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The Insider

JOSH WOLFE, EDITOR

As a reminder, do not forget to join me and the entire team for the 2nd USA Science & Engineering Festival in Washington, DC on April 28-29. I will be sitting for an exclusive Forbes interview panel with earth shattering entrepreneurs Elon Musk, video game pioneer Richard Garriott and George Whitesides, a pioneer in modern space travel.

This issue features three similarly brilliant shining stars of science. We start with Peter Agre, Nobel Prize-winning chemist and head of Johns Hopkins' Malaria Research Institute. A few years ago, Peter was also inducted as the presi-

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Dr. Peter Agre: Putting New Proteins To Work

PETER AGRE

Peter Agre is a medical doctor, professor and molecular biologist who currently serves as a director of the Johns Hopkins Malaria Research Institute at the Johns Hopkins Bloomberg School of Public Health. Dr. Agre was awarded the 2003 Nobel Prize in Chemistry for his discovery of aquaporins, the proteins responsible for moving water through cell membranes. Agre has been elected to membership in the National Academy of Sciences and to the American Academy of Arts and Sciences. He also previously served as the 163rd president and chairman of the board for the American Association for the Advancement of Science, the nation's largest scientific organization. He holds two U.S. patents on the isolation, cloning and expression of aquaporins and is the principal investigator on numerous current National Institutes of Health grants. He received his B.A. from Augsburg College in Minneapolis and his M.D. in 1974 from the Johns Hopkins University School of Medicine.

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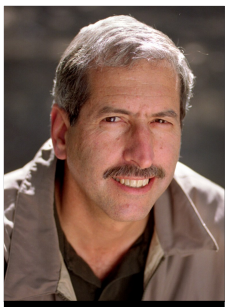

MARK ZOBACK

Dr. Mark Zoback: Geologist Finds No Fault With Fracking

Mark Zoback is the Benjamin M. Page Professor of Geophysics at Stanford University. Dr. Zoback conducts research on in situ stress, fault mechanics, and reservoir geomechanics. He was one of the principal investigators of the SAFOD project in which a scientific research well was successfully drilled through

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CAROL GREIDER

Dr. Carol Greider: Unraveling DNA

Dr. Carol Greider is the Daniel Nathans Professor and Director of the Department of Molecular Biology and Genetics at Johns Hopkins University. Dr. Greider is one of the discoverers of telomerase—a chromosome-protecting enzyme identified in 1984. This discovery led to the award of the 2009

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Dr. Peter Agre: Putting New Proteins To Work

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Why did you want to become a doctor?

I grew up in Minnesota, and my dad was a Chemistry professor, first at St. Olaf College, and then at another small Norwegian school, Augsburg College. A number of active medical missionaries lived in our town—nurses and doctors who went off to places like China, India and Africa to establish clinics, and they had an influence on me. Opportunities like these, to do good work locally and globally, attracted me to medicine.

As a student, I worked in several laboratories on problems related to Third World conditions, like cholera and diarrheal diseases. The people I met were not stereotypical, dogmatic, nerd-like scientists; they were vibrant, colorful people from all over the world. During medical school my passion to serve as a mission doctor in the field shifted to a desire to understand disease through molecular and cellular research. After my clinical training, I joined the faculty and made some discoveries in the lab, researching the proteins that control the entry of water into and out of cells—and got swept up in the excitement of that science for a couple of decades.

The research you refer to ultimately led to a Nobel Prize. How did you initially discover these proteins?

I joined the faculty at Johns Hopkins in 1984, in the Hematology Division of the Department of Medicine. I studied red blood cells and worked on one of the big unsolved problems in red cell biology related to the nature of blood antigens. In solving that problem, we identified proteins we didn't expect—aquaporins. The discovery was a very humble event—just a contaminating protein that was curious because it had unusual staining properties. It turned out to be extremely abundant in red cells, and eventually we realized this was the putative channel for water—a theory that was proposed a century ago, but never proven in terms of molecular identity. Based on the suggestion of our colleague, John Parker, at the University of North Carolina, we tested whether this new protein was, in fact, a conduit for water, and it turned to be amazingly active. There was nothing magical in the discovery—just the good fortune of having wise colleagues who could stick with a problem.

> **"I studied red blood cells and worked on one of the big unsolved problems in red cell biology related to the nature of blood antigens. In solving that problem, we identified proteins we didn't expect—aquaporins."**

Have any medical treatments resulted from your discovery?

