



The Royal Academy
of Engineering

NEW FRONTIERS IN DRUG DELIVERY

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on

Thursday, 22 October 2009

Speaker: Professor Robert Langer, MIT Langer Lab

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Welcome and Introduction

Sir Mark Walport

Good afternoon, and welcome. Before we begin, we have the standard housekeeping notices. [*Fire alarm procedure; mobile phones off*].

I am absolutely delighted to be able to welcome Bob Langer on behalf of the Royal Academy of Engineering and the Wellcome Trust. We are absolutely delighted that you are here. A full introduction of Bob would take quite a long time because he has had a very spectacular career. It probably says as much as anything to say that he is actually an MIT Institute professor, and there are very, very few of those. He is an engineer who saw the importance and the opportunities in biology very early in his career: he went into the laboratory with Judah Folkman who was working on angiogenesis and the rest, as they say, is history. Robert has been awarded the Gairdner Prize and he is a fellow of each of the three American national academies, which is an extremely rare event. He is here because he won the 2008 Millennium Prize, which is an extremely large technology prize awarded by Finland.

Robert encapsulates interdisciplinarity in a single person. We tend to think about interdisciplinarity in terms of bringing teams of people with different skills together but it is not so possible for people to bring the interdisciplinary skills within themselves but Bob epitomises that. He became interested in the delivery of compounds following his work with Judah Folkman and so we are delighted that today he is speaking to us on New Frontiers in Drug Delivery.

Bob, you are very welcome, and we look forward to hearing what you have to say.
[*Applause*]

NEW DIRECTIONS IN DRUG DELIVERY

**Dr Robert S Langer
David H. Koch Institute Professor
Massachusetts Institute of Technology**

Thank you very much. It is a pleasure for me to be here today. I was both honoured and very surprised when I was fortunate enough to win the Millennium Prize.

This afternoon, I would start by saying that people might ask how an engineer even got into the medical area, certainly in the 1970s. I will start with that and then I will go over some of our early work on drug delivery, leading up to other things that we did in drug delivery. I will end up by saying just a little about how we try to use materials not only for drug delivery but for the delivery of cells, to create what we called 'engineered tissues', or regenerative medicine.

I will just make this a little autobiographical. I was an undergraduate chemical engineer at Cornell and got my graduate degree in chemical engineering at MIT. I gained that in 1974 and in the United States in 1973 and 1974 you will have heard about an energy crisis. As a consequence, if you had a car, you would not only see the price of gas keep going up but, at least in Boston where I lived, if you had a car, you had to wait in line for two hours to get your gas, which was not very pleasant. The other consequence of that was that, if you were a chemical engineer, there were lots of job offers. I actually had four job offers from Exxon alone, and one from Shell. Pretty much all my colleagues in chemical engineering in 1974 went into the petrochemical industry.

I remember having an interview at Exxon at Baton Rouge, Louisiana. When I went there, one of the engineers said to me at the interview that if you could increase the yield of this petrochemical by 0.01 per cent, that would be wonderful and it would be worth billions of dollars. I flew back to Boston that night, thinking to myself that I really did not want to do that. [Laughter]

After all that interviewing and everything, I was trying to think about what I wanted to do with my life. One of the things I had done as a graduate student at MIT was to help start a school for poor children and I had become very involved in developing a chemistry curriculum. One day I saw an ad in *Chemical Engineering News*, which is one of the chemistry journals, for an assistant professor to develop the chemistry curriculum at the City College of New York. I was very excited about that and wrote to them about the position, but

they did not reply to me. However, I liked the idea and so I then kept looking for other ads for similar jobs as someone who would develop chemistry curricula. I actually found about 30 different schools around the United States which had such positions and wrote to all of them, but none replied. I guess that even if you went to MIT and you had studied chemical engineering, you were not good enough to receive a letter back. Some of these schools, by the way, weren't even that good. At any rate, I wasn't doing very well at that.

Another thought I had, and something I was very interested in, was that I always wanted to help people, and I wondered whether I could use my chemical engineering background to help people in the health area. I therefore wrote to a lot of hospitals and medical schools, but they did not reply to me either. Then one day, however, one of the post docs in my laboratory told me that there was a surgeon in Boston named Judah Folkman and said, 'sometimes he takes unusual people.' [Laughter] So I wrote to Dr Folkman and he offered me a position.

[Slide]

The first slide shows a picture that came out in the *New York Times* in 1971, describing Dr Folkman's theory at the time. What Dr Folkman had proposed – and at this point, even in 1974 it was still a theory – was that tumour cells would somehow become abnormal. They could grow to about 1mm in size, but he said they would not grow beyond that unless they had blood vessels which enabled them to grow bigger. The idea was that it was some kind of a nutrition problem. They would not grow beyond, say, 10^6 cells (1 million cells) because cells in the centre had no way to obtain nutrients or get rid of waste. Cells on the outside, however, could proliferate – but you would have this equilibrium where these cells on the inside would die, and those on the outside would live.

Dr Folkman said that tumours made a substance which he called TAF (tumour angiogenesis factor). The idea was that in the blood vessels that were in your body, the endothelial cells are normally incredibly quiescent and they do not divide or anything. However, under certain conditions, as in the case of cancer, they do divide actually quite rapidly and form new blood vessels. He said that that could initiate a second phase of tumour development, where new blood vessels sprout from the surrounding capillaries, leading to this second vascular phase. The tumour grows larger and larger and can spread through the blood vessels, metastasise and kill. Dr Folkman wondered whether you could stop the blood vessels from growing by initiating this anti-angiogenesis.

For my job, he wanted me to see whether I could actually isolate what would at that time be the first angiogenesis inhibitor. Could we actually prove this theory, and could we stop the blood vessels from growing?

One of the things we talked about using was cartilage, which is a tissue in your nose, your knee and other places, and it does not have blood vessels. We thought that perhaps we could find a diffusible substance in cartilage that might stop blood vessels from growing. One challenge I found was getting enough cartilage. I originally started using rabbits but I could not get enough cartilage there, so then I scaled up – that is one of the things they teach you in engineering - to scale up, and so I went to cows. Even with a single cow, however, I could not do that well. I then thought, where do all the cows go? I found that they went to a slaughterhouse, which then sent them to a meat packing place in South Boston.

[Photo – bone]

I therefore made an arrangement with this meat packing place so that I would have all their bones. I took the bones and probably spent 40 hours a week scraping meat off them. This, by the way, is one of the bones that I scraped – there would normally be a lot of meat on it, but I would scrape all of the meat away because that was the first step of the purification. It would then look like this [on slide]; I would then slice off some of the cartilage and that is what I would use as a basis.

There are two problems I should point out, when trying to do this - to isolate an angiogenesis inhibitor. The first is to isolate the substance but another – as anyone who has done biological research will realise – is, what is your bio-assay? That was actually the biggest challenge. So I would try isolating all these different things. I would take the cartilage and put it in different extraction solutions, like guanidine hydrochloride, and I would try to purify it and so on. But then, what would I do with the different fractions? What we wanted to do was to develop a bioassay.

