

**Keynote Speech**

Dartmouth Medical School Class Day  
June 13, 2009

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**Tales of Discovery from a Life Without Borders**

Thank you Dr. Green, and thank you all for this wonderful opportunity to share this special day with you. And it's an incredible day because it is not only the end of your student days; it's also the first day of the rest of your professional life.

Looking out at you, I remember sitting in my black gown under a tent just like this one at my own medical school graduation exactly 25 years ago. I can still remember the feeling of sheer relief when I realized that I had completed all of the courses, and the rotations with every-other-night on call, and the sub-internships, and the boards, and my dissertation, and that I actually had come to a decision about my future plans. It was a great feeling to know that it was all over, and I thought there finally would be some rest.

But the reality is that everything you have done until now – all of the knowledge, skills and understanding of the human condition you have gleaned so far- it's simply to 'prime' you for the future. It's a gunpowder charge that is about to be lit afire, and to drive you forth at full speed like a cannon ball. It sounds a bit terrifying, and at times it is. But because a life in medicine can improve the lives of others, it's one of the most exciting and rewarding paths that anyone can follow.

Having gone through the gauntlet of medical school myself, I know that no matter how varied your interests were before you entered, you've had to put on the blinders for the past four years or more. You've had to focus all of your attention on the task before you, and to move forward systematically one-step-at-a-time to get where you are today.

My main message today to you is simple: When you are shot out of that cannon, stay focused, but take off those blinders, and be willing to weave this way and that, as you fly forward into the future. I say this because we live in a nonlinear world where moving forward step-by-step in a straight line doesn't always get you to where you want to be. Even worse, you may get side swiped, without even knowing what hit you.

Most of you are familiar with paradigm shifts in science. This is when one dogma that has dominated a field for many years is abruptly replaced by another

competing theory or viewpoint. It's like when tourists clustered behind a tour guide who holds up a black umbrella rapidly shift their direction in unison, like a school of fish, because someone else by chance opened a new umbrella. These abrupt all-or-none responses can turn a scientific field on its head, and it happens in medicine as well.

Not long before I entered medical school, the standard care for treatment of serious stomach ulcers was a major surgical procedure to remove a large part of the stomach. Not long after, the same condition was treated with antibiotics, H2 blockers and proton pump inhibitors; and many gastric surgeons were looking for new sources of income.

Midway through my clinical rotations, patients began to present with strange fungal pneumonias, and red and purple patches on their skin. I remember collecting tracheal aspirates and blood samples on one of these patients without taking any precautions. A year later, fears of transmission of what we eventually called "AIDS" were so great, and the safety precautions so onerous, that hospital staff sometimes refused to enter their rooms and simply left their meals outside their doors. It took us all by surprise.

When I left medical school to join the laboratory of Judah Folkman as a postdoctoral fellow, his theory that capillary blood vessel growth, or what is known as "angiogenesis", could be a clinical target for cancer therapy was belittled and scorned. Now the FDA describes anti-angiogenesis as a new modality for anti-cancer therapy, alongside surgery, radiation therapy and chemotherapy. And who would think that blind people with macular degeneration would regain their sight by treating them with an anti-cancer drug, which is exactly what has happened.

There is no doubt: we live in a nonlinear world where transformative change does not occur incrementally bit-by-bit; it happens quickly and often with little forewarning. For you parents out there: just think of the Stock Market over the past year.

In fact, this is a fundamental property of all living systems. In the embryo, stem cells do not turn into lung or liver or kidney by turning genes on and off one at a time; they change thousands of genes simultaneously and then make an all-or-none decision to become one cell type or another.

Those of you who are medical students, think back to when you were on the wards. If you spun down a urine sample and counted more than 100,000 bacteria/ml, you diagnosed the patient with a urinary tract infection and treated them patient with antibiotics; whereas if you only counted 99,999 cells, you'll called it normal.

This empirical value of 100,000 bacteria is an example of a ‘tipping point’: a small change leads to a huge difference in outcome. This is a central feature of all nonlinear systems, and it’s something we all have to learn to accept as a governing force in medicine, as well as in our everyday lives. If you move through life moving straight ahead one-step-at-a-time with blinders on, you might just walk into a wall that wasn’t there when you started.

Now there is a trick to deal with this type of rapidly changing world, and virtually all of the cells know how to do it. When an immune cell, such as a macrophage or a neutrophil, senses an invading pathogen in our body, it doesn’t move towards it in a straight line. The cell darts about this way and that, sniffing like a hound dog searching for a scent; but with each dart and weave, there’s always a slight bias in one direction, moving the cell closer and closer to its goal. Although the path is different every time, the cell always gets to its target. By wandering, the cell can patrol much larger expanses of its territory and as a result, it can make serendipitous discoveries along the way, such as uncovering previously hidden invaders.

Physicists describe Brownian motion of gas molecules that move about aimlessly as a ‘random walk’. Biologists describe this type of movement in which the cell darts about, but always leans in the same direction towards its goal as a ‘biased random walk with persistence’. I am very familiar with this behavior, because this is precisely how I have moved through my life.