No major changes in the practice of medicine have come about to date, but sometimes it takes a while before basic insights can be applied practically. This discovery explains how rapid osmosis occurs in some tissues, but not all tissues. All children in grade school learn about the process of osmosis through semi-permeable membranes. But osmosis moves extremely rapidly in some cells, like in the cells lining the salivary glands, the sweat glands or the renal tubules. If we could inhibit these water channels selectively, we might be able to prevent or ameliorate brain edema. The third leading cause of death in the United States is stroke and the demise of most stroke victims is due to uncontrollable swelling in the brain, which involves one of the aquaporins, known as aquaporin 4. On the other hand, some practical applications are starting to unfold. A group of researchers at the Mayo Clinic reported a breakthrough a few years back, related to a variant of multiple sclerosis known as Neuromyelitis Optica, or NMO. They have very clearly demonstrated that antibodies to the aquaporin 4 are the cause of this disease. Now we have a molecular diagnostic tool for 90% of NMO patients, and there's a foot race of people trying to develop treatments.

What about applications outside of human health?

Plants depend on aquaporins for the uptake of water from rootlets, and the biotechnology field is developing plants that have overexpressed rootlet aquaporins. Some plants do this naturally—that's how they compete for water during drought. This is a field where we need young scientists to stay at the bench and make observations.

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dent of the American Association for the Advancement of Science, the nation's largest science organization. His research delved into "aquaporins" the so-called plumbing system for cells and he once considered running for U.S, Senate.

We then sit down with Stanford's Mark Zoback, whose expertise is faults—more technically "crustal stress and geomechanics"—which you will care about in the context of fracking and the growing abundance and controversy of the extraction methods of natural gas. We dig into issues of sustainability, collapse and energy resources.

Also exclusive in this issue is yet another Nobel Laureate, Carol Greider, also at Johns Hopkins, who won the Nobel Prize for Physiology or Medicine in 2009. She discovered and explained the relationship of the most important structures in biology: the telomere and the enzyme telomerase (while at Berkeley). Telomeres are the ends of chromosomes and as cells divide the telomeres get shorter and play a key role in aging.

As always, here's to thinking big about thinking small...and to the emerging inventors and investors who seek to profit from the unexpected and the unseen….

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You mention a need for young bench scientists. Are there not enough young people pursuing science in the U.S. today?

That question is right on the money. In terms of our ability to attract young Americans into the field of science, the numbers are discouraging—especially when we look at the number of individuals in science that have not been siphoned off into the practice of medicine. However, we have a unique situation here in the U.S. For several generations, we have attracted brilliant young scientists from around the world, and many of them have stayed here. A third of American Nobel Prizes since World War II have been given to Americans who were born in other countries, but came here to do science. I'm optimistic that American science will, at least for the time being, remain eminent. It's a huge national resource—half of our economic gains come from scientific or engineering innovations, so we have many practical reasons to support American science.

When you look at the career decisions that young people are making today, what strikes you as a factor that may be different from when you grew up? Why are fewer people choosing science?

I grew up during an extremely exciting time. I was eight years old when *Sputnik* launched, and education had bipartisan support for major investments in science and engineering. The Eisenhower administration formulated NASA, and fellowships became available for people to do sabbaticals. My dad, for example, wrote a National Science Foundation fellowship, and the whole family moved to UC Berkeley for a year. We were the Norwegian equivalents to the Beverly Hillbillies, crossing the country in an old station wagon! In the 1950s and 1960s, scientists themselves were also in the public eye. Everybody in the country knew the name of Jonas Salk, the polio vaccine discoverer. Even on television, *The Disney Show* regularly featured science and technology episodes. Every little kid sat in front of the television watching Glen Seaborg, the Berkeley chemist, demonstrating chemical chain reactions.

Is science just not as exciting today? Or is there a challenge translating that excitement and interest to young minds?

Science is just as exciting now—or more so. I think the problem lies in the number of distractions. You might have 100 channels on cable television, and most of them are junk, which dilutes the quality of any science programs that are offered. There are so many news channels, but too many political talking heads and not enough science journalism. Too often only the controversial science stories hit the news. Cold fusion got a lot of press, for example, and it turned out to be a fallacy. I also have to be critical of my own scientific community. It takes time to go out and volunteer at the schools, especially when you're busy and hustling to get grants. But there's a point when we should be expected to promote science in the community.

At one point you considered a political race. What was the turning point for you, when you decided that science was the area where you choose to make a difference?

Early in my faculty career, it dawned on me that I didn't want to be hustling at a lab bench to the very end of my academic life. I hoped that by about age 50, I would serve as a public advocate for science, or promote science for peace in some way. The Nobel made that goal easy to achieve, because it brought so much visibility. But I had already become active in promoting science through the National Academy, where I served on the Committee for Human Rights—this is a behind-the-scenes organization that has worked for the release of more than 600 imprisoned scientists, engineers and health professionals around the world. I found that an effective and meaningful activity.

In 2008, I explored the idea of running for the Class B Senate Seat in Minnesota. I was deciding between making a run for the Senate and taking a new job as director of the Malaria Research Institute at Johns Hopkins. My interest in the Senate seat was largely altruistic—if we're going to have a health care debate, we should have doctors on both sides. Yet without profound inside support, or great personal wealth, it's very difficult to succeed. At that point in my life, there were too many wonderful things I would have had to give up, including my whole laboratory and the research activities.

