

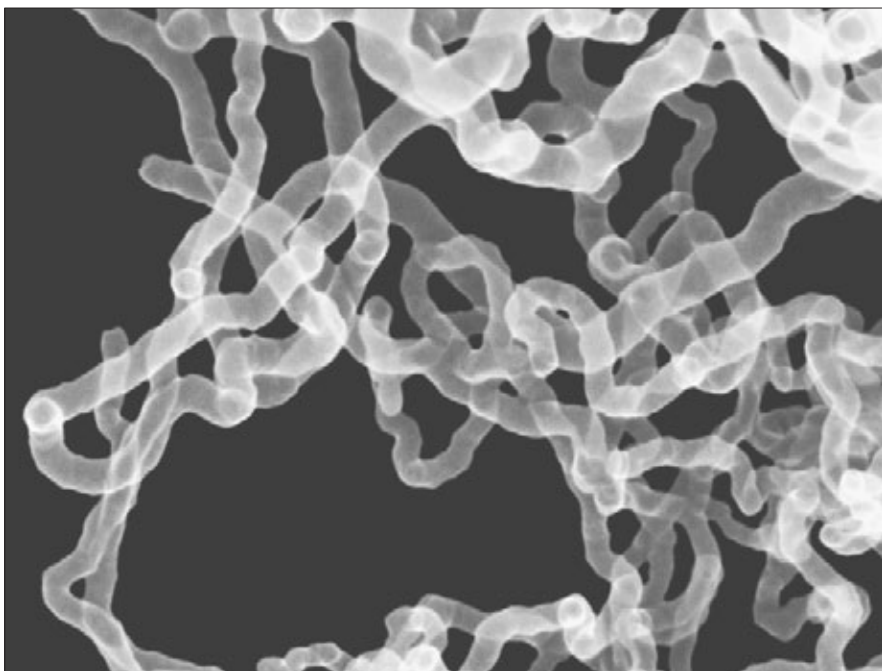
Nanotechnology: Novel Applications

Robert Langer, Angela Belcher, and Evelyn L. Hu

Phillip A. Sharp, Moderator

This presentation was given at the 1941st Stated Meeting, held at the House of the Academy on March 11, 2009.

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Magnified image of carbon nanotubes



Phillip A. Sharp

Phillip A. Sharp is Institute Professor at the Massachusetts Institute of Technology. He has been a Fellow of the American Academy since 1983.

Introduction

Tonight's program on novel applications of nanotechnology features three outstanding engineers, some of the very people who created this field in which material is fabricated on a nanometer scale. Such materials are smaller than the single proteins that are components of human cells, much smaller

than organelles. And these materials usually are composites, comprising multiple components capable of directing the nanoparticle to certain sites, reporting on the environment of those sites, and – when appropriately fabricated – changing the environment; for example, by releasing a drug or modifying an electrical signal. To be useful in a variety of applications, nanoparticles must be made in quantity, with uniformity, and at reasonable cost. Once made, however, they can be applied to any number of problems in fields ranging from health care to electronics to computing. Already nanotechnology has changed how we approach many problems in fundamental and exciting ways.

In my time at MIT I have learned to love engineers. (You either love them or you don't stay there!) Engineers do not approach problems in the same way scientists do. The engineer's primary approach to a problem – as I interpret engineering – is to solve the problem he or she faces. Sometimes engineers might need to understand the physics, chemistry, and/or biology behind a problem, but if that's too complex they

solve the problem with the tools they do have without understanding the process. Those tools are describing, measuring, quantitating, modeling, and then gaining control of the complex system and changing it to their own ends. Their tools have been remarkably powerful, and with them they have created many of the benefits of modern society. Now comes a new tool, a new science, for creating the present and the future: nanotechnology.

The first of our guides through this new science will be Robert Langer, currently Institute Professor at MIT but long associated with MIT's Department of Chemical and Biomedical Engineering. Robert has been doing pioneering work for decades at MIT in the area of delivery systems and tissue engineering. He has published more than a thousand articles and holds over six hundred patents. For this outstanding record he has received numerous awards, including the U.S. National Medal of Science, the Charles Stark Draper Prize, and the Millennium Technology Prize. He is a member of the Institute of Medicine, the National Academy of Engineering, the National Acad-

emy of Science, and the American Academy of Arts and Sciences. Just today I discovered that the latest issue of *Nature* includes a profile titled “Being Bob Langer” that in three pages follows his activities over one day.¹ He has created an enormous amount of technology that has benefited all of us.

Our second speaker is Angela Belcher, Germehausen Professor of Materials Science and Engineering and Biological Engineering at MIT, where she also directs the Biomolecular Materials Group. She has been at MIT for six years. Her research is interdisciplinary in nature, bringing together the fields of inorganic chemistry, material chemistry, biochemistry, and molecular biology. In addition to receiving a MacArthur Fellowship Award, the Presidential Early Career Award in Science and Engineering, and the DuPont Young Investigator Award, Angela has been named a Top Ten Brilliant Scientist by *Popular Science* magazine (2002) and *Scientific American*’s Researcher of the Year (2006).

Our final speaker is Evelyn Hu, Gordon McKay Professor of Applied Physics and Electrical Engineering at Harvard University. She just made the transition to Harvard from the University of California, Santa Barbara. She has worked on nanodevices made from solid semiconductors in novel devices by integrating various materials, both organic and inorganic. She and Angie Belcher have combined efforts in a new biotech start-up in Boston. Evelyn is a member of the IEEE, the American Physical Society, and the American Association for the Advancement of Science. She was elected to the National Academy of Engineering and to the National Academy of Sciences.



Robert Langer

Robert Langer is Institute Professor at the Massachusetts Institute of Technology. He has been a Fellow of the American Academy since 1994.

Presentation

*N*ano means “one billionth” and in the word “nanotechnology” it refers to one billionth of a meter, or about one ten-thousandth the width of a human hair. Nanoparticles have a number of important properties: nanoparticles have much greater surface area than larger particles such as microparticles; you can give them novel surface patterns; and they are small enough not to clog the bloodstream. Particles less than 200 nanometers wide have the potential to get into cells, at which point all sorts of potential uses open up; for example, novel treatments for cancer and other diseases.