[Slide]

The bio-assay we decided to use is shown here. Of course, we had not developed it yet, but this was what we wanted to do. The idea was that we could use the eye of a rabbit. Normally, the cornea has no blood vessels but it turns out that, if you put a tumour in the eye, blood vessels will grow from the edge of the cornea to the tumour. We wondered what would happen if we could put a polymer in, which would be inert in the eye, but which could release the different molecules in cartilage. Many of the molecules in cartilage were fairly large, like proteins, peptides and glycoproteins, so we wanted a material that could release molecules of virtually any size. This assay would probably take at least 30 days. So that is what we wanted to do.

I will come back to that point in a few minutes, but I should also add that it turned out when we did this in 1974, that it was pretty much for this reason alone: to solve the angiogenesis problem.

[Slide: List]

However, what happened in the mid- to late-1970s, was that the whole area of biotechnology and genetic engineering emerged and so, for the first time, people would begin making lots of different macromolecular drugs. But those molecules faced serious delivery challenges. If you tried to swallow them or put them in a patch, they were too big to go through the intestine or the skin. If you injected large molecules, they often had very short lifetimes. You can imagine that, if they had such short lifetimes, if you injected them in the body, you would have to keep injecting every few minutes. What we were looking for, therefore, was a way to give them that would enable them to be continuously released, but to protect them from harm.

Dr Folkman was on the advisory board of a company, Alza, which was really the only company working in this area. He went to see them, and we talked to other people but, basically, no matter who you talked to, people said this was not a solvable problem.

[Slide – quotation]

If you look in the scientific literature from the 1970s, you often see quotes like this one:

“The agent to be released is a small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g. proteins, could be released because of their extremely small permeation rates through polymers.”

In fact, the only real advantage that Dr Folkman and I had is that we just did not know that. In fact, this quote was actually very helpful to us in getting some of our early patents in this field.

I spent several years in the laboratory, experimenting with different techniques – purely empirically – to see whether I could address this. I actually found over 200 different ways to get this not to work. However, I eventually found a way where we could take different hydrophobic polymers – it could be ethylene vinyl acetate or lactic glycolic acid copolymer or be any hydrophobic polymer. We would dissolve it in organic solvents and mix in the molecule – the drug – and then slowly evaporate off the solvent.

[Slide]

We could make little microspheres. Here is a picture of one, and here is one cut in half. This was published in *Nature* 33 years ago, when we showed that you could release molecules of almost any size for over 100 days. We also found later that we could work out designs where one could achieve constant release.

[Slide – graph]

Here is an example of releasing albumen over 50 days, at steady release.

As everybody here knows, if you are in the academic world, you end up having to give a lot of talks. In any week now, I probably give five or six talks but in 1974 I never gave many talks. In 1976, however, I was asked to give a talk at a big scientific meeting in the middle of Michigan and this was the first scientific talk I had ever been asked to give. The only talk I had given prior to that had been in eighth grade, and that talk had not gone very well.

In eighth grade, I had to give a speech lasting a minute and a half to my class. I wrote it out on a sheet of paper and, two nights before the talk, I stood in front of my parents' mirror for two hours, reciting the talk. The night before, I stood in front of it for four hours, reciting the talk. The day came for me to give my talk. I got up in front of my eighth grade class and I started reciting it. I did not bring the sheet of paper, but I should have done that. For the first minute and two seconds, it was going okay but then all of a sudden, I just could not remember the next word I was going to say. So I stood up there for a further minute and just froze – I said nothing. Finally, my eighth grade teacher told me to sit down, and did not give me a particularly good grade – I think it was an F. Ever since that, I had always tried to avoid public speaking. However, in the academic world, you just cannot avoid it.

In 1976, I had to give a 20-minute talk so this time I stopped working about two weeks beforehand, and kept reciting the talk over and over into a tape recorder – this was before VCRs or DVDs. Finally the day came, and I was giving this talk in the middle of Michigan. This was 33 years ago, so I had much more hair and it was darker. I was much younger then, giving this talk to a very distinguished group of older chemical engineers, chemists and polymer scientists. I gave the talk and this time I thought I did alright. The 20-minute talk went by and I did not forget much of what I was going to say, and I did not stammer too much.

So, when I had finished this talk, I thought that these older scientists, being nice people – [*Laughter*] (I can always tell if I am talking to a scientific audience, because they always laugh if you say that scientists are nice people). I thought they would want to encourage me, as a young guy. When I had finished, I stepped off the podium and a number of them came up to me and told me they did not believe anything I had just said. They said that these molecules just could not get through these polymers. It really wasn't until three years later that different groups began to repeat what we did, at NIH and elsewhere, that the question shifted. People asked, how could this happen, and how do the large molecules get through?

[Slide – photograph]

To understand that, I had a graduate student, Rajan Bawa, and we would take thin sections of the polymer and cut them with a cryomicrotome. Here, you are looking at a 5-micron thin section of a polymer. There is no drug in it and, if you did a permeability study, you would find that molecules of 300 molecular weight or greater cannot diffuse from one side to the other. So how do the large molecules get through?

If we put a reddish molecule in – and now we are doing this before any release has taken place – we get a phase separation. The polymer is white and the drug is red, so we see this in two distinct phases.

[Slide]

The next question is, what happens if we take a system like this and release it for over a year? What does it look like? What we found is that, if we did a release experiment and then we cut a thin section, left behind where the drug was are these pores and these are large enough so that molecules, even millions of molecular weight, can get through. However, they have tight constrictions between the pores, and the pores are also incredibly winding and tortuous, so that it takes a really long time for the molecules to get through. One analogy I sometimes use when explaining this to people is that, living in Boston as I do, it is rather like driving a car through that city. Boston has what I call ‘very high tortuosity’, whereas most other cities are much easier to get through. Boston, however, has a very intricate porous network, so to speak, with slow release, and that is what you have here.

It turns out that, by various modelling approaches, done by Ron Siegel, Rajan and other people, you can actually make these systems last anywhere from a day to many years, or any time in between.

Having established this as a basis, we and others could now use these for various applications. Larry Brown and Marsha Moses and others began to use these to try to address the cancer problem that I mentioned with Dr Folkman. If we wanted to look at angiogenesis, we would put the tumour – the V2 carcinoma – in the eye. We would put a polymer next to it and then you could either put an inhibitor in, or controls – and we had lots of controls, which were the fractions that did not work.

Rabbit corneal pocket assay

Let me just show you a very positive result as an example. What we found is that if we had this cartilage-derived inhibitor, without the inhibitor, you have these sheets of blood vessels. This is about 30 days after the start of the experiment, but they start to grow from here. You get the sheets of blood vessels growing over the polymer on their way to the

tumour. By contrast, if you have the inhibitor, notice how you do not have the blood vessels going nearly as high. They are much sparser and in fact they avoid the polymer. In fact, this tumour will grow out of the orbit of the eye, while that one never will.