Let's talk about your work with the AAAS and the Malaria Research Institute.

I was president of the AAAS (the American Association for the Advancement of Science) in 2009 and 2010, and chair of the Advisory Board in 2010 and 2011. During my term there, I got involved in the Center for Scientific Diplomacy. In that capacity I have become heavily involved in science diplomacy efforts. This work is non-governmental—it's a matter of U.S. scientists interacting with scientists in countries like North Korea, Cuba, Burma or Iran, where their governments may see us as adversaries.

My main job now is director of the Malaria Research Institute at Johns Hopkins Bloomberg School of Public Health. The Malaria Research Institute has now just celebrated its 10th anniversary. This wonderful program resulted from the private sector and the research community coming together, beginning with a donation by the Mayor of New York City, Michael Bloomberg. Mayor Bloomberg embraced the idea of a basic science approach to the curing of malaria. He funded it very generously and continues to support it, both financially and personally. Because of that large gift, the Institute has grown from only two full-time malaria scientists at the Bloomberg School to 25 faculty positions, each with a staff of four to 10. We have research activities in Zambia and Zimbabwe, and collaborate with a wonderful not-for-profit organization, the Matha Research Trust, which is affiliated with a regional hospital in rural Zambia.

We have dozens of graduate students and large federal grants for our research. My work on Malaria began 10 years ago, with a pilot grant from the Johns Hopkins Malaria Research Institute. I've gradually refocused my lab to work only on malaria, and reduced our numbers to a tidy group of three, because of the extensive need for travel, for science diplomacy efforts as well as malaria efforts. I view myself as an ambassador for science and a cheerleader for the fight to eliminate Malaria.

"When you cross the finish line with something important, something never before seen, you experience an intense joy that only scientists know."

Peter Agre

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What words of wisdom do you have for people considering pursuing a career in science?

First, the joy of a discovery is something that very few people will ever experience, outside of the field of science. The love of discovery has to be more important than personal or financial advancement. It's clearly an ultra-marathon. But when you cross the finish line with something important, something never before seen, you experience an intense joy that only scientists know. You have to really savor that, and you have to tolerate frustration and disappointment for long periods of time.

Quite frankly, this is not a business where the score sheet records financial gains. Intellectual capital is the goal. While I'm not underpaid as a university faculty member, when compared to my friends in clinical practice—well, our family vacations were always in a tent in a national park or someplace pretty affordable. But those are great vacations, and the kids loved them. But it's a competitive field nonetheless, it's not an easy road, and certainly not for someone who's faint-hearted.

What inspired you to get involved with the USA Science and Engineering Festival?

Any opportunity to bring science in front of kids and the public in a fun way is something that I like, and I was pleased to be included. I look forward to participating every year that I'm asked. One of the factors in the decision to take the job at Johns Hopkins was the location, which is just a commuter ride from Washington, D.C. That makes it very easy to participate in activities like the science festival. Young people have many ways to experience science, through school, scouting, camping, family activities—but it's important to show that science really does open doors. We need to keep developing the global community of scientists.

Who would you say is your personal hero?

Journalists sometimes assume that Albert Einstein would be my hero. I usually smile, and I say no, Huckleberry Finn is more like it—because if something looked interesting, he'd go for it. ET

Dr. Mark Zoback: No Fault With Fracking

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the San Andreas Fault at seismogenic depth. He is the author of a textbook entitled *Reservoir Geomechanics* published in 2007 by Cambridge University Press, the author/co-author of 300 technical papers and holder of five patents. In 1996 he co-founded GeoMechanics International, where he was chairman of the board until 2008. He currently serves as a senior executive adviser to **Baker Hughes** [BHI]. Dr. Zoback has received a number of awards and honors, including the 2006 Emil Wiechert Medal of the German Geophysical Society and the 2008 Walter H. Bucher Medal of the American Geophysical Union. In 2011, he was elected to the U.S. National Academy of Engineering. He recently served on the National Academy of Energy committee investigating the Deepwater Horizon accident and the Secretary of Energy's committee on shale gas development and environmental protection.

What insights can one take away from studying geology or geophysics?

People can talk about the subsurface from many different perspectives. For instance, how the rocks beneath us were formed and changed over millions or even billions of years. The way I look at the earth is as sort of a mechanical system—studying the forces in the earth's crust, and more recently, what those forces and active processes mean for oil and gas reservoirs, CO_2 sequestration, and how to apply these ideas and theories to the questions surrounding shale gas development.

What are the primary forces to consider?

