanning electron micrographs are shown in the top and middle frames with scale bars of 500 and 100 μm, respectively. The bottom frame shows an optical micrograph of stained, cultured neonatal rat heart cells grown in the scaffold, scale bar 100 μm. Reproduced with permission from ref 28. Copyright 2008 Macmillan Publishers Ltd. (http://www.nature.com/nmat).

ful. The way one structures these is with all these kinds of microfabrication approaches that can be used and developed.[27] You can structure what you want. Jeff is very good at that kind of thing.

PSW: Are those largely two-dimensional or are they built up?

Robert Langer: For some of the templates we've been working on, we can actually make them 3D. There are ways to stack things, ways to print things, and ways to create channels. We've been creating 3D structures with Jeff [Figure 2].[28]

PSW: What are your ultimate goals?

Robert Langer: Well, my ultimate goals probably haven't changed very much. I think there are three: (1) to invent things that I think will change the world, (2) to take the things we've already done and get them out to the public to do good for people, and (3) to train the best people in the world, the leaders that are going to be the bioengineers of the future that will train others all over the world. That's what I've tried to do and I love it. I want to do that more and more, because I think that's the most important thing I can do.

> Dream big dreams, and try to do whatever you can to fulfill those dreams.

PSW: How do you divide your time on a day-to-day basis? You have many, many demands, including me!

Robert Langer: No, no, it's fine! You know, I do all of it. To me that's part of the fun. You do a lot of different things, all of which are important. I view what you're doing as important; I view communicating what we do as important, because hopefully it gets people excited about nanotechnology, about science in general, about engineering.

I have a pretty stacked day. My days could go from early in the morning until 7:30 at night, and when I get home, I'll probably work on a few more things that people in lab have given me.

PSW: What advice do you have for young scientists?

Robert Langer: I have a couple of things. I think it is important to dream big dreams, and to try to do whatever you can to fulfill those dreams. To not give up if things don't go well, because very often they won't and you just have to hang in there.

I think being a scientist is an incredibly rewarding and fulfilling life. It's not necessarily an easy life, but I feel that the personal rewards you get and the satisfaction you get working with students, out of seeing students do well, at seeing your science and discoveries—that is incredibly exciting and rewarding. I think it's a wonderful life.

PSW: What career advice do you give your children?

Robert Langer: My children are 15, 18, and 19. My advice to them is kind of minimal, sort of like what my parents gave to me. I just want them to be happy kids. That said, my oldest son is thinking about business, my daughter is actually interested in chemistry, and my youngest son is interested in computers. I don't know if that's where they'll end up; it's hard for me to know. By far the most important thing is that they be happy. That's what my parents wanted from me; they didn't put a lot of pressure on me. I put it on myself.

I just want them to be happy; that's what I tell them. I do think that part of being happy, sometimes if you do things for others, if you do work that can have an impact and help others, that helps make you happy. I hope that they see that.

[Literature citations and figures were added after our conversation to assist and to direct the reader to relevant publications.]

— Paul S. Weiss

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