This actually provided several things. First, it enabled us to publish in *Science*, now 33 years ago, the isolation of the very first angiogenesis inhibitor. Secondly, it would establish the bioassays by which all future angiogenesis inhibitors would be isolated.

Angiogenesis inhibitors approved for clinical use

I think it took 28 years from when we published this paper until the first angiogenesis inhibitor to be approved by the FDA. In the last four or five years, however, an enormous number of angiogenesis inhibitors have come on the market. I stopped making the list at 2006, but a great many have been developed and they have become huge blockbusters. Avastin is a drug that is widely used for colorectal and other cancers. We have seen various other drugs also approved.

Not only do we see these angiogenesis inhibitors treating cancer, but there are also other diseases – such as eye diseases where, heretofore, with macular degeneration for example, there was no drug that could treat it. The only way they would treat patients with macular degeneration was by lasers, to do what is called photocoagulation, when you have vascular proliferation. There are now new drugs like Lucentis, which actually reverse this disease. Dr Folkman passed away about a year and a half ago and they noted, when he passed away, that something like about 1.5 million patients a year – and this figure is rising a good deal – now use angiogenesis inhibitors for different medical treatments.

[Slide – Graph – plasma glucose]

You could also use this not only for angiogenesis but it certainly occurred to us and to others that you could use these approaches for delivering other molecules as well. Larry Brown, in our lab, picked insulin just as a model molecule. He made a tiny little aspirin-sized pill, put it in diabetic rats, lowered their blood sugar from 400 to 100mg/dl, and it stayed there for 100 days.

We published these papers in journals like *Science*, *Nature* and so on, but I also wanted this technology to be used medically. To do that, we became involved in various things. We licensed some of our patents to companies, and we taught people from companies and developed collaborations to try to get these used. I even became involved in starting companies myself. Today there are all kinds of new microsphere-based drug delivery systems from companies like Alkermes, and others. This is the work of thousands and thousands of people, but it ends up being very critical because many of these molecules

cannot be delivered orally or by a patch because they are too big, and if you inject they are destroyed immediately. So we really cannot give them to patients. People have tried to give some of these nasally but the bioavailability – the amount that is absorbed – is less than 0.01 per cent.

[Slide – *pharmaceutical products*]

Today, there are numerous clinically used microspheres. This is one developed by Takeda. Originally, these microspheres released luteinising hormone for a month, but now they have them that last for four months. These are little microspheres that you inject. This, today, is the most widely used treatment for advanced prostate cancer or endometriosis. Then there are many others, including different treatments of schizophrenia, alcoholism, human growth hormone and so on. There are new ones being evaluated at the FDA for the treatment of diabetes, for example.

Today, it is clear that you can use this kind of microsphere technology and various people are doing this to make different kinds of controlled release systems. This enables you to deliver a drug for a long time.

Overview of targeted therapies

Another thing people would like to do is not just to deliver it for a long time, but to target it to a particular site in the body. Could you target the drug to a cancer cell? We will now adapt this technique just slightly, to use nanoparticles rather than microparticles, to see whether we can achieve targeting.

[Slide – *targeting molecule*]

Let me just explain why you might want to do that. There actually are a number of targeted therapies, like single molecules, which you can use. However, our thinking, and the thinking of others, is as follows. Let's say you get a single molecule aimed at a target: you have some chance of hitting that target. However, if you could put those molecules in a nanoparticle, you could put in a nanoparticle 1000 to 100,000 molecules and therefore, if you could get the nanoparticle to the target, if you thought about this from the standpoint of shots on goal, you would have much greater ability to hit your target. So we wondered whether we could make nanoparticle conjugates, so that we could put any drug in a nanoparticle and make it go where we wanted.

We published a paper in *Science* in the 1990s, where we made special kinds of nanoparticles. Ruxandra Gref led this work and the idea was that to do nanoparticle targeting you have to do two things. First, you have to avoid the macrophages, and that can be achieved by polyethylene glycol. Secondly, you have to have some type of targeting and

that could be achieved, for example, by using an aptamer, which could be a small piece of RNA, for example. Omid Farokhzad, who was a fellow in my lab and now is a professor at Harvard, actually worked exactly out the right concentration of each of those. You can imagine that this is certainly an engineering challenge: if you had too much of the polyethylene glycol, you would not be able to do targeting, and if you had too much of the aptamer, the particles would be taken up by the macrophages. He worked out the right concentration of these and then, just as a model, we worked on one of these aptamers that would be targeted against the prostate cancer cell line, in particular against a prostate specific membrane antigen.

[Slide: graph – targeted NP]

We made nanoparticles directed against that and we did various *in vitro* studies to optimise these, and then took this into animals. This is what we published in *PNAS* about two years ago. The idea is that if you had a control nanoparticle, the tumour grows; if you have the drug, the tumour grows. However, if you take the drug, docetaxel, and put it in the nanoparticles and inject it in, the tumour goes to zero. These are an N of 7 for all graphs..

You can also see the same thing by looking at the animals themselves. If you have control nanoparticles, the tumour grows and is highly vascularised, and that is also true for the drug. However, with the targeted nanoparticles, you get no tumour and you can see that it is not vascularised. This is something that we are hoping to take into the clinic some time next year, for the treatment of prostate cancer.

Prototype chip device

One always wonders, what else could we do that might be helpful? The systems that I have talked about so far were able to deliver drugs, and they may even be able to target drugs, but I kept wondering whether we could make systems smarter and smarter. One day about 15 years ago, I was watching a TV show on a public broadcasting station, about how microchips were made in the computer industry. When I watched the show I thought to myself that this would be a great way to make a drug delivery system. Again, if you had spent 30 years of your life working on drug delivery systems, perhaps any TV show you saw might make you think that. [Laughter] However, I thought about this and I had this idea of a drug delivery chip.

I contacted Michael Cima, a ceramics expert at MIT, and we came up with this idea. What if we could make a chip which, rather than being a computer chip would be a chemical

chip? The idea is that we would make little wells in the chip, put the drug in those and cover them with gold. These would then just stay like this but, if we activated the gold – and I will talk about that in a moment – then the gold might come off and whatever was beneath it could come out.

[Slide]

John Santini, our graduate student, made these chips. This slide shows an early chip that he made, with 34 wells in the top and 34 in the bottom, and this is shown on the slide against a United States dime. There are little nanowells in the chips, but you could make these chips almost any size or shape. You could make them big, or you could make them injectable, or you could make them degradable. Let me just show you how they work.

Reservoir activation

Here is a single well, covered with gold. This would actually stay in a body – at least in an animal – like this for over a year or perhaps longer.

Reservoir activation (2)

However, if you just apply one volt selectively to this, here is what happens in two seconds. The gold starts to come off and, after 10 seconds, the gold has gone. When you do that, whatever is underneath it comes right out.

One question we looked at was safety: does it cause any toxicity? Jim Anderson from Case Western, who is probably the top biomaterials pathologist in the world, looked at this and found that, even if you took 16,000 times this amount of gold, you would not see damage, at least in the animal tissues, within 24 hours. So, so far, it seems safe, although we are not in patients yet.