A lot of recent pharmaceutical research has been guided by the metaphor of the magic bullet – the idea that you can target drugs to specific cells. The drawback to this approach is that it uses a single molecule. If, instead, you could put a thousand to a hundred thousand molecules in a nanoparticle and deliver that nanoparticle to a target, you would (to use a hockey metaphor) be able to take a lot more shots on goal, potentially more of which would make it into the net.

What challenges need to be overcome in order to make a nanoparticle that targets a particular cell, say a tumor cell? First you need to trick the body’s own defenses. If you simply injected a regular nanoparticle into the bloodstream, cells called macrophages

would come along and eat it. So that’s no good. But we discovered a way to fool the macrophages. By using materials that the U.S. Food and Drug Administration (FDA) has already approved and by adding in some polyethylene glycol (PEG) – which is useful because it gets surrounded by a lot of water on their surface – we created nanoparticles that look like water. When the nanoparticles are cloaked in this way, the macrophages don’t recognize them as foreign and thus don’t quickly eat them.

We tested this idea by injecting rats either with nanoparticles that were not coated in PEG or with nanoparticles coated in one of several weight chains of PEG. Then we watched to see which nanoparticles the macrophages ate. (Nanoparticles attacked by the macrophages appear as an orange

Having made nanoparticles that could pass through the bloodstream undisturbed by the body’s own defenses, the next challenge was to get them to target specific cells.

dye.) The nanoparticles without PEG were devoured by the macrophages. The nanoparticles with PEG fared much better, mostly escaping detection or, in the case of particles with 5,000 molecular weight, triple-chain PEG, completely escaping detection. Thus, we showed that by making nanoparticles with PEG on them, we could greatly frustrate the macrophages’ ability to detect and eat them. (See Figure 1.)

Having made nanoparticles that could pass through the bloodstream undisturbed by the body’s own defenses, the next challenge was to get them to target specific cells. Several types of targeting molecules are known; for example, antibodies and aptamers, which are pieces of RNA. Omid Farokhzad, now a professor at Harvard Medical School, had the idea when he worked with me to put targeting molecules on the PEG particles. Implementing this idea involved its

¹“Profile: Being Bob Langer,” *Nature* 458 (7234) (March 5, 2009): 22 – 24.

In vitro phagocytosis of surface-modified polymeric particles

Rat alveolar macrophages - 1hr

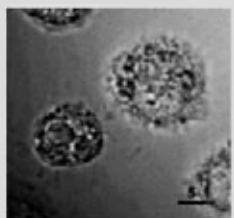
Polymeric particles without PEG



PEG (5000 M.W. Single chain)



PEG (20,000 M.W. Single chain)



PEG (5000 M.W. Triple chain)

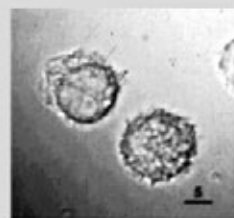


Figure 1

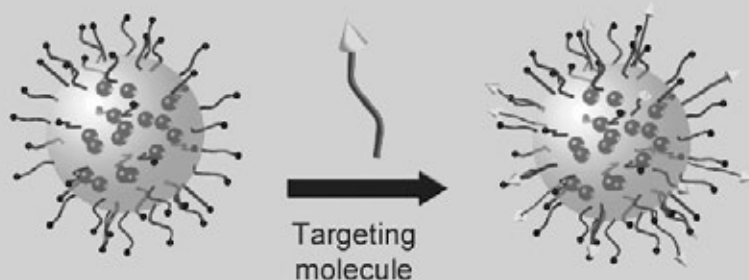


Figure 2

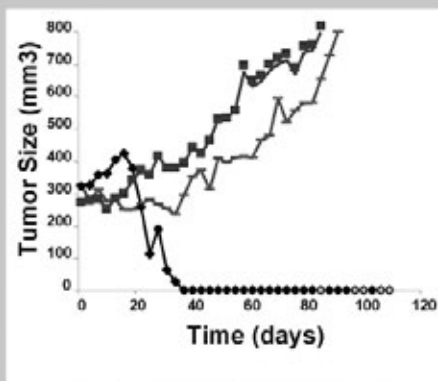
Targeted NP



Docetaxel



Control NP



■ Control NP
 — Docetaxel
 ◆ Targeted NP

Figure 3

own set of challenges: too much PEG and you don't get targeting; too much targeting molecule and you lose PEG's protective effect against the macrophages. Get the concentration just right, however, and you can both target the cell you want, say a cancer cell, and avoid the macrophages. (See Figure 2.)

In an early animal experiment, Omid used a targeting molecule aimed against prostate cancer cells. We created a targeted nanoparticle to deliver the cancer drug Taxotere (Docetaxel) and tested it against a control nanoparticle (nontargeted) and against Taxotere by itself. With the control nanoparticle, the tumors grew. With Taxotere by itself, the tumors grew. But with targeted nanoparticles delivering Taxotere, the tumors shrunk. The tumors in the control and Taxotere groups got big and were highly vascularized. (See Figure 3.) This was an early experiment, but we are hopeful that with further work we can apply the principle to human beings. Our goal is to start clinical trials within the next year or two.

We proposed the idea of using the magnetic nanoparticles, in conjunction with MRI, to monitor how someone is doing.

Another use for nanoparticles was developed in collaboration with Ralph Weissleder at Massachusetts General Hospital and Michael Cima at MIT. Ralph developed nanoparticles with a metal core for use as an imaging agent. We could also add a binding moiety specific for, say, glucose or a certain type of cancer molecule, like human chorionic gonadotropin (HCG), or whatever else we want. If we use a binding moiety and an analyte to which the moiety binds specifically (like the moiety, the analyte can be whatever we want), the nanoparticles will aggregate rather than remain separate, thus changing the MRI signal.