Most people are familiar with the theory of plate tectonics—that the upper hundred kilometers or so of the earth is broken into these plates, and the plates move with respect to each other. Along the places where the plates interact with adjacent plates is where most earthquakes occur. But what most people don't think about is that the forces that actually drive the plates and cause them to move with respect to each other are actually transmitted through the plates, so everywhere you go there is force in the subsurface. It turns out that to solve a lot of interesting and important problems, we really have to understand what those forces are, and that's been my area of specialty for the last few decades.

When did you start applying your research in the world of oil and gas development?

I actually worked in the oil industry for two years before starting graduate school. In graduate school, I got very interested in earthquakes and some of the questions surrounding forces in the earth's crust. And about 20 years ago I started to see that some of the fundamental questions we were addressing about how the earth works were similar to the types of questions arising in oil and gas development locations. In fact, there was even better data to address those questions in those development environments. So I started to apply the methodologies and experimental approaches we had developed in research to actual problems in the oil and gas industry. That led me to work for a number of years on CO_2 sequestration, and about four years ago, I started working very hard on shale gas development, where geomechanics plays a big role.

What got you interested in shale gas?

As I started digging more into shale gas, I learned two things of great import. One was about the resource itself. By mid-century, the world is going to need about twice as much energy as is consumed today. The discovery that we can produce these enormous quantities of natural gas from shales located all around the world is a tremendous breakthrough. So in the context of just energy needs, the size of the resource is simply remarkable. When we consider different sources of energy, we need to look at everything, including the environment, the economy and national security. Natural gas also happens to be a relatively clean fuel. Yes, it's a fossil fuel, but when compared to coal (which is responsible for about half the electricity in the U.S.), natural gas only emits about half the CO_2 and also avoids problems with mercury, particulates and other pollutants. It's a much cleaner fuel.

Personally, I was also fascinated by these very complex rocks and the challenges involved with extracting gas as efficiently as possible with as small an environmental impact as possible. I realized the techniques my students and I had developed over the years were perfectly suited to help answer a number of really timely and interesting questions about what goes on in these horizontally-drilled, hydraulically fractured wells. We have ideas with immediate applications, because as we improve our understanding of what's going on in these reservoirs, we can make suggestions about altering operational practices that could produce more gas, for less money, from

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"By mid-century, the world is going to need about twice as much energy as is consumed today. The discovery that we can produce these enormous quantities of natural gas from shales is a tremendous breakthrough."

fewer wells. Literally tens of thousands of wells are going to be drilled over the next decade or so, and hundreds of thousands of hydrofractures are going to be done.

How old is the hydrofracking technique that kicked off this shale gas boom?

It really all happened in the last 10 years. About a decade ago, the techniques we used to drill and complete wells were beginning to turn the corner. You need to remember that these shales have permeabilities that are a million times smaller than a typical reservoir—gas does not flow through them very easily. George Mitchell, the founder of Mitchell Energy, is really the father of shale gas. They developed the technique that is most widely used today, which involves horizontal drilling and then successive fracturings, where pressurized fluid (effectively water, sand and a little soap) is injected to help increase the permeability of the shale. Hydraulic fracturing itself has been around for about 60 years, but this specific technique is what has made all the difference.

So from a geomechanical standpoint, do we understand what's happening down there in these shales?

Yes and no. Basically, what happens is the water penetrates pre-existing fractures and faults in the rock, causes these faults to slip, and that slipping of the faults makes miniscule little earthquakes that change the permeability of the shale. (These earthquakes are tiny—about the equivalent energy release of a gallon of milk falling off the kitchen counter). The effect is to increase the permeability from a point that was so extraordinarily low that gas could not be produced, to a point where commercial quantities of gas begin to flow.

Have we always known about these shales?

Everybody knows where these shales are. Places like the Barnett Shale are classically the source rocks for conventional hydrocarbon deposits. In many cases, they've known about these sources for 100 years. But finding these source rocks—these organic-rich shales—was just never very interesting because you couldn't get the hydrocarbons out. The traditional oil and gas industry has been about finding reservoirs where hydrocarbons have migrated out and accumulated over time. The whole shale gas boom is really about deriving hydrocarbons right from their source, as opposed to needing to find a reservoir.

Globally, source rocks are found all over. There are places where oil is also trapped in these rocks, so the technology invented for shale gas recovery is also being used to exploit oil from very low-permeability reservoirs. It's a true revolution in the oil and gas industry. It's now much more of an optimization problem as opposed to an exploration and discovery problem.

The environment is a topic that is often discussed in the context of natural gas. What do people need to know, and what are some common misconceptions?