Single compound release

John Santini did a couple of studies showing that you could have triggered release. Here, he has put different amount of drug in different wells, which give triggered release at different times.

Multiple compound release

You could also do something like a pharmacy on a chip some day, we think. You could take whatever drugs you need and trigger the release of multiple drugs at different times. John actually started a company on this, too, and a couple of years ago he and his colleagues published this in *Nature Biotech*, having done the following study. They took little chips and put them in dogs for nine months. They took a fairly large molecule, luteinising hormone releasing hormone with a molecular weight of 1200, and put it in these chips. One

of the questions was, would they be encapsulated and so on? They then did release by telemetry – in other words, you could take something like this little device, the same sort of thing you would use to open your garage door, for example, and you could just trigger release whenever you wanted.

That is basically what they did. Our idea is that, some day, they will have a special wrist watch that you could wear, and this could be pre-programmed or turned on whenever you wanted, and it would just do the release. They did that over nine months, and the same amount of drugs came out after nine months as came out after one hour. Some day we hope – and this is much further into the future – that you could not only do delivery but also put sensors on these chips. You could actually make a smart system, sense whatever you want, and then tell the chip how much to deliver.

New Biomaterials

So far, I have talked to you about how you could use existing materials and use engineering to make them do things they could not do before. One of the other things I became curious about, however, was the materials themselves. How do materials find their way into medicine? This was really fascinating to me. I worked at Harvard Medical School and Children's Hospital as a young chemical engineer and I was curious to know: what type of scientists were responsible for enabling materials find their way into the human body? Was it biochemists, or engineers? It turns out that that was not true. Almost always, the way that materials found their way into the human body was that medical doctors were urgently trying to solve a medical problem, so they went to their house to find a material which resembled the organ or tissue they were trying to fix, and then they would use it in a person. That led to some progress but it also led to some problems, as I shall illustrate.

[Slide – list of household materials put to medical use]

Sometimes people see this slide and think it is funny, which to an extent it is, but it is also true. It is remarkable, so let me tell you a few stories. In 1967, some of the clinicians at the NIH in Maryland were trying to make an artificial heart, so they asked, what object has a good flex life like a heart? The answer was a lady's girdle, which was made out of polyether urethane, so that is what they used to make the artificial heart. Anybody who has followed this story will probably know that that is what they started making artificial hearts from in 1967. Today, 42 years later, that is still what it is made of because, once you start down this path from a regulatory standpoint, it is not so easy to change.

Why does the artificial heart not work very well? The biggest problem has been that when blood hits the surface of the artificial heart, the lady's girdle material, it forms a clot sometimes, and then that clot goes to the patient's brain, they have a stroke and may die. However, if you think about it, something that is designed to be a lady's girdle is probably not the optimal blood-contacting material.

This problem pervades all of medicine. Dialysis tubing: sausage casing. Vascular graft – that is the blood vessel, and it was a surgeon in Texas going to a clothes store to see what he could sew well with. Breast implants – one was a lubricant, and the other was actually a mattress stuffing, and you can probably think of the logic.

One of the things we started thinking about was that, rather than taking these materials that were in your house, what if we could ask the question – and this is what engineers do, to make this more of a design problem – what do you really want in a biomaterial from an engineering standpoint, a chemistry standpoint and a biology standpoint? Then, could you synthesize it from first principles?

Bulk erosion

When we started, the only material that was approved by the regulatory authorities was the polyester sutures that were synthetic and degradable. They would degrade by what we would call bulk erosion. They would start by looking like this [*on slide*], then they become spongy, and then they fall apart. If you put a drug in them, then the drug has the potential to burst out as you have this type of catastrophic break-up. That might be OK for some drugs but, if you had a potentially toxic drug like insulin, or an anti-cancer drug, that might not be so good.

Surface erosion

So Jorge Heller, ourselves and others, would say that what you really wanted from an engineering standpoint was not bulk erosion but surface erosion – which would look like this, layer by layer. If you could do this, the drug should not be able to dump out. You would also have other positive features, that you could design to do what you wanted.

Structure of the polymer

How could we make a polymer to do this? This gets into engineering design. I will not go through this in detail, but just give a few design questions. The first question we might ask is, what should cause the polymer to dissolve? Should it be an enzyme, or should it be water? All of you probably have different enzyme levels, but you all have excess water (constant water activity), so we said that if we wanted this to be reproducible, water should be the catalyst.

Then you go to the next question: what should the material be made of? We said that if you wanted to have this kind of surface erosion, it should be made out of building blocks, which we call monomers, that repel water.

Then you go to the next question: if you do that, how will the polymer ever dissolve fast enough? We then went to organic chemistry and tried to work out what chemical bonds would dissolve quickly enough, and we would hypothesise that the anhydride bond was what we wanted. Then we would bring in outstanding chemists and toxicologists, like Michael Marletta, who is now head of Berkeley's Chemistry Department, to come up with the building blocks that they would know would be safe.

[Slide – graph]

Ultimately, we came up with this chemical design. It is a polyanhydride with two monomers. There is this one, which is very hydrophobic, and that one which is slightly less so. We would make polymers out of it and, if you use zero per cent of one of the units, as a basic acid, only about eight per cent dissolves in 14 weeks. However, as we add more and more – and this is 15 per cent, sebasic acid, or 55 percent, or 79 percent – what you can see is that you can simply dial in the monomer ratio and, at zero per cent, eight per cent is gone at 14 weeks and it would take three or four years for this to dissolve fully. However, as you add more and more of the other unit, this is all gone in two weeks. Therefore, you could simply control the degradation rate, and hence the release rate, by changing your monomer ratios. So we did that.

You can probably tell from what I am saying that one of the things that was very important to me was whether we could move the work that we are doing into the clinic, so that it could have an impact on patients. In the mid-1980s a young neurosurgeon named Henry Brown, who was just starting at Johns Hopkins, came to see me. Today, in part because of some of the work I am going to go over, he is Head of Neurosurgery and Cushing Professor at Johns Hopkins.

Glioblastoma multiforme

What he was looking for was a better way to treat glioblastoma multiforme. This slide shows some of the statistics then, showing that regardless of how you treated it, the mean lifespan was 50 weeks.

Structure of BCNU

The drug used at that point almost exclusively was BCNU. What Henry and I talked about was that perhaps we could introduce a new paradigm. Rather than giving this drug systemically, intravenously, which was what was normally done, could we do it locally?

Principle of the therapy

Specifically, could we allow the neurosurgeon like Henry to operate on the patient, which he would be doing anyhow, and take as much of the tumour out as possible but, before closing the patient up, he would line the surgical cavity with these little polymers. They wanted a polymer that was degradable, so that it would not accumulate in the brain. It had to be surface degrading, so that it could not dump this potentially toxic drug. From animal studies they did at Hopkins, they wanted it to last for four weeks.