Michael Cima and I had previously created a series of microchips that can be used for drug delivery. We then proposed the idea of using the magnetic nanoparticles, in conjunction with MRI, to monitor how some-

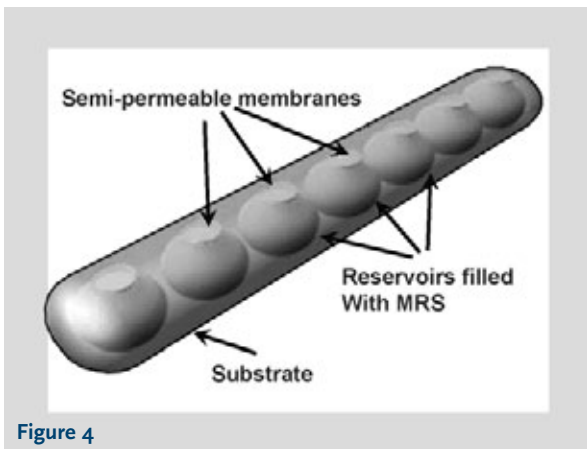


Figure 4

one is doing. The microchips are about the size of a grain of rice, small enough that we can inject them. To modify them for use with MRI, we add different sets of MRI beads to the various wells on the chip. (See Figure 4.) Each well can then be used to determine what the MRI signals are. For example, one could be for glucose, one for the cancer marker HCG, and one for something else. By creating something specific for the different signals in the body, we can monitor how someone is progressing. For example, a chip could be used to monitor for the presence of HCG. If no tumor is pres-

Another use of nanoparticles is in medical devices.

ent, we get one signal on the MRI; if a tumor is present, we get a different signal. These signals can be followed and quantitated over time. Researchers are even working on wearable MRIs that would allow for continuous monitoring. We hope that before long we will have a system that can detect all kinds of signals in the body, tell you how you are doing, and maybe even deliver the drugs you need to get better.

A third use of nanoparticles is in medical devices. In many situations doctors can use sutures, sealants, and other materials to close wounds. In some situations, however, such as in a gastric bypass surgery, closing wounds can be difficult with the usual materials. So, Jeff Karp – formerly a postdoc in my lab; now a professor at Harvard Medical School – and I began to wonder whether we could find better ways of adhesion by look-

ing at things in nature that build on nanotechnology. Our investigation eventually led us to the gecko, which has tiny nanoprotusions on its feet. The nanoprotusions create so much surface area that the gecko can adhere to surfaces. Jeff and I worked out a way to nanopattern structures and make a gecko-like system. We also designed a special polymer called polyglycerol sebacic acid that is rubbery and sticky to begin with but

when combined with the nanopattern system and used in wounds has a strength much higher than normal.

A fourth use of nanoparticles involves a field called tissue engineering. With tissue engineering, by putting one type of cell in the right polymer – growing it the right way – we can make different types of tissue. An exciting example of this type of work is the research Yale professor Erin Lavik began when she was a graduate student at MIT. Working with Evan Snyder and Ted Tang, two neuronal stem cell experts, Erin nanopatterned the outer surface of a polymer. In the inner part she then put stem cells. The result was an artificial tissue, a patterned polymer scaffold with neuronal stem cells. The outer part of the tissue has fine, intricate structures that we hoped would help with axonal guidance. To test the tissue, we made rats paraplegic by removing a part of their spinal cord. We then put in a section of the artificial tissue. After a hundred days the control rats showed little sign of improvement. They dragged their limbs, and their paws splayed awkwardly. Rats treated with the artificial tissue fared significantly better. For example, the mean of the treated group was able to bear its own weight, and its paws splayed in a more normal manner. The rats weren't "cured" – their movements were still quite clumsy – but the progress made by the ones in the treatment group was encouraging enough that we have moved on to primate trials. We still have a long way to go before we'll see human applications of this technology, but we are hopeful that it and other applications of nanotechnology will someday prove useful in the medical area.



Photo: Donna Coveney, MIT

Angela Belcher

Angela Belcher is Germehausen Professor of Materials Science and Engineering and Biological Engineering at the Massachusetts Institute of Technology.

Presentation

Bob did a wonderful job talking about manipulating the physical properties of materials – for example, polymers and magnetic materials – in order to probe important biological problems such as cancer and paralysis. I'm going to come at the topic

Can the strategies that life has evolved over millions of years be applied to nonbiological systems?

from a different angle and talk about how biology can make use of materials to address problems more commonly associated with electronics, energy, and the environment. My research with biomolecular materials involves harnessing the lessons of biology and millions of years of evolution in order to develop new biotechnologies, using both existing and newly developed materials, chemistries, and technologies. The whole world is my toolbox: biology, chemistry, materials science. As an engineer, I want to make something work; so I'll use chemistry, I'll use biology, I'll use engineering to get the particular kind of device properties I'd like to have.

I am interested in whether we can give genetic information to a solar cell or to a battery so that it can grow itself, assemble in an environmentally friendly way without using toxic materials, and become better, more efficient, over time.

Much of the molecular machinery that biology uses is nanoscale in size: ribosomes, proteins, DNA, chloroplasts. All of these biological molecules are more or less on the same scale as current electronics. So when thinking about how I might go about making new electronics and nanoscale devices, I wonder what I can learn from biology, what new ways of making interesting electronic materials I can tease from millions of years of evolution. Through evolution, biology has “learned” to compartmentalize, to put things exactly where they need to go to have optimal performance. Life is also self-assembling. Wouldn't it be great if your cell phone could self-assemble? If it had a “genetic code” that would allow it to repair itself whenever you broke it? In short, can the strategies that life has evolved over millions of years be applied to nonbiological systems?

The abalone shell is an amazing example of how life evolved to work with nanomaterials. The shell is 98 percent by mass calcium carbonate and 2 percent protein; it's basically chalk. But it's 3,000 times tougher than chalk, which you can easily break with your hands. You can't break an abalone shell with your bare hands. How the abalone evolved to create such a hard material is interesting, but even more interesting is that when a male and a female abalone get together they make millions of offspring to whom they pass the genetic code that explains how to make this exquisite nanomaterial. The same is true of diatoms. Whenever they reproduce, they pass along the genetic code that allows every diatom to make its own beau-

tiful glass structure. What's more, the abalone and the diatom make their shells at room temperature using nontoxic materials! I am interested in whether we can give genetic information to a solar cell or to a battery so that it can grow itself, assemble in an environmentally friendly way without using toxic materials, and become better, more efficient, over time.