I am very pleased to serve on a DOE subcommittee looking at the environmental impact of natural gas development. We've looked at these issues very closely, and there are a number of environmental challenges, but there are also a lot of misconceptions in the minds of the public. Most people think the problem with shale gas development is hydraulic fracturing or "fracking" as they call it. It turns out that hydraulic fracturing is really not the issue at all. The fluids that are used in fracking are relatively benign—basically water with a little friction reducer. People are suspicious about those fluids because the gas companies were given an exemption from having to declare the chemical composition, but our committee has recommended full disclosure of the fluids and you're seeing that happen—it's really not an important issue.

People are also concerned hydrofracks are going to contaminate water wells. Hydrofracks are typically made at depths of around 7,000 feet, whereas most water walls are within a few hundred feet of the surface. We know this contamination doesn't occur. There has never been a documented case in which hydraulic fracturing has contaminated a water supply. Any contamination that has occurred has typically been the result of old wells or wells that were poorly constructed. The three keys to protecting the environment in shale gas development: well construction, well construction and well construction. That's where the problems lie, and wells need to be constructed under local regulations that take the geology into consideration to determine what the best practices should be.

What about the produced water that comes back out of these wells? Is that an item of concern?

Yes, a little bit. When you inject water during the hydraulic fracturing process, the water picks up a lot of contaminants, and 25-50% of that water is then returned to the surface. The traditional thing to do with that water is to inject it into a disposal well. In a couple of cases in 2011, that has triggered small earthquakes. We've known for more than 40 years that the injection of water at depth can trigger earthquakes. No injection-induced earthquake has ever caused significant damage or harmed the public. It's a problem we can manage; we just need to be proactive about it. The other problem is that in some places, there are not good formations to be injecting this flow-back water. In those cases, operators have moved to recycle the water by placing it in man-made holding ponds to use for subsequent fractures.

How do you see this huge surge of inexpensive natural gas being utilized over the coming decade?

That's a very good question, because gas is a flexible fuel. I don't think there's any right or wrong strategy. What I predict will happen is that more gas will be used for electrical power, particularly in place of coal, and gas will start to be used more in transportation—mostly for large fleets that could be refueled easily. In a number of large cities in China, every taxi cab works on compressed natural gas. There are 10 million compressed natural gas vehicles in the world, and only around 150,000 in the U.S., so transportation is certainly one big potential use. I don't think we're ever going to see gas prices spike up the way they did in the past, because now you know there really is an abundance of the resource which will always damper upward price spikes. ET

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Nobel Prize in Physiology or Medicine, which Dr. Greider shared with Drs. Elizabeth Blackburn and Jack Szostak. Dr. Greider's research has included the role of telomere length in cell senescence, cell death and in cancer. Together with Dr. Calvin Harley, she showed that human telomeres shorten progressively in primary human cells. This work, along with work of other researchers, led to the idea that telomere maintenance and telomerase may play important roles in cellular senescence and apoptosis. Dr. Greider moved her laboratory to the Department of Molecular Biology and Genetics at The Johns Hopkins University School of Medicine in 1997. Her group continues to study the biochemistry and structure of telomerase, as well as the cellular organismal consequences and diseases related to short telomeres. Dr. Greider received a BA from the University of California at Santa Barbara in 1983 and a Ph.D. in 1987 from the University of California at Berkeley.

What made you decide to pursue molecular biology?

I was always interested in biology, and planned to become a marine ecologist. As an undergraduate I got to try out four different research labs during my freshman and sophomore years. When I hit the molecular biology lab, I realized that this was the environment where my interests lay. There's sort of a click when you solve a puzzle in the molecular biology and biochemistry realm, and I found that exciting and fun.

What were some of the puzzles that you found most intriguing when you first started out?

I realized right away that I wanted to focus on DNA. When I interviewed for a graduate program at UC Berkeley, I was able to interact with Elizabeth Blackburn, and she was working on a couple of really intriguing puzzles; my goal was to work with her on those projects.

Do you think you were drawn to the science itself, or were you intrigued by the way it was presented?

Both of those factors. Liz is certainly a charismatic person, and I was excited about her work. At the same time, the science was very different than what was happening in mainstream molecular biology. Many labs were doing a lot of experiments on development and transcription, but she was working on chromosomes. At that time, the topic of chromosomes was under-explored, and I like to go where other people aren't going, so that attracted me. These were interesting questions, without a whole of lot of people answering them.

Could you give us a quick overview of the research that ultimately led to your Nobel Prize?

We were interested in how the ends of chromosomes are maintained. Because of what we knew about how DNA copying works, we predicted that the ends of the chromosomes shorten every time a cell divides. The question was: How can they actually be maintained?

Liz Blackburn and Jack Szostak had proposed a surprising model, where they thought that cells had a way to elongate the telomeres. Again, this went against current thinking in the field. I wanted to test that, and see whether or not there was any kind of evidence to support that idea. While working with Liz Blackburn in her lab, I discovered the enzyme telomerase that actually does elongate the ends of chromosomes. It was an exciting finding, because it solved a very basic problem. At that time, however, telomerase seemed to have no apparent medical relevance, because we didn't even know the composition of the ends of human chromosomes. The clinical relevance was not recognized for several years.