BCNU normally just lasts for 12 minutes, but if you put in the right polymer with the right ratios, as I showed you before, it could last for four weeks, and do the other things that I mentioned. Most importantly, if you did this type of model, you would leave it behind at the end of surgery and you would have high concentrations in the brain where you wanted it to be, but low concentrations in the rest of the body where it might cause harm.

One of the things that is critical in the United States, as everywhere else, is that if you are in academia and you have an idea like this – like a new material or a new treatment – you have to raise funds. The way we would generally raise funds was that we would write a grant to the federal government – in our case, the National Institutes of Health (NIH). This would then be reviewed by professors at other universities, who would say what they thought about it.

This approach will not work because:

Actually, our great proposals did not do very well. I saved some of the reviews and I entitle this slide 'This approach will not work because'. In 1981 when we first proposed this, the professors - chemists at NIH - looked at it and said that you could never synthesize this polymer. However, I had a very good graduate student at the time named Howie Rosen, who would later become president of the Alza Corporation, which was the leading drug delivery company, later bought by Johnson & Johnson for \$12 billion. Howie was elected to the National Academy of Engineering about four years ago and he was able to synthesize this.

After we had done this, the reviewers – who do not do the reviews very quickly – sent it back and said that the anhydrides are reactive, they will react with whatever you put in. I had another couple of post-docs, Bob Linhardt, who is now the Constellation Professor of chemistry at RPI, and Kam Leong, who is the James Duke Professor of Bioengineering at Duke. They worked out ways, using salts and so forth, so that there was no reaction. We sent it back again and they said 'We still should not fund it because these polymers are low molecular weight. They are fragile, they will break in the body and it will not work.'

I had another couple of post-docs, Edith Mathiowitz, who is now Professor at Brown University, and Avi Domb, who would later become Chairman of Medicinal Chemistry at Hebrew University. Using the right kind of catalyst, and time and temperature conditions, they worked out ways to make the polymers really high molecular weight and very strong. So then we sent it back again and they said that new polymers would never work because they would be toxic.

I had another graduate student, Cato Laurencin, who is now Dean of Medicine at the University of Connecticut, who has also been elected to the Institute of Medicine of the US National Academy of Sciences about three years ago. He showed that the polymers were quite safe – proving what Marletta and others had said. Anyway, this kept going on and on until 1996, when the Food and Drug Administration in the United States approved this treatment. This was the first time in over 20 years that they had approved a new treatment for brain cancer and the first time they had ever approved this idea of using local chemotherapy for cancer.

You can probably tell from the way I am talking that I am very proud of how well the graduate students and the post-docs who worked on this project did. They became chaired professors at major universities around the world, or presidents of major companies. The reviewers have not done so well. *[Laughter]*

I would like to show you what this operation looks like. If anyone is squeamish and does not like the sight of blood, they should not look.

[Slide – photo of brain]

Let me just show you a human brain. They usually put seven or eight wafers in and then close it up. It is very hard to get good advice when you give a talk but, about 10 years ago, I was giving a lecture at MIT, which my wife, Laura, attended. At the end of it, I asked what she had thought of it and she said, ‘Well, Bob, the lecture was alright’ – and that is actually very high praise. *[Laughter]* But she said, ‘Do you know, you had those two bloody slides on for nearly 10 minutes. I don’t know if you were looking, but all those poor engineers were turning green.’ So ever since then, I do what I have done today – give people a warning, and just show the slides for a few seconds.

I will also tell you the sequel to that story. About three years after that talk, I was asked to give a dinner speech, but this was to a group of neurosurgeons. I told them the same story and at the end of it, a group of the neurosurgeons came up to me and said, ‘You know those two bloody slides that you showed after dinner? Those were fine – you could have left those on as long as you wanted. But those chemical formulas – to leave those on

for neurosurgeons!' I have ended up giving neurosurgery talks quite a bit, and I always do the opposite of what I have done today.

[Slide- graph]

These are some of the Phase III data. This is the final clinical trial which was published in *Neurosurgery*. Some of this was actually done in Finland and Sweden. In this particular trial, which is certainly a good result, you see that there is much greater survival – about 31 per cent at the end of two years, compared to six per cent at the end of two years. As a consequence of this and many other clinical trials, this was approved – initially for recurrent glioblastoma, and now for primary glioblastoma. It is probably used about 30 per cent of the time, although the decision as to whether to use this really depends on imaging – in other words, how localised the tumour is. But it would introduce an entirely new kind of paradigm.

[Slide – photo]

Then, with companies, as well as one of my other students, Elazer Edelman, the same principle would not only be applied to this and other types of cancer, but also to another really huge area, which is drug-eluting stents. For people who are not familiar with this, if somebody has heart disease, today one of the major treatments for that is to put in a stent. This is rather like a Chinese finger puzzle and it keeps the blood vessel open. The problem is that, nearly 50 per cent of the time, when you put these in they cause proliferation of smooth muscle cells and so on, which leads to restenosis with the blood vessel being blocked again. That could kill a patient or, at minimum, you would need to insert a new stent. Now, what is being done is pretty much exactly what I said – you take a polymer, and put in an antiproliferative drug, perhaps in this case taxol rather than BCNU in the polymer, and deliver it locally. This has had a marked effect on changing restenosis – in the US, these are used about 70 per cent of the time, in probably over 1 million patients a year.

All of this made us wonder whether we could create other new materials that might be useful. I will go over another story where I thought about this. I had to give another speech, this time in Orlando, Florida, which is where Disneyworld is, and I don't know whether you have ever been there. I remember getting off the plane in Orlando, and noticed that everyone there was really overweight. I then went to the hotel – and this was an American Heart Association meeting – and found that everyone was really thin, so I decided I should go to the exercise room. I always like to do two things at once, so I picked up *Life Magazine* there, and started to read about cars of the future. It said that if you had a car in the future and it was involved in an accident, all you would have to do if it had a dent would be to heat it up, and the dent would snap back into place. I thought to myself that this was interesting,

and I started to think that perhaps we could do something interesting in the medical area. As an aside, people may be familiar with minimally invasive surgery – and pretty soon, I will try to connect cars with minimally invasive surgery, but let me tell you about that for a second.

In minimally invasive surgery, let's say you had a gall bladder operation 30 years ago. They would make a big incision in you and take the gall bladder out but, because they had made a big incision, you would be in the hospital for a week or two to recover and you would not be back at work for several months. Today, because of minimally invasive surgery, they make a tiny incision in you and then put these scopes down a little hole. You can pull the gall bladder out – and they can watch this on a TV screen – and, because they have made a little incision, you are out of the hospital in less than a day, and back to work within a few days.

I started thinking that if you could make metals snap back into shape, or change shape, could we not do this with plastics? In particular, could we do this with degradable, biocompatible plastics? I started to think, what if we wanted not to take objects out of the body, like a gall bladder, but what if we wanted to put objects into the patient, like a medical device, some of which are bulky? It could be a stent, or a sheet to prevent adhesions. I started to wonder, what if we could make shape-memory materials? Could we make a material, for example, that at room temperature might be like a string that could go through the hole in the body but then, when it gets to body temperature, which is hotter, could it snap into whatever shape we would want it to be, and could we programme it to do that?