My favorite biomaterial is my son. Anyone who has had a three-year-old knows that they are highly complex organisms, fiendishly difficult to train. So when we think about how to train an organism to start working with a completely new toolbox, we think about much simpler organisms such as benign viruses and bacteria. Can we retrain a virus, a bacterium, or yeast to make a battery instead of a protein coat? Can we train it to make a solar cell or a fuel cell? Can we train it to capture and store carbon dioxide?

The answer is yes. In my lab, we have done all of these things. The real challenge, however, is to create nanomaterials that self-assemble; that self-correct (like human beings, who are, for the most part, self-correcting systems); that are self-healing; that can grow and recycle their own templates; that can grow to an exact size and stop (in nanomaterials and much modern electronics, exact size is really, really important). Basically, what I and other scientists and engineers involved in this type of research would like to be able to do is to genetically control the properties of any kind of device that we might want to grow. That is why I am so interested in what can be learned from millions of years of evolution. Can I take simple eukaryotic or prokaryotic cells and have them work with a different tool kit?

Life existed on Earth for billions of years before we had hard materials, before abalone evolved. Organisms with hard structures such as shells and bones and nanoparticles of magnetite and iron oxide are not found in the fossil record until about 500 million years ago. Yet long before this, life was doing replication and photosynthesis. Why was making hard materials so difficult in the Precambrian era? The answer is lack of opportunity. During the Cambrian geological time period life had access to increased iron, increased calcium, and in-

creased silicon in the ocean. Organisms had a new toolbox with which to start building. Life seized the opportunity and started making hard materials.

Life did a great job; it produced the coccolithophorid, a unicellular algae made out of calcium carbonate; it took calcium carbonate and produced the abalone shell; it eventually made people and all kinds of other organisms. But what if it had had more opportunities? Could it have made different kinds of structures and different kinds of materials? And what can we human beings do with the biological tool kit to which we have access? Can we use DNA to make devices and materials?

By looking at the abalone shell with a scanning electron micrograph, we can see that it's actually made up of little tiles, little tablets stacked on top of one another and laterally offset. This stacking, this nanoscale brick wall-like structure is what makes the

The real challenge, however, is to create nanomaterials that self-assemble; that self-correct; that are self-healing; that can grow and recycle their own templates; and that can grow to an exact size and stop.

abalone shell so tough and strong. The amazing thing about the abalone shell's nanostructure is that it's all controlled by DNA. Life figured out how to control the production of these materials – everything from the abalone's calcium carbonate shell to the diatom's glass “skin” to the nanoscale magnetite magnets made by some ocean bacteria to spider silk – all controlled at the genetic level and made in nontoxic ways. DNA provides the blueprint for building proteins with different chemical functionalities that when linked together in the right sequence can grab atoms out of the ocean and build calcium carbonate or silica or iron oxide. Looking again at the abalone shell,