If you look at the description of my academic titles in the Class Day program, you will see that I have an endowed chair in the departments of pathology and surgery at Harvard Medical School and Children’s Hospital Boston. Yet, I never completed training in either pathology or surgery, and I am not a pediatrician. I am also a Professor of Bioengineering in the School of Engineering and Applied Sciences at Harvard, and the Founding Director of Harvard’s new Wyss Institute for Biologically Inspired Engineering. But I have never taken an engineering course in my entire life. So how did I get here?

Strangely, my story starts in an undergraduate art class, which I elected to take even though I was a science major. One day my professor brought in a ‘tensegrity’ sculpture into class made of sticks and elastic strings that looked much like this toy I am holding before you right now. This structure is composed of sticks connected by elastic strings. Without the sticks, the network of strings would lose its shape and become limp, like a spider web cut from its attachments. But because the sticks resist the inward pull of the strings, the whole structure is placed in a state of isometric tension that stabilizes it in this round form. The tensegrity building system was first described by Buckminster Fuller, the inventor of the geodesic dome, and the sculptor Kenneth Snelson. It gains its shape stability by balancing tension and compression between struts and strings, just like bones and muscles do in our body. For example, the stiffness of my extended arm depends on the level of isometric tension or ‘tone’

in muscles, just like in this model.

As my art professor spoke, he pushed this round sculpture flat, and when he let go, it leapt up in the air. This was interesting, because I had seen the same behavior just days before when I first learned how to culture cells across the campus in a medical school laboratory. Cells flatten when they adhere to a culture dish, but when you detach them, they round up and jump off the dish just like this toy. This was in the mid 1970s when people still thought of cells like water balloons filled with molasses. But scientists had recently discovered that all cells have an internal skeleton made of molecular 'acto-myosin' filaments that generate mechanical tension, as in muscle. So I just assumed that cells must be tensegrity structures.

Later, when I went back to the medical school lab, and saw cancer cells changing shape under the microscope in response to a drug we were testing, I spurted out something like, "Oh, the tensegrity must have changed". The postdoc I was working with said, "What did you say?", and I explained about my art class and Buckminster Fuller, and the sculptor Snelson, and sticks and strings; and he said, "Well, never say that again". And, as they say, that was the beginning of the rest of my life.

This strange encounter at the border between art and science led me to think about biology in entirely different ways than my peers or my mentors, when I entered medical school and graduate school as an MD/PhD student. I came to realize that mechanical forces, such as tension on skin, compression on bone, shear in blood vessels and pressure in lung, are as potent regulators of cell growth and function as chemicals and genes. I also began to see cancer as resulting from a breakdown of the rules that normally guide how cells form into tissues, and tissues into organs. Perhaps the reason cancer is so terrifying is that it is essentially a disease of what makes us us.

When I graduated from medical school, I decided to do a combined research-residency in pathology, but I began by doing full time research in the lab of Judah Folkman. I joined his group for two reasons: one was because he was one of the few scientists who did not view cancer as resulting entirely from uncontrolled cell growth; he too saw cancer as a disease of the tissue and organ. The other was that he had recently published a breakthrough paper, which suggested that the physical shape of a cell – whether it is spread flat or round - controls its proliferation, with spread cells growing faster. But he had no idea how this could work. I thought that tensegrity and mechanical forces had something to do with it. So I joined his group to study cell shape and growth control in capillary blood vessel cells.

One day, about a year after I joined Folkman's lab when I was working on a weekend, I discovered a fungus contaminating one of my capillary cell cultures. If you work in a lab, you're trained to sterilize a contaminated dish as soon as you

find one, so that it does not spread to the other cultures. But this fungus was different than any other I had seen. The others caused all the capillary cells to die and pop up off the dish, whereas this one appeared to induce a gradient of cell rounding, with the cells farthest from the fungus appearing fully spread and completely healthy.

Because I believed that cell spreading is important for growth, I thought that this fungus might be producing a chemical that inhibits capillary cell proliferation, and perhaps cancer growth as well. To make a long story short, that observation led to the development of the first angiogenesis inhibitor to enter human clinical trials, and eventually to a *New England Journal of Medicine* article that described the first complete cancer remission in a human patient with metastatic cervical cancer using this drug.

But then how did I move from being a cancer researcher to my current position as Director of a new Bioengineering Institute? Again, the migration took the form of a random walk with a persistent bias in one direction. The strange idea I had - that physical forces regulate cell and tissue development - required that I seek out ways to test my hypothesis. And this required that I learn how to play with others, in this case engineers, physicists, chemists, experts in magnetism and lasers, and eventually computer scientists as well. Along the way, we were able to confirm that cells are indeed built like tensegrity structures, and that mechanical forces are critical for control of tissue formation, wound healing and various disease processes, including angiogenesis and cancer. In the course of these explorations, I also was provided with the opportunity to get involved in the world of business by starting new companies, one focused on engineering artificial tissues, and the other on crafting new medical devices.