I mentioned this to Andreas Lendlein, one of my post-docs who would later go back to Germany, and – for the polymer chemists in the audience – we made a series of what we called phase segregated, multi-block copolymers. Without going into the science too much, one block would control the shape at one temperature, say, at room temperature, and the other at another temperature, perhaps at body temperature. We actually built one of those blocks in as a series of cross-links that might have a transition melt, for example, at 30°C. The idea is that one block then controls it at room temperature, while the other at body temperature, and we could switch from one to the other.

We actually made some of these polymers. I will show you a quick video of what would start out as a string at room temperature, in air, and we will drop it into body-temperature at water. Hopefully, it will change from a string to a coil – like a stent.

[Video]

Here, it is at room temperature in air and we are dropping the string into body temperature water, and it goes into that shape. We could have made it go into almost any shape.

Let me give you a second example. What if someone had a surgical wound on their face or their hand? If you did, you might want to tie a surgical knot, which is not that hard to do. I could do it, although you probably would not want me to. However, what if you had it inside your body, perhaps in your lung or in your stomach? How could you tie the knot then? So we wondered, what if we could loop in the knot, like a loose knot or a lasso at room temperature but then, when it got to body temperature, it would tighten.

[Video]

Here is a second video, where we will loop in a loose knot like a lasso at room temperature. Here is the loose knot but, hopefully, it will tighten as soon as it gets into body temperature water. Again, this is just an illustration and you can use your imagination and think of perhaps even better applications than what I have just shown. These are just examples of new materials that you might think about.

In fact, we did this initially with temperature but later we also published a paper in *Nature* where we showed how we could also do it with light. You might even think about using this with a fibre optic, so that you could activate it with heat or light, and perhaps there are other stimuli as well.

[Photo – child in hospital]

One of the last topics I will cover today is to mention not only using materials for delivery, but possibly creating new tissues or organs. About 26 years ago, Jay Vacanti – a very good friend of mine – was head of the liver transplant programme at Boston Children's hospital at the time, and he would see patients like this little boy, dying of liver failure. The only way a child like that lives is if somebody else dies, and somebody like Jay would do a transplant. The problem, as you know however, is that there are not nearly enough transplants to go around.

[Slide – biodegradable polymer scaffold]

What Jay and I therefore thought about was whether we could take the patient's own cells, or those of a close relative – and, today, of course, one might think of using stem cells and converting them to whatever cell type, but here we could say use bone, cartilage, liver, intestinal cells, urothelial cells. If you took those cells and injected them at random in the body, not that much happens, but cells are smart. For example, groups at Berkeley have shown that you can take mammary epithelial cells, put them close enough together and they will actually form acini and make milk. Others have shown that you can create blood capillaries *in vitro* with endothelial cells. Our thought was, what if we made a polymer scaffold in three dimensions and have the cells be close enough on these polymer fibres, so

that they could communicate with the potential of remaking these structures? It would also be key to figure out the right way to grow the cells, which might involve a variety of things. Partly, you would have to figure out the right media. It also turns out that there is a great deal of engineering in there too.

Just as an example, we published a paper in *Science* about how to make a new blood vessel. We tried growing the blood vessels cells under regular tissue culture conditions but it did not work. The only way we could get it to work, and Laura Niklason, one of our fellows, did this, was to create a series of bioreactors that were like a heart, which pulsed the media through this, in the same way as a heart would. So we actually had a bio-reactor pulsing media through at 165 beats per minute. So there were a number of different tricks that one might want to use to do this. Ultimately, after you grow it and figure out the right media reactor conditions, you could make whatever tissue you wanted.

[Slide – photo of polymer fibres]

This slide shows polymer fibres that we made, in this case with liver cells. Prasad Shastri, who was one of our post-docs at the time – actually, he did some work with Molly Stevens who is here now at Imperial College – worked out a way to make these scaffolds in almost any shape.

Cartilage tissue engineering

Here, for example, is a nose. What I am about to say is all fiction, but let's say, what might the future of plastic surgery be? Here, he made these three-dimensional forms using CAD/CAM techniques – computer-aided design. The thinking was that perhaps 30 to 40 years from now, somebody might come in wanting a new nose, so you could have a computer screen and choose whatever nose you wanted. Some people might want a regular nose, while others might want an upturned nose, and that is not so hard because, if you make it with a polymer, you just take a little bit off. Some people might want a hooked nose – although probably not – and if they did, we would just give them a little more polymer. Then you could take their own cells, perhaps from their ear or somewhere, through a minimally invasive procedure, and make the nose.

To end this talk, let me just give you three quick examples of what we and our colleagues are doing. First, could we make new cartilage? Here is an example of what Chuck Vacanti did, and people like Molly have taken this much further, but I will just show you some of our earliest work.

[Slide – photo of mice]

These are nude mice. Again, if you are using a person's own cells, you should not have rejection, so here he did this guy's skull.

[*Slide*]

Here, we re-did this guy's cheek.

[Slide – photo of cartilage]

If you open the animals up and look at them, you get pure white glistening cartilage and, histologically, it actually looks exactly like cartilage. The only issue is that it is not perfect cartilage by any means. Histologically, it is good but, if you really examine it, the mechanical strength is perhaps about one-third of that of regular cartilage, and therefore with this particular approach you cannot solve weight-bearing issues, although you can solve cosmetic problems, as I will show you.

[Slide]

One of the ones we looked at with Chuck Vacanti, one of our collaborators whom I have mentioned, actually saw patients without ears. Linda Griffith, who was one of my post-docs, made a scaffold in the form of a human ear. Here is the high-powered scanning electron micrograph of these fibres and, in this case, with cartilage cells, over time you get the cells and matrix. Over time, the polymer will totally dissolve, and it will be all cells and matrix. Chuck has not yet put this on patients, but he has put it in rabbits.

Here is a rabbit with a human ear. Of course, people ask why you would do that to rabbits, but the reason it is done is to show that it is safe for humans.

[Slides – photos of patient] Here is the first patient who was treated under physician-sponsored IND. Jay did this. This little boy at this time has no chest covering his heart but, like other boys in the US, he likes to play baseball. As you can imagine, however, if he was ever hit in the chest, he could die. So Jay operated on him, we made a polymer scaffold for him, took his cells and made him a new chest. That was over 10 years ago and he is still doing fine.

[Slides – photos of patient]

In another example, and this was approved by the FDA, you could make new skin. This was actually done by a company that licensed it from us. This slide shows a little boy who was very badly burned, but you could take the product, which is neonatal skin fibroblasts, and you can actually cryopreserve these. You put it on the child at the time of the injury and, if you come back three weeks later, he looks like this. If you come back six months later, he has pretty much healed.