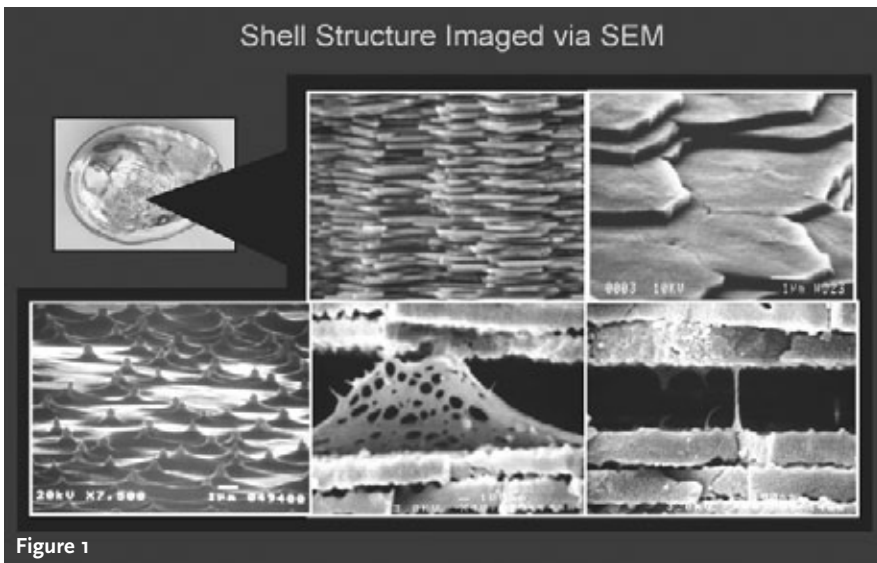


Figure 1

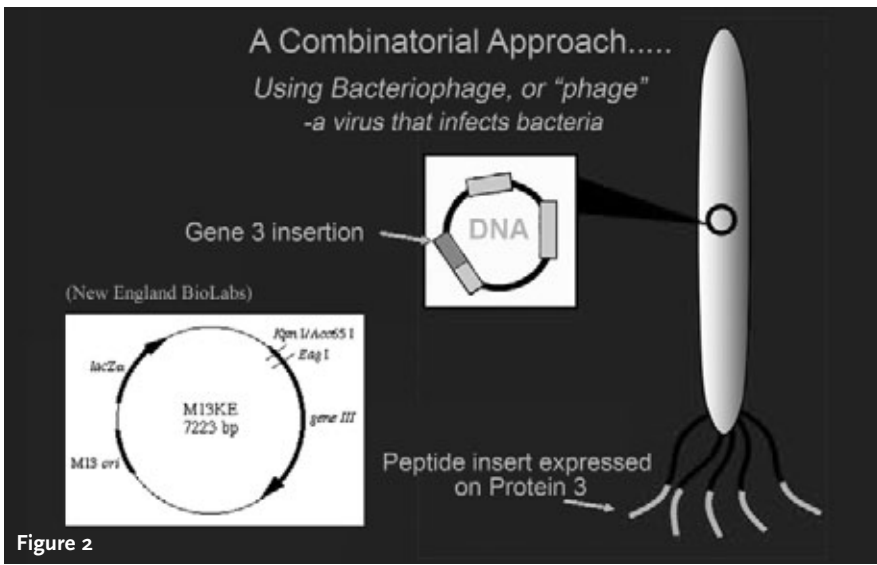
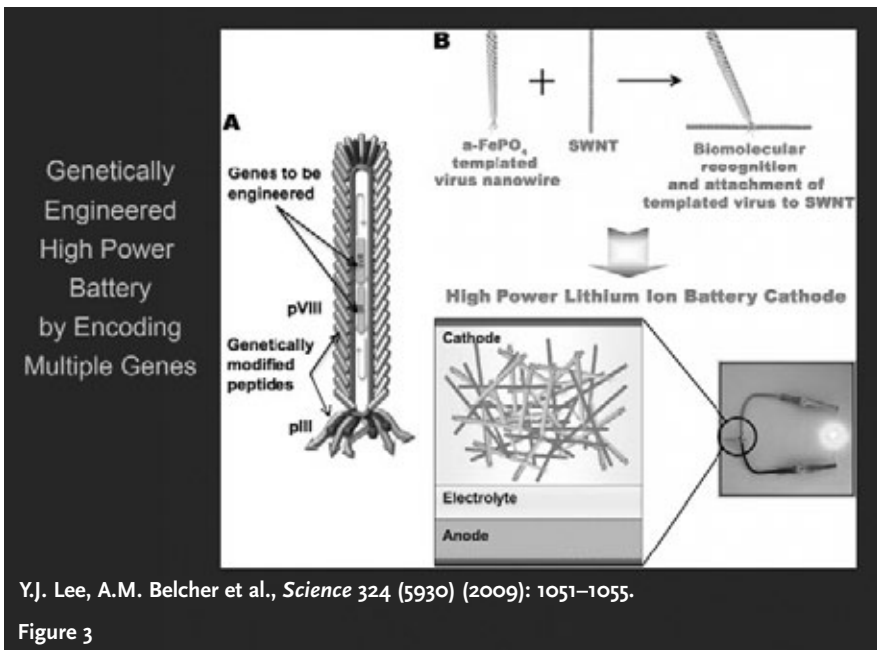


Figure 2



Y.J. Lee, A.M. Belcher et al., *Science* 324 (5930) (2009): 1051–1055.

Figure 3

we see that between the tablets are protein pieces that help give the shell its nanostructured regularity. (See Figure 1.)

In thinking about growing electronic materials, I look to nature for inspiration, starting with those proteins that, because of their different chemical functionalities, can grab ions out of solution. In the case of the abalone, the proteins grab calcium, then carbonate, then calcium, then carbonate, and in that way begin to build the brick structure that we eventually see as the abalone shell. Nature mostly uses calcium, barium, iron, silicon, and phosphorous. But what if biology used materials from different parts of the periodic table, say those elements used in semiconductors and solar cells, lasers and electronics, batteries and catalysis? With different building materials, what new kinds of structures would emerge?

Much of my work involves thinking about the living/nonliving interface. How can I take something produced through evolution, such as an antibody binding to an antigen, and put it together with something human made, such as a microprocessor? Such combinations are called evolved hybrid materials. By giving genetic information to nonliving structures, we make them better than they are without that genetic component. To do this, we use simple viruses called bacteriophages (literally, “bacteria eaters”), viruses that infect a bacterial host. They are beautiful structures about one micrometer by six nanometers in size, and they have single-stranded DNA that is easy to manipulate. (So easy, in fact, that this work is not confined to highly trained postdocs and graduate students. In my lab, every time we invent something new – we’ve had several new biological batteries this year, biological solar cells, biological displays, and so on – we transition it to the undergraduate teaching lab within a year. The chemistry and materials processing are easy for our sophomores and juniors to pick up. We even have high school students working on this in the lab.) Using traditional molecular biology techniques, we make small changes in the bacteriophage DNA, perhaps adding extra DNA that will then add an extra protein to the tip of the virus. If we do this a billion times, we add a billion possibilities to the virus, and by adding a billion possi-

bilities we are able to perform a billion experiments simultaneously. This is useful when you consider that nature needed about 50 million years before it got good at making hard materials. Fifty million years just won't cut it in today's academic environment where I'm expected to show significant progress every few months. (See Figure 2.)

The reason we need to try so many possibilities is because we just don't know what the sequence for growing a battery or a solar cell looks like. But through a combinatorial, trial-and-error approach, we can in about three weeks train a virus to grow about fifty different kinds of materials in my lab. We can have them figure out the protein sequence that allows you to grow the inorganic sequence that can self-assemble into a battery.

One of the most exciting branches of my work on growing batteries has involved carbon nanotubes. Working with Professors Gerd Ceder and Michael Strano at MIT, we engineered a virus to first grow a benign material, amorphous iron phosphate, at room temperature, on the coat of the virus; second, to pick up a carbon nanotube; and third, to self-assemble into a battery electrode. The resulting battery weighs about 1.5 milligrams and can power a green LED. What's exciting about this is that, except for the carbon nanotubes, everything is made at room temperature and no toxic materials are used in or created by the process. To get to this point took about a year. Even more amazing, though, is that from this point we needed only about six months to train our organisms through selection and genetic engineering to make a high-powered lithium ion battery that is as good as state-of-the-art, traditionally produced batteries. (See Figure 3.)

By using biology to control nanostructure, we are opening up new vistas of opportunity for creating devices and structures that will improve the quality of life in areas as far apart as battery technology, cancer detection and treatment, and environmental remediation.



Evelyn L. Hu

Evelyn L. Hu is Gordon McKay Professor of Applied Physics and Electrical Engineering at Harvard University.

Presentation

The idea of combining novel materials by using nanoscale building blocks is relatively easy to grasp, and one can easily imagine the uses of nanotechnology in medicine or in creating energy-efficient devices. But what applications does nanotechnology have in photonics? What, for that matter, is photonics?