It was likely because of this history of crossing boundaries between disciplines that the Provost of Harvard University invited me to co-chair a committee that was challenged to envision the future of Bioengineering across the entire university. What we found is that up until now, bioengineers have applied engineering principles to solve medical problems. It's sort of a technology push. But we are now at a tipping point in the history of science and engineering: we are beginning to understand enough about how Nature builds, controls and manufactures, that we are going to uncover entirely new engineering principles that will transform medicine, as well as non-medical areas that were never before touched by the biology revolution. And so we proposed that Harvard form a research Institute focused on discovering Nature's design principles, and on applying these insights to engineer bioinspired materials and devices to confront these challenges.

In January of this year, we received the largest philanthropic gift in Harvard's history - \$125 million - from Hansjorg Wyss to make this vision a reality by launching the Wyss Institute for Biologically Inspired Engineering. Over the past six months, we have undergone a process of self assembly in which faculty from

engineering, medicine, biology and the physical sciences have begun to work together in entirely new ways. Unlike many bioengineering efforts, we are not looking to make incremental near-term improvements in biomedical technologies. We have been challenged to carry out high-risk research that will lead to transformative change. The Donor has told us, “If you don’t fail at a lot of what you set out to do, then I will view the whole Institute as a failure.”

At the Institute, we now have teams developing what we call “Anticipatory Medical Devices”. Right now medicine is static: you go to visit your doctor once a year for a physical, have your heart and breathing rates measured, and then you’re sent off again for another year. But scientists are discovering that there’s incredible richness in the dynamics of our body’s natural rhythms. If your heart rate is perfectly sinusoidal at a rate of one beat per second it actually means you are likely near death, as seen in patients with congestive heart failure. Normal heart rhythms have subtle rate variations that physicists are now using to develop algorithms to predict and diagnose disease processes.

Imagine a future where we all wear medical iPhones on our belts that remotely sense our body’s natural rhythms, such as breathing rate, heart rate, gait, brain waves, and someday, changes in glucose levels and even gene expression. These devices also would have on-the-fly software to detect adverse events before they happen. And then they would provide actuation signals using mechanical stimuli, infrared light, electrical signals or magnetic fields that reboot the rhythm back to normal, or prevent it from ever happening. The parents in the audience might remember the old TV commercial with an elderly woman who would call out: “Help! I’ve fallen and I can’t get up!”. In this case, it would be: “Help! I’ve fallen and I can’t get up!, Oh, no I am okay!”. We view this as the future of Autonomous Home Healthcare.

Other groups are designing and synthesizing what we call “Programmable Nanomaterials”. In the news, you hear a great deal about stem cells being used for tissue and organ regeneration. Scientists in this field currently isolate stem cells, culture them outside the body, and then reinject them. I am a cell biologist, and this doesn’t make much sense to me because we can never create culture conditions that are as good as those of our body. We are trying to create nanoscale materials that can be programmed so that when they are injected through a needle, they will target to injury sites, such as a heart infarct. Once there, they would self assemble into scaffolds that recruit endogenous stem cells, and guide these cells to promote tissue and organ regeneration. Or imagine injectable microscopic robots that target to every atherosclerotic plaque in your coronary arteries, and then swarm together to form into many small stents that expand from within.

Different engineers are creating miniaturized devices that contain microscopic fluid channels lined by human cells, which function like organs-on-a-chip to replace animal testing for drug development, and some are even being

used as therapeutics. We now have a breathing lung on a chip that has a channel lined by airway epithelial cells, which are attached to a flexible porous membrane that has capillary cells and a blood channel on the other side. And the whole structure extends and relaxes rhythmically like cells do in the living lung. This device is being used to study aerosol-based drug delivery, lung inflammation and the effects of airborne toxins. We also have developed an artificial spleen to remove pathogens from blood in patients with sepsis.

Other groups are harnessing the natural processes of evolution and selection at the molecular level to create new gene circuits to reprogram living cells. Imagine someday having a bacterium that normally inhabits your tooth plaque, which is engineered to sense variations in blood glucose and to manufacture and secrete insulin when needed, at no additional cost. We are even exploring the possibility of using this cellular reprogramming strategy to reboot cancers so that they stop growing and turn into normal tissue. This may sound strange, but this is what I see coming down the line in your lifetime.

So to close, let me remind you that the future is not something that you confront; it's something that you can craft and sculpt, if you set your mind to it. At the end of this ceremony, each of you will march off in a different direction, and no two paths will be the same, just like with living cells. At times you may feel lost, but each of us has an internal compass that is governed by a balance of forces, much like my tensegrity model; only in this case, the forces are those of boredom and exhilaration. You need to walk away from monotony, and to allow yourselves to be pulled towards intellectual passion like iron to a magnet. Your path might take some confusing turns, and you might even find yourself in some dead ends. But the elation of discovering something no one has ever discovered before - whether it's a new therapy for Alzheimer's, an implausible but likely cause for an epidemic, an element of a patient's dream that illuminates their hidden conflict, finding the perfect nursing home for a desperately ill elderly patient, or developing a solution to our healthcare reimbursement problems – this is what will make it all worthwhile, and it will be impossible for you to turn back.

So I wish you all the best of luck, and I hope that you all follow your own passion gradient and find your own inspiration, whether it be in biology, medicine, business, healthcare policy or any other path that you might choose to pursue in the future.

Thank you.