[Slide]

The very last example that I would like to give you to end this work concerns work that is still ongoing and still in animals. Could we make a scaffold that could help patients who are paralysed? This work was done by Erin Lavik, Ted Tang and Evan Snyder, who was our collaborator. The idea was, could we make a scaffold that had a structure that would mimic

the spinal cord, the grey matter and the white matter? Could we put neuronal stem cells, which Evan had isolated, on the inside of the scaffold, and on the outside we would have an oriented portion that would help provide axonal guidance, that Erin designed? We would make defects and put them in animals and do various controls. There were about 50 animals and this is one of the controls – the mean of the control group. Controls are cells by themselves, polymer by itself, or a sham operation.

[Slide – photo of rat]

Here you can see the animals, and there are two things to notice. This rat is dragging his feet – this is 100 days after the start – and the paws are splayed in a rather awkward fashion. There is actually a BBB scoring system and he achieves about a 5, which is the mean of the control group.

[Slide – photo of rat]

In the very last slide, I will just show you the mean of the treated group. This is by no means a cure but it is a big improvement. This is also at 100 days. You can see that, even though he is a bit heavy, he is able to bear his own weight. He walks quite clumsily, but he can bear his own weight and his paws are splayed in a much more normal fashion. You can contrast this animal to the previous one. The mean of the treated group was about 12, compared to the control groups of about five or six. [Video shown] My wife told me not to leave this on too long either.

In fact, we have recently started primate trials. The numbers are still low but they are showing exactly the same trends in terms of the four different groups, with the treated ones doing significantly better, even at about eight or nine weeks, compared to the control groups.

I will stop here. I should point out that I have probably raised more questions than I have answered. With some of these things that we are trying to do in both drug delivery and tissue engineering, we have a very long way to go. However, it is my hope that engineers working together with biologists and clinicians will be able to develop principles like these and others. We are just at the tip of the iceberg and it is my hope that, through all of this kind of work that everyone here and elsewhere is doing, we will be able to continue to create new treatments that will relieve suffering and prolong life. Thank you very much. [Applause]

Questions & Answers

Professor Robert Mair: We have heard a wonderful talk on many different aspects. As the Senior Vice President of the Royal Academy of Engineering I would like to chair this part of the proceedings where Bob has very kindly agreed to answer questions.

Ainomaija Haarla (Technology Academy Foundation): Thank you very much, Bob, for a most thought-provoking and stimulating presentation. I represent the Technology Academy Foundation in Finland. Our academy awards biannually the Millennium Technology Prize, which Robert Langer won last year. It was for innovations that improved the quality of life for many people and encouraged simultaneously sustainable development. I think Robert Langer is excellent evidence of fulfilling the mission of this prize.

I would like to raise the following question. Where do you think the next big leap forward in bioengineering will come from?

Robert Langer: So the question is, where will the next big leap forward in bioengineering come from? It is hard to pick a single area. There are a tremendous number of areas to which I would like to think that bioengineering can contribute. I have picked examples in drug delivery and regenerative medicine in tissue engineering, but I also think one could potentially make breakthroughs in the immunological area in terms of new vaccines, with better use of engineering approaches to understanding the immune system. There are certainly all kinds of work going on, looking at engineering to help modelling in areas like systems biology and so on. There are a great many areas where engineering can be used to help either explain things better or possibly to create new products and devices.

Sir Mark Walport: The cord regeneration experiments are absolutely extraordinary. Have you started doing any experiments on tracking where the neurons are coming from and where they are going to? I could see how you could combine that with the sort of 'brainbow' technology.

Robert Langer: Yes, the question is whether we have done any tracking experiments. Once again, I have not done those myself but we have had people like Evan Snyder, who has looked at that. It is important, when they look at the tracking – from what I understand, they are certainly imperfect by any means, but you do see some migration from

the surrounding tissue. You see some tracking of the neurons in the space where you put the neuronal stem cells.

You also see – and this seems to be the biggest aspect of the mechanism – much less scar tissue. If we were to look at one thing that the neuronal stem cells appear to do, and perhaps this is through growth factors or other things, there is much less scar tissue when the histology and other types of analysis have been done in the treated animals, compared to the controls. That has been true for both the primate studies, which I did not show because that is still early, as well as the animal studies that I showed you.

Richard Guy (University of Bath): Bob, you alluded to the issue of delivering insulin from a controlled release system over a long period of time. That has been a Holy Grail for many years – for most of the years that you have been working in this area – and yet we have not made a great deal of progress. Do you see that there will be the possibility of providing a diabetic with a delivery system that is not a subcutaneous injection three or four times a day?

Robert Langer: That is a great question. What Richard is asking is whether insulin delivery by a polymer, or even by other means – and we have worked on other means too, such as aerosols – will come to pass. To me, it has been really disappointing that better things have not happened, despite the work by many people. The answer is that I hope so, but I do not know.

The problem with insulin, in contrast to, say, cancer, is the fear that something could go wrong. In other words, if you had an insulin depot and, for some reason, there was a leak – even if that happen one out of 10,000 times, that would be enough to deter people from doing it. I don't know the answer to this. Bioengineering can probably provide some advances in insulin delivery but we have seen enormous efforts not only in the polymer area but even more in the aerosol delivery, which I have not talked about today. That was even approved but it was then pulled off the market.

When these diseases are often fatal, or have the potential to be fatal, history has shown us that these kinds of devices are approved by the FDA and they are widely used by patients – such as the cardiovascular stents and the various cancer treatments. However, although insulin may shorten life it is not necessarily perceived by the FDA as being fatal, and it has been much more difficult. So the answer is that I hope so, but I do not know.

John Egan (BITECIC): With a future of increasing pressure on healthcare budgets, does that influence the way you think about these technologies and how you have to make compromises in them to adjust to the health economic scenarios they are likely to face?

Robert Langer: I should break that question into two parts. In the way we do most of the things that we start in the laboratory, I should say that the answer is that I really don't. In almost all these cases we have tried to come up with new gadgets, new delivery systems, or new approaches to problems, like tissue engineering and drug delivery. When we publish a paper in a particular journal, the goal has been to make a finding, make a discovery, understand how something works – and perhaps make a device that could be used some day. So I would say that when I do that, I do not.

However, what we have sometimes done is that, after we have published a paper in *Science* or *Nature* then, through some of our students or post docs, we have started a company on it. There, as someone who has been involved in founding a company, or been on the board of directors, I would say that we spend a great deal of time thinking about the health economics because that is necessary if something is going to become a medical product. I would say therefore that, if I think about things from a purely academic standpoint, I do not dwell on the health economics but, whenever we have been involved in company things, we frequently do so.

Lord Alec Broers: You have made such remarkable progress in so many different areas, but what about nerve repair? I am just another engineer who does not know a great deal about medicine, but nerve repair could be so beneficial, particularly for injured people, soldiers in warfare and so on.