At the nanometer scale, the region between molecules and atoms, we have new opportunities. We can design optical materials that have any kind of performance we want – designer materials not found in nature.

The root of the word *photonics* is *photon*. A photon is a unit of light. So, photonics has to do with light, which comes in different colors and energies. By “colors” I mean more than just the colors in the visible range, which is the vast array of colors that gives us a sense of our external world and helps us to identify and label what's around us that we find aesthetically gratifying. The definition I'm using, however, encompasses the full electromagnetic spectrum, some-

thing that's been known since the nineteenth century. Only a small part of this spectrum is visible. Beyond the visible range are radio waves, microwaves, infrared, ultraviolet, X-rays, gamma rays – portions of the spectrum that most people tend to think of as being involved in communications, the transmission of energy, or in sensing parts of the world around us that are not usually accessible to the naked eye.

What is special about the nanoscale? How is nanotechnology applied to photonics? The electromagnetic spectrum is something we've lived with for a long time. How can we hope to change what is a given of nature?

At the nanometer scale, between 10^{-8} and 10^{-10} meters, the region between molecules and atoms, we have new opportunities. We have the ability to make efficient, compact, new light sources that have nanometer scales and functions in environments that are also measured in nanometers. We can design optical materials that have any kind of performance we want – designer materials not found in nature; for example, energy-efficient materials that can take in the full energy of the solar spectrum, store that energy, and then efficiently convert it into electrical signals; or an optical material that is transparent at a certain frequency (i.e., it will let certain frequencies of light go through, blocking all others).

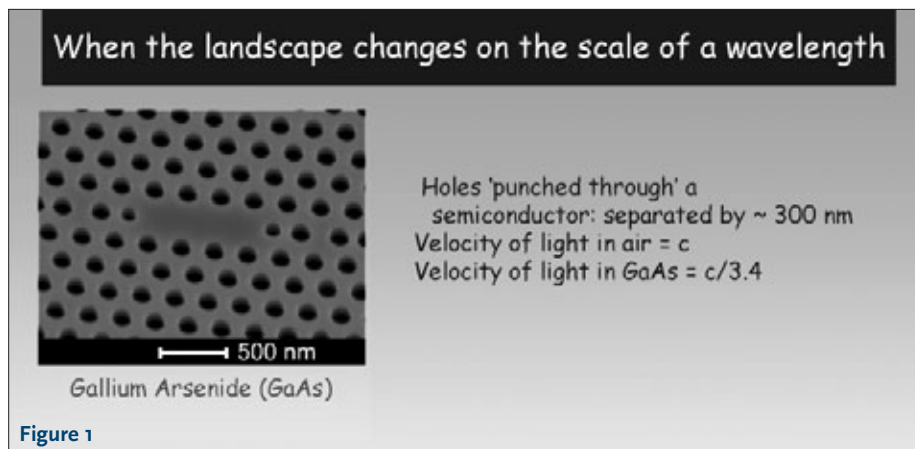
By the very fact that we can see light, we know that photons are active. They travel back and forth. They come into our eyes. They're full of energy. They have unique frequencies, which are related to their energy. Atoms also have energy, and part of their energy is given out in a signal that we can view as light or X-rays, gamma rays or UV signals. If we could design switches that would uniquely tune a particular atom or particular quantum dot – a particular beacon – to the exact frequency we wanted, if we could even change the frequency of the atom's or quantum dot's vibration, we could make uniquely tuned photonic switches and antennas. Such switches and antennas would take the information – the energy that is unique to that beacon – out of the ether and focus it onto that beacon. With the ability to make these uniquely tuned switches and antennas, we would also have the unparalleled capability to

make ultra-efficient sources of light: ultra-low-threshold lasers, light-emitting diodes, and other photonic sources.

These individual building blocks could then be combined to make photonic systems – photonic integrated circuits analogous to the electronic integrated circuits that power a PowerPoint presentation on a laptop computer and through an LCD projector. The photonic systems would provide information rapidly and with high output; yet they would be much more energy efficient because, unlike today’s electronic integrated circuits, they would dissipate far less energy in delivering information.

That intrinsically different properties emerge as size changes on the nanoscale is part of the mystery or the wonder of nanotechnology; it’s also an incredible capability, an amazing way to go beyond what Mother Nature has given us and design our own optical materials.

Most of the nature-given materials we have to work with come in a certain color, be it red, blue, and so on, and display certain properties such as fluorescence or absorbency. We’ve found, however, that we can define optical emission if we take, say, a single-crystal cadmium-selenium semiconductor with a regular, checkerboard-like array of atoms and carve little beacons (quantum dots) out of that semiconductor. The color, the absorption of the beacon, changes according to size. Certainly the material matters, but just as important is whether we make the beacons five nanometers in diameter, six nanometers in diameter, or eight nanometers in diameter (and so on). That intrinsically different properties emerge as size changes on the nanoscale is part of the mystery or the wonder of nanotechnology; it’s also an incredible capa-



bility, an amazing way to go beyond what Mother Nature has given us and design our own optical materials.

A given photon will have a certain wavelength, perhaps 100 nanometers or 10 nanometers or 300 nanometers. What happens when we change the landscape through which one of these photons passes? Specifically, what happens when we change the landscape in a periodic way so that it is no longer smooth and homogenous but is patterned at intervals roughly the same as the photon’s wavelength? I experimented with this idea by punching 100-nanometer holes in semiconductors made of gallium arsenide (a material that can also be used to create infrared light sources). The holes were set 300 nanometers apart. I then sent a photon with a 300-nanometer wavelength through the material. The result was incredible: the photon was confined within the landscape I had engineered. (See Figure 1.)