You made this discovery almost a quarter century ago. Can you describe what it was like working in the lab at that time?

We were exposing our results to X-ray film, and these kinds of experiments took a number of days to complete. The most important part of this discovery happened over the holidays—it was actually on December 25 that I was in the lab, developing the results of the experiment. I wasn't ditching the holidays—I was just excited and wanted to see the results!

What was it like to get that call and find out that you had won the Nobel Prize?

Of course, it's a thrill when you get a call like that. I hardly even understood what they were saying on the phone, because once I realized who was calling, my adrenaline level shot up so high that it was hard to take in the specifics. I went to tell both of my kids, and their first comment was, "Do we have to go to school today?" And no, they didn't go to school that day. They came with me to the press conference, which was fun.

I saw winning this prize as an opportunity to highlight science in the public realm. People pay attention to the Nobel Prizes, and it gives me a useful soapbox to talk about science in the press. We hear a lot about sports and murders and things like that, but not enough about science.

Is your Nobel-winning discovery the work you are most proud of, or is there another puzzle or challenge that holds more meaning for you?

I'd say that the initial discovery of telomeres started it all, but we continue to follow our curiosity. I'm very proud to have contributed to a number of exciting discoveries that have stemmed out of the initial discovery that gave us a basic understanding of how the ends of chromosomes are maintained. We continue to study the role of short telomeres, which actually limit the number of times that cells divide, and can limit tissue renewal and cell turnover. To go from the study of molecular interactions to creating the potential to actually help patients is really very rewarding.

Can you tell us more about the clinical applications you are currently studying?

We're still at the fundamental cellular level, looking at how this research plays out in terms of human disease. We've been collaborating with a group of clinicians here at Hopkins who study people that have defects in maintaining the telomeres. As it turns out, there are devastating diseases that result from short telomeres, like bone marrow failure and pulmonary fibrosis. We never would have predicted that short telomeres would play a major role in human disease. But we pursued our interest through the use of mouse models—we identified what happens to mice when they can't maintain telomeres, and then six or seven years ago it became apparent that this same issue plays a major role in human disease. For the first time, we are beginning to understand the molecular basis of some of these diseases.

We live in a miraculous age, having benefitted from decades of scientific discovery and innovation. What big breakthroughs do you see driving us forward from here?

We have made tremendous technical strides over the last 20 years, especially as a result of genome sequencing. The genome is often discussed, but I don't think it's possible to

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"Because of what we knew about how DNA copying works, we predicted that the ends of the chromosomes shorten every time a cell divides. The question was: How can they actually be maintained?"

overemphasize the degree to which the sequencing revolution has changed the way we do science—and we now have access to the whole genomes of many organisms, as well as the human genome. It changes the way that we do day-to-day work in the lab, because what used to take five, six months now can be done in a day, because all of the information is already there. The sequencing revolution is opening up new avenues. I can't predict where we are along the trajectory, but our learning is accelerated.

What research, outside of your own, do you find exciting? Are there other researchers or other spaces that you are following?

The genomics area, certainly, and new gene-finding abilities. A huge amount of research is happening at the level of computation and predicting diseases. I call myself a human genetics groupie, and I like to keep up and see what's going on there. The area of stem cells has received a lot of hype, but there's a lot of interesting science. Sorting out the true breakthroughs from those that are overstated takes a bit of discernment, but it's very exciting.

If you could predict what the world of biological research will be like in the future, when your own kids have reached your age, how do you think the field will have evolved?

I certainly think that using genetics will be a part of medicine. We're trying to do that now—to apply our understanding of genetics and to use it as a predictor in medicine. I think that will be the norm, by the time my kids are my age. We can't even imagine the kinds of things that we will be able to see in terms of gene-gene interactions.

Let's switch gears for a moment and talk about your passion for science education and your involvement with the USA Science Festival.

Science education has always been important to me. Since the Nobel, however, I've realized that there is very little discussion in our society about science in general. If you ask the man on the street about a scientific issue, he'll rarely have any idea about any current controversies in science. The more science-literate our public can be, the more informed they'll be about their own health and about areas of revolutionary thinking. I believe it is very important to be able to put that in front of people.

It's also rewarding to interact with kids. I've been going into my kids' schools and talking to the classes, even taking over a class for a day. These kids are fun to talk to—they ask great questions without really having a lot of background, and they're full of excitement and enthusiasm. Where does that excitement go by the time they've graduated from college? Many college graduates will tell you "I don't know anything about science. It scares me." Well, the younger kids I worked with weren't scared at all! They were just interested. If I can spark an interest in just a couple of kids, I'll be happy.

Do you think this lack of science awareness among the general public has changed from the time that you grew up, or do you think this is something that's always been a challenge?