Robert Langer: We are actually working on that. In fact, the army came to see us and we have a significant grant from them to look at just that issue. Some of this might be more futuristic, but we have created some new electrically conducting polymers that, at least in some initial *in vitro* and animal experiments, look promising in that regard. It is still early days but I agree with you that that would be a really good thing. There are a variety of groups working on this – not only ourselves, but also some of my former students, like Mike Yaszemski at the Mayo Clinic, and he is actually a brigadier general but has a PhD in chemical engineering, and an MD. We are working on that but it is early – I completely agree with you.

David Clarke (Imperial College): You mentioned silicon chips and smart sensing. How do you wish to extract the signal, so that you can recognise things within the material?

Robert Langer: I will just give an example and also the potential advantage of this kind of approach. Let's just pick glucose as an example. With glucose, it is not as though we do anything special. We would take the sensors that now exist but the point is that those sensors generally get fouled and they go bad. Our thinking here is that all you would do is to take the existing sensors that people would use and then they get fouled: as soon as they are fouled, you could have another gold window open up and have a new sensor. Literally, if you think about it, you could put 100 sensors – the same sensors – on a chip, so that as soon as one was fouled you would open up another. So it is not as though we are doing anything special on the sensor part but we would just be using existing sensors. I would be delighted if we did, but what I am saying is that we are basically using existing sensors but the big advantage is that we have what you can call a 'strip on a chip': if a sensor normally has a two-day lifetime and you have 100 sensors, that could have a 200-day lifetime, or you could have more than that.

Heather Thomson (University of Southampton): I am a vision scientist. In relation to AMD, macular degeneration, do you foresee a long-term release mechanism or release product for Lucentis or Avastin?

Robert Langer: Just to give a little background on that, I have spoken a little about Lucentis and there is another drug called Macugen that people use for treating macular degeneration which is a cause of blindness. At the moment, people are given shots through the eyeball every month. This question is directed at whether it would be better if you did not have to deliver it every month – and would it be possible to deliver it perhaps every six months or a year.

The answer to that question is yes. There is a great deal of work going on, using the types of principles that I mentioned earlier, but they are not there. However, there are different clinical trials going on, and a great deal of activity. The technology is there to do it, but the question is about the best way – is it a microsphere, or a gel, or something different? Nevertheless, I think we will see that come to pass.

Raymond Oliver (Arrow Science Consulting): I am at the Royal College of Art and my question is really about an interest in anti-delivery, negative delivery. Can you

foresee how we could use active devices which would have an affinity to pull materials towards them, which could then be extracted, rather than taking material out of the delivery lozenge or reservoir, and going to a site of action?

Robert Langer: I think you could do that. We have done some work on immobilised enzyme and immobilised antibody systems where you can pull things out. We have not done the next step, however. We have basically just tried to design some systems to remove things from the body that we thought were bad, like heparin or certain other molecules, by immobilised antibody or enzyme systems. However, I imagine that one could probably take the next step, particularly if you had some type of antibody system: you could pull something out and then do something to release it. I have not seen that done but I think one could probably go the next step. That might be expensive, but I think it could be done.

Daniel Steenstra (Cranfield University): I would be very interested to hear your opinion about the patent system, because I understand you hold many patents. Is it helpful towards progress or does it sometimes stand in the way?

Robert Langer: I will tell you a United States story and then I will answer the question. Abraham Lincoln was once asked what were the three most important things in history and he said they were the printing press, the founding of America and the patent system. I think the reason why he said the third, and why I would support him on that - while it is not perfect in every way and it certainly has some downsides - is because it has encouraged innovation.

The bargain that it has created is that people get protection for a certain period of time and then anybody can use it, and both aspects of that have been good. You have that protection for a certain period of time, which has encouraged enormous investments in all kinds of scientific things and it has led to all kinds of industry. At the same time, since the patents are only valid for a certain period of time, it forces even those companies to continue to innovate. It gives everybody an opportunity to say that they cannot be satisfied with what they have: if you want more protection, and if you want to be more capitalistic, you have to come up with new inventions.

For the most part, I think patents have been terrific. As someone who has been involved in this, and having dealt with venture capitalists, I would say that if you do not have a good patent, they will not give you money. I do not know whether the Wellcome investments share the same criteria, but I would say that they look at the patents extremely carefully: they have all kinds of lawyers to look at them and scrutinise them. If you were doing it from a capitalist or commercial standpoint, if you do not have a good patent, it is just

very hard to get the investment and, without the investment, you do not find the money to develop things. This is particularly important in medicine because everything in medicine is so expensive to develop.

Daniel Steenstra: It seems to me that the issue is that there are the inventions of humans, which should be patented, and then the inventions of nature, which should not. You cannot work round the sequence variate that gives you BRCA1 mutations, or breast cancer 2 mutations. Patenting DNA sequences, which then leads to a monopoly on a test, seems to me to be an abuse of the patent system. Everything you have described, which can genuinely be described as an invention by humans, is in a different category.

Robert Langer: I completely agree with that but, if someone developed a new way of detecting that, that would be different, or if somebody found a new drug based on that. However, I completely agree with what you said and I would share that view. It depends on what is the discovery and what is the finding.

Daniel Steenstra: It is a discovery versus an invention.

Robert Langer: That is fair – I agree with that, although if somebody is clever, one would hope that with some of those areas, one could turn those discoveries into perhaps new diagnostics or therapeutics. However, the line that you are drawing is the same as the line I would draw.

Ainomaija Haarla (Technology Academy Foundation): I have a question regarding what can be seen on the horizon. Can we think of such innovations which have appeared, shall we say, in the past five to seven years, which could have a similar potential to drug delivery in the future?

Robert Langer: There have been some very exciting findings and I will just give you a couple of examples. Certainly, the recent work that has been done on creating IPS cells is very exciting as an example, and that is only three or four years old – the idea of inserting several genes to change the nature of a cell into an induced pluripotent stem cell is an example. RNAi, which is a little older, is also potentially very exciting as a new therapeutic. Actually, although I did not include that in my talk today, from a delivery standpoint, the delivery of siRNA and the delivery of DNA, is an exciting area and one on which we and others spend a great deal of time. Those are a couple of examples.

[No further questions]

Professor Robert Mair: We have had the most amazing experience and you, Bob, have delivered the most wonderful talk to us. Thank you very much. You were described at the very beginning by Mark Walport as a spectacular engineer and that has certainly been demonstrated in your talk this evening. We recognise also that what you do encapsulates the interdisciplinarity – the wonderful way in which engineering and medicine can combine in this way that you have demonstrated so superbly.

We come away from this with many lessons, which I will not try to summarise in any way, but several points come to mind. We recognise that when you have poor reviewers over a period of 12 years, that is a very good sign: just keep going. The other point is that we are very grateful to Exxon for not giving you a job in 1974.

I would ask everyone to join me in thanking Bob Langer for his absolutely superb lecture this evening. [*Applause*]

Professor Langer is a man of extraordinary energy, as I am sure you have all appreciated. He arrived by plane this morning and he is about to leave by plane very shortly, which is why we need to let him go now. Tea, coffee and refreshments will be served for those of you who would like to stay on. Thank you all very much. [*Applause*]