To understand why, we need to recall that light does not always keep the same velocity. The velocity of light in a vacuum is constant and is famously represented by c . But when light enters a material like glass or a semiconductor, it doesn’t always keep that same velocity. The velocity of light in gallium arsenide is slower than that in air or in a vacuum – slower by a factor of 3.4. (The factor by which light is slowed in a given medium is often called the index of refraction.) Imagine a photon traveling through the gallium-arsenide structure I created. As the photon passes through this landscape, it “sees” a periodic variation where it goes faster, slower, faster, slower. The modula-

tion is on the order of the photon’s own wavelength. By going faster, slower, faster, slower through a periodic medium, the photon “learns” that it is going through something, going faster and slower. One of the things that happens is that the photon may encounter – by going faster, slower, faster, slower – a region where this faster, slower, faster, slower ultimately, because of all the variation in the landscape, confines the photon to a unique location in space. Once the photon has been confined in a very, very small volume, a powerful electromagnetic field is generated. The electromagnetic field has a unique identification, a unique frequency that pertains to the engineered structure in which the photon has been confined. Because these kinds of structures are capable of confining photons for very long times without loss, we have, in effect, created a way of storing photons.

Now suppose we were to take this powerful electromagnetic field that is confined to a tiny volume of space and we were to put in the same location a quantum dot, a beacon capable of giving out light. Suppose we then turned on a powerful switch designed to resonate with that particular quantum dot. The result would be an exquisitely sensitive filter with applications ranging from selective transmission of information, controlled generation of single photons, to ultra-low-threshold lasers.

Currently, the filters found in most people’s radios allow for tuning to one or a few decimal places. For example, we might tune to a station broadcasting at a frequency of 102.3 MHz. But imagine being able to tune

The most exciting opportunities will come as we combine nanostructure building blocks. For example, by combining the full spectrum of colored quantum dots, we might create a new material that captures the full spectrum of the sun with high efficiency.

to 102.3444444556 MHz and getting a unique signal. Then tuning to 102.34445629 MHz and getting another unique signal. That's the level of sensitivity we can achieve with our nanoscale filters, antennae, and switches.

This level of sensitivity also allows for the creation of ultra-low-threshold lasers. Because we uniquely match the energy that we give to an optical component with the characteristics of that component, no energy is lost. Lasers that are made in this way have a threshold of about 100 nanowatts, a billionth of a watt: the lasers we use for laser pointers generally require *milliwatts* or more of input energy to turn them on. (See Figure 2.)

The most exciting opportunities will come as we combine nanostructure building blocks. For example, by combining the full spectrum of colored quantum dots, we might create a new material that captures the full spectrum of the sun with high efficiency. This new material could then be used to design ultra-efficient solar cells or designer coatings that reflect, absorb, or generate energy at a desired wavelength. Looking far into the future, we can see computers that process information with photons rather than electrons. Modern computer microprocessors such as Intel's Pentium 4 might make information processing fast and inexpensive and may be marvels of compact design, but as they switch, store, and guide electrons they dissipate tremendous amounts of energy. Photonic microprocessors would operate

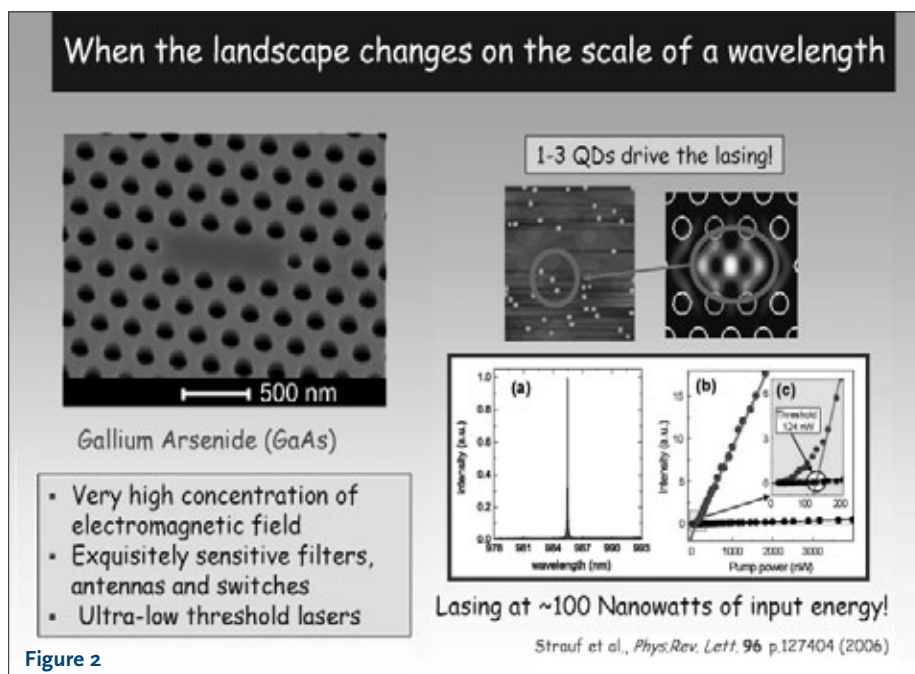


Figure 2

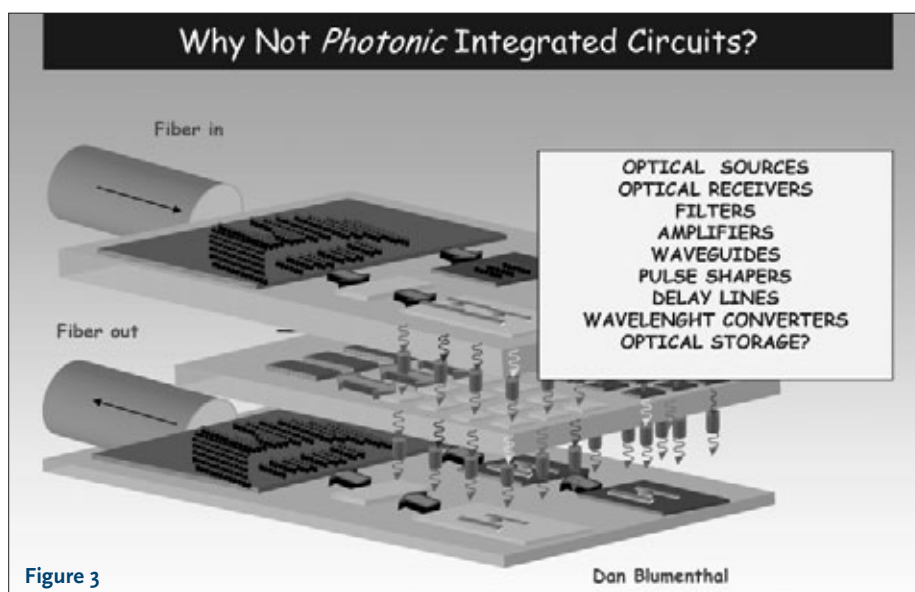


Figure 3

with almost no energy loss. My colleague Dan Blumenthal suggests that we already possess the necessary building blocks to do with photons what we can now do with electrons. (See Figure 3.)