I don't think it's gotten much better or much worse since I was in high school. It's always been a challenge, in this country, to make science a priority. I lived and studied in Europe two separate times, and I think that there is more of a sort of a general discussion of science in Europe. That's my anecdotal experience, at least.

What do you think are some of the levers that we can pull, as a society, to help affect change in that area?

I'd like to see science made as accessible as possible, by having it be in the news, in the papers, and on the radio, in a way that can demystify it. Certainly it's possible to talk about complex things and say them in a relatively straightforward way. I make a point to try to do that in presentations that I give, and especially with high school kids and the general public.

Have you noticed a change in the demographics of the students that come to your own labs?

In general, there is a very large influx of Chinese students in the population of both graduate students and post-doctorate fellows at John Hopkins, as well as other places that I visit. That's a big difference from when I went to graduate school. I'm not sure that my particular lab necessarily reflects that trend, but these kinds of things can depend, to some extent, on the funding stream. Some training grants require that only U.S. citizens can be paid. But overall, I would say that there has been a major shift, not just in terms of Asia, but specifically China.

Do you see most of these post-graduate students sticking around to work in the U.S. or heading back to China?

Until two or three years ago, they all stayed. When I was a graduate student, there were a few Chinese students, and typically they just understood that they would stay here. But that has been shifting, because China has made a big effort to hire back the people that came here to train. People that made it up to full professor status and are running research labs are now recruiting students that had been trained, but they elect to return and work in China.

Throughout our discussion, you've mentioned curiosity and puzzle-solving several times. Can you leave us with your thoughts on why those ideas are so important?

Research that is fundamentally driven by curiosity and that is not necessarily targeted to one outcome can have truly profound effects on understanding human disease. That is really the key. Our labs have been able to make these connections from research on a molecular level to research on clinical diseases because we have been able to follow our curiosity. Yet freedom in academia depends on funding—as long as you get some funding for an idea, you can pursue whatever it is you want. ET

The Emerging Tech Portfolio

Company[symbol]	Coverage Initiated	Current Price	52-week range	Mkt Cap ($mil)
INTELLECTUAL PROPERTY INCUMBENTS Leading researchers in the physical sciences, with big potential for spin-offs and revolutionary breakthroughs				
GE [GE]	8/07	$19.24	$14.02-$21.17	$203,290.00
Hewlett-Packard [HPQ]	3/02	26.64	21.50-43.86	52,770.00
IBM [IBM]	3/02	197.76	151.71-199.23	229,400.00
LIFE SCIENCES Companies that are working at the cutting edge of medical technology				
Life Technologies [LIFE]	11/05	47.69	35.30-56.71	8,500.00
Nanosphere [NSPH]	11/07	2.05	0.89-3.60	89.06
ELECTRONICS Companies that have corralled the key intellectual property that will be the foundation for next generation electronics				
Nanosys [private]	3/02	n/a	n/a	n/a
ENERGY Companies that are developing high-efficiency, low-cost alternative energy technologies				
First Solar [FSLR]	8/07	35.58	29.87-163.00	3,070.00
A123 Systems [AONE]	9/09	1.95	1.51-9.66	245.85
ENABLING TECHNOLOGIES Tools and instrumentation that enable critical science and technology discoveries				
Veeco [VECO]	3/02	28.83	20.35-57.67	1,100.00
FEI Company [FEIC]	1/03	44.40	26.61-48.31	1,680.00
Accelrys [ACCL]	3/02	8.00	5.68-8.90	443.77
INVESTMENT VEHICLES Funds that have investments in promising emerging technology companies				
Harris & Harris Group [TINY]	5/02	4.27	3.17-6.00	132.37
PowerShares Lux Nanotech Portfolio [PXN]	8/07	6.65	5.41-10.30	22.75
PowerShares WilderHill Clean Energy [PBW]	8/07	5.93	4.80-11.00	210.68

Stock prices as of February 24, 2012

Word on the Street

GE: Shares were flat on the month. GE launched a 50-50 JV in health care IT with **Microsoft** [MSFT] called Caradigm. GE will begin independent operations in 1H 2012 to develop an open, interoperable platform and collaborative clinical applications. GE trades at less than 13x 2012 EPS estimates, as analysts expect the company will earn $1.54 per share in FY 2012 on revenue of $149.3B.

HPQ: HP fell nearly 6% after reporting a Q1 sales shortfall and warning that a turnaround would be a multi-year journey. Q1 profit was $1.47B ($0.73 per share), down 44% from the prior year period. Adjusted EPS was $0.92, above estimates of $0.87. Revenue slipped 7% to $30.04B. A shortage of hard disk drives accounted for half of the revenue decline. For the current quarter, HP expects EPS in a range of $0.88-$0.91, below the $0.95 consensus. HP reiterated a forecast for adjusted 2012 EPS of at least $4. Citigroup reiterated its Buy rating.