Despite all we have learned about engineering nanostructures from the inorganic side, we still have far to go before we begin to emulate the engineering prowess of Mother Nature, which has had plenty of time to orchestrate her own nanophotonics. Consider the *Polyommatus* butterfly. The colors of its

wings are given by a photonic crystal nanostructure that modulates light on the scale of a wavelength. What is remarkable about this butterfly is the fact that two species – *Polyommatus daphnis* and *Polyommatus marcidus* – have adapted to have different colors (predominantly blue and predominantly brown), which tells us that these nanostructures can somehow be naturally generated. How we might begin to emulate nature's own engineering prowess is a story for another day, however.

Question: The prospects and the possibilities of nanotechnology are fantastic, but we also all know that new technologies always have a reverse side. I'm curious about your views on this and what measures you would take or would like to see taken to prevent the misuse of nanotechnology – either unintentionally in the case of materials that turn out to have toxic effects or intentionally in the case of materials designed to be misused.

Robert Langer: On safety: anything can be toxic, but I don't know that just because something is nano it is necessarily worse. The FDA has already approved nanoparticles that have been used for years on patients, including children, without any problems. So, being small doesn't necessarily equate to being toxic, which is sometimes the impression one gets when reading about nanoparticles in newspapers. I find it curious that although things exist that are smaller than nanoparticles (e.g., smaller molecules) and things exist that are bigger than nanoparticles (e.g., micro-particles), neither gets the same kind of bad publicity.

Being small doesn't necessarily equate to being toxic, which is sometimes the impression one gets when reading about nanoparticles in newspapers.

On misuse: I always like to hope and be an optimist that people will use things in a good way and that society will develop rules and laws so that new technologies are not misused. But I have no special expertise in that area. Other people may have better ideas.

By using biology to control nanostructure, we are opening up new vistas of opportunity for creating devices and structures that will improve the quality of life in areas as far apart as battery technology, cancer detection and treatment, and environmental remediation.

Angela Belcher: I agree with everything Bob said. I find it notable that the agencies funding nanotechnology research are also funding centers to study its environmental impact. Traditionally, organizations and individual scientists have not done that. They've just gone ahead and started making materials, doing the science and then twenty years on looking back to see whether anything bad happened. The fact that today's research is being conducted with an awareness of its environmental impact is a positive change. Even more significant is the fact that because research with nanomaterials occurs at a much smaller scale than does traditional materials research, it generates a lot less waste. Thus, even if someone is working with toxic materials – and some of the materials used in biological imaging and in solar cells are quite toxic – a smaller overall amount of those materials is being used, which should have a definite positive impact on the environment.

Question: What was the discovery that permitted nanoparticles? Was it material or theoretical? And, despite the extraordinary and awesome progress in nanoresearch, what is blocking the next advances? Is it material, or is it theoretical?

Evelyn Hu: Long before the launch of the National Nanotechnology Initiative, work was being done on colloidal chemistry, on metallic nanoparticles, on aerosol particles. What brought together the various research of materials scientists, chemists, applied physicists, and so on was the realization that they all shared an intrinsic interest in the properties of materials and how they scale. Many people say that all of a sudden they discovered they had been doing nanotechnology for most of their career, and so they just renamed themselves. I don't think it was quite as superficial as that. I think that people in different fields were made aware of the commonalities – the challenges, the instrumentation, the possibilities

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of putting materials together. Eventually colloidal quantum dots, semiconductors, and metal nanoparticles came into the hands of people who were interested in biofunctionalizing those materials, who realized they had their hands on materials that could be slipped through a cell membrane and used to do diagnostics or therapy. That's when nanotechnology came into its own and became much more than the various separate types of materials research being conducted in any number of discrete scientific fields.

Looking far into the future, we can see computers that process information with photons rather than electrons.

I think the next major challenges to be overcome in nanoresearch will involve creating the big systems and realizing the potential of nanostructures. Angie and Bob talked about systems. Angie talked about putting everything – all these smart, intelligent components – into a beaker and coming out with a battery or some other full system. The big future challenges will be getting the various components to articulate with one another, working out the secondary interactions, and making something that is robust and durable. In short, it's a challenge of complexity.

Question: Will you eventually develop a variety of nanoparticles that receive different signals? You might want a diagnostic system, for example, capable of bringing together a number of signals through a whole set of nanoparticles. How do you combine those nanoparticles so that they interact with one another? Can the effects of many nanoparticles be combined in an orderly sequence? Similar to antibodies, could you line them up, say, on DNA?

Angela Belcher: Much research has focused on how to put different nanostructures together, how to combine different optical, magnetic, and electrical properties in order to create something that is better than the individual components. A lot of beautiful work has been done decorating DNA at different base pairs by bringing in a semiconductor or a magnetic material, by mineralizing wires, or by using DNA specificity. Such research has been an active part of bionanotechnology for at least fifteen years. In my lab we create diagnostic nanodevices that, for example, use an antibody or a designer protein to grab a

magnetic or fluorescent material and put it on a cell that we're interested in while at the same time delivering a therapeutic agent to that cell. Nanostructures can be combined in a lot of different ways. For example, we can grow them together or coat one on top of the other. One of the problems that can arise, however, when we try to put two very different materials together is that chemically or physically or geometrically they don't match. Sometimes working with biological materials makes this less of a problem. For example, we might be working with a protein that will bind a semiconductor and a magnetic material in close proximity, but we don't need to worry about them matching because the protein provides a nice, soft biological template. ■

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