IBM: Big Blue advanced 3.1% to a new 52-week high. Warren Buffet is a big fan—**Berkshire Hathaway** [BRK] now has $10.3B invested in IBM shares. Sterne Agee initiated coverage of IBM with a Buy rating and a $230 price target, saying that the stock's current 11.4x forward P/E multiple on projected 2013 EPS of $17 should be more like 13.5x. Stern Agee called IBM's goal to reach $20 per share in profit by 2015 "achievable."

LIFE: Life dropped close to 3% on the month. Its Q4 profits rose to $127.4M (or $0.69 per share), from $70.7M (or $0.37 per share) a year ago. Excluding one-time items, Life earned $1.06 per share versus $1.04 consensus estimates. For 2012, Life expects 2-4% revenue growth and forecast EPS (excluding items) between $3.90-$4.05. The Genetic Systems unit was the star performer, with revenue rising 13% to $278M, driven by increased sales of Life's Ion Torrent genetic sequencing equipment. Life remains hedge fund Glenview Capital's largest holding (with $536M in value).

NSPH: Nanosphere spiked 21.3% after releasing Q4 and FY 2011 results. 2011 revenues were $2.5M, compared to $2.0M in 2010. Product sales increased from $1.4M in 2010 to $2.4M in 2011, driven by an increase in consumables revenue and system sales. Costs and operating expenses decreased from $43.4M in 2010 to $38.0M in 2011. NSPH's 2011 net loss was $35.4M, compared with $40.6M in 2010. NSPH ended 2011 with $39.3M in cash and equivalents.

FSLR: First Solar lost nearly 8% on the month after disclosing the DOE had not released loan funds to support the 230MW Antelope Valley Solar Ranch One project in California because of a delay in receiving a construction permit. Later in the month, First Solar said changes to a construction permit for a giant California solar project had been approved, potentially clearing the way for initial funding of the $646M loan. The DOE had originally approved the loan guarantee in September 2011. The delay will nevertheless cause a substantial hit to First Solar's Q1 earnings. UBS raised its price target to $49.50 from $36, asserting that FSLR could have upside from its three other large U.S. utility projects. First Solar will release Q4 results after the close on February 28. Analysts expect FSLR will earn $1.55 per share on revenue of $782.2M.

AONE: A123 dropped 10.6% after its largest customer, EV maker Fisker, had its DOE funding suspended. Wunderlich downgraded the stock to Sell (from Hold), and lowered its price target from $3 to $0.50. The bank believes Fisker will lower production expectations further, reducing A123's sales prospects. A123 separately announced a deal to sell six of its grid battery systems to Northern Powergrid, a U.K. subsidiary of MidAmerican Energy Holdings. A123 has shipped more than 90MW of battery systems that utilities use instead of gas-fired peaker plants. A123 said its grid business now comprises 40-50% of the company's sales.

VECO: Veeco rocketed 18.6% higher after weak Q4 results still topped investors' pessimistic expectations. Veeco posted Q4 revenue of $191.7M, with non-GAAP profit of $0.61 per share. Wall Street had expected revenue of $193.4M and non-GAAP EPS of $0.68. VECO now sees Q1 revenue of $115-$140M, with non-GAAP EPS of $0.13-$0.34. Analysts had expected $0.41 in non-GAAP EPS on revenue of $153.89M. Veeco said business conditions in LED deteriorated during the quarter, with customers rescheduling shipments. LED and solar bookings declined 40% sequentially to $67M. CEO John Peeler said VECO sees no signs of near-term improvement in the LED industry and current overcapacity could mean that tool orders remain at depressed levels for multiple quarters. Veeco has nearly $500M in cash at and virtually no debt to ride through the downturn.

FEIC: FEI slipped nearly 2% despite breaking all-time records for Q4 sales and EPS, completing what CEO Don Kania called a "transformational year." Quarterly sales increased 14% to $213M, while net income jumped to $29.1M (or $0.72 per share). Wall Street analysts had expected $0.64 in EPS on $210.7M in sales. FEI reported record FY 2011 sales of $826.4M (up 30% YoY), while profits nearly doubled from $53.5M (or $1.34 per share) to $103.6M (or $2.51 per share) in 2011. FEI's cash and equivalents stood at $456.1M at year-end.

ACCL: Accelrys gained 7.4% on no news. ACCL will report its Q4 results on March 6; analysts expect Accelrys will earn $0.07 on $38.8M in revenue.

TINY: Harris & Harris Group lost 6.8% despite a recovery in its largest portfolio company **Solazyme** [SZYM].

PXN: The PowerShares Lux Nanotech edged almost 1% higher.

PBW: The PowerShares WilderHill Clean Energy portfolio gained 2.6%.

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