Last year the College adopted a logo: “we change the way the world works”. It couldn’t be more appropriate. Engineering has revolutionized every aspect of our lives: the aerospace engineers have conquered space, the electrical and computer engineers have transformed our most basic institutions, from business and finance to science; the civil engineers have introduced methods of waste disposal that have drastically reduced infectious disease, prolonging life by decades; the manufacturing engineers have redefined the factory floor, stimulating large segments of our economy—and the list goes on. Engineering has changed demography, shaped the global power balance, and made modern society possible, immeasurably improving the human condition.

Engineering has been so successful, and it is so infused into science and everyday life, that when news headlines herald a scientific breakthrough, most people aren’t aware of the engineering behind it. A commonplace example is the word processor and the sophisticated engineering mathematics that makes it possible. A more recent example, and one that I and a number of other faculty here in our College have been involved in, is the Human Genome Project.

The Genome Project is an engineering project. It was conceived as an engineering project in its technical methods—robotics, high-speed computation, massively parallel nanotechnology and so on; and it was planned and managed as an engineering project—with goals, milestones, timelines, target budgets and the like. As with all engineering projects its general goal is to improve the human condition—in this case by providing the knowledge and technology that will revolutionize the practice of medicine.

But the history of the Project contains messages that are more general than the technical and medical. These can best be understood by starting with some biological context.

A genome is a set of instructions written in an alphabet of four letters, the chemical bases that are components of the DNA molecule, whose sequence contains the information required to manufacture proteins, much as the sequence of letters in a sentence might contain the information required to manufacture a machine. The manufacturing process in the cell, with its receptors that transduce environmental signals, and its network of feedback loops that control the timing and production of proteins, that buffer against and utilize stochasticity, has been honed and optimized over hundreds of millions of years of evolution by natural selection to arrive at an engineering miracle.

In the haploid human cell, the full set of instructions is written on some 40,000 genes distributed over 23 chromosomes that contain 3 billion bases. It’s this set of genes and multiple regulatory regions that, in the fertilized egg, guides the development of a human being— from embryo, to fetus, to infant to adult. It’s the genome that determines the formation of the heart, the lungs, the central nervous system, the immune system and every other organ in the human body. It’s also the genome that determines whether we are free of, or contract, some 3 000 genetic diseases including sickle cell anemia, Huntington’s chorea, Down’s syndrome and cystic fibrosis. And it’s the genome, along with environmental factors, that shapes our predisposition to more complex disorders including cardiovascular disease, stroke, obesity, diabetes, Alzheimer’s disease, and virtually all mental illnesses.
The goal of the Human Genome Project is to determine the complete sequence of all 3 billion bases. But there are, of course, many human genomes. One of the most striking characteristics of the human population is diversity. You only need to look around this audience. No two of us appear to be alike, so when the idea of completely characterizing a human genome was proposed, it seemed senseless to most people. The common question was whose genome would be characterized. After all, there are several billion different human genomes on the planet. But in spite of appearances we are all very much alike. We differ from one another by only about 1 base in a thousand. At the most fundamental level of life, we are 99.9% identical. That’s the first message I’d like to leave you with: science teaches us that in spite of appearances, we are all very similar. Actually, the best literature has been teaching us the same thing for centuries, but in a different context.

Earlier this year researchers announced that they had obtained a draft of the human genome. With a reference genome in hand we can now compare genomes and begin to understand the variation in susceptibility and resistance to disease found in the human population. Each of our genes has three or four common variants, or alleles. If you compare one of your genes with the same gene in your neighbor, the chances are 1 in 3 or 1 in 4 that they are identical. Even when they are not identical, they differ only slightly from one another, but those slight differences are sometimes medically important. For example, a gene called Apo E, which is related to proteins that carry cholesterol, has 3 forms: E2, E3 and E4. About 7% of the population has the E4 allele. Those who have it, also have about a 50% chance of contracting Alzheimer’s disease.

One way to determine the genetic basis of risk is by comparing the alleles of a group of people having a particular disorder, with those of a suitably chosen control group that does not have the disorder. In that way association can be found between sets of alleles and propensity toward specific diseases, just as Alzheimer’s has been associated with Apo E4. The best technology for cataloguing alleles has been developed by our former Chair of Biomedical Engineering, Charles Cantor. As a result of studies using his technology we will in time learn how to predict susceptibility to disease, decades before onset. Predictive, proactive medicine with intervention well before the appearance of disease will be the paradigm of the future.

The reference genome will also permit more effective intervention and therapy. Many disorders that are now classified as a single disease, actually consist of many closely related diseases. For example many older men have prostate cancer, but only a small percentage require surgery. Those that do cannot be readily distinguished from those that do not; the result is many needless surgeries with sometimes debilitating side effects. New technologies that use the results of the Genome Project provide the ability to stratify and diagnose disease at a sensitivity never before possible.

The technologies consist of small silicon chips—much like computer chips--that can be used by scientists, engineers and physicians, to compare the genes that are active in a cancer cell with those that are active in a normal cell of the same type. For example a group of scientists at the Whitehead Institute compared cells from patients with acute lymphocytic leukemia and acute myeloid leukemia, and found that the two closely related diseases can be distinguished by 38 genes. The finding and its verification are important because correct treatment requires correct diagnosis. One of our own Biomedical Engineering faculty, my friend and colleague Simon Kasif, has gone further. He used a machine-learning algorithm well known in computer engineering circles, and found that the two leukemias can be distinguished using only a few genes. If that holds, it can provide the basis for a simple, inexpensive diagnostic.
The ability to determine which subset of thousands of genes expressed by a cell will distinguish closely related diseases, rests on a nanotechnology that has become an entire industry. A sophisticated version of that technology is being developed right here at Boston University, in a collaboration between biomedical and manufacturing engineers, the Fraunhofer Institute, researchers from the medical school, and faculty in our chemistry department. The machine for manufacturing these microarrays will be operational later this summer.

Now that the Genome Project is complete, it seems as though it was inevitable, and everyone is excited about it. In fact it was highly controversial 15 years ago. I thought long and hard about what the critics were saying, discussed it with members of our advisory committee and with many other people, modified plans when modifications seemed appropriate, but in the end concluded that there was no reason to abandon the Project.

Although we went forward, it was not without deep concern. My major concern was not technical, it was moral. It concerned privacy, discrimination and other civil liberties that would be challenged by the new technology. All major technologies that are destined to change society are beset with dilemmas. So we made a decision to set aside 3% of the funding for ethical and legal studies; i.e. we did not want the technology to move ahead without simultaneously thinking hard about how we would control it, and guard against its misuse.

What lessons can be gleaned from the history of the Genome Project? I’ll mention only a few. The Genome Project is first and foremost a human enterprise, and like all human enterprises, technology is only a part of it. To initiate it required overcoming psychological barriers raised by the awareness that a very expensive project could easily have failed for numerous reasons, many non technical. The project was carried out during the longest period of economic prosperity on record, making it relatively easy for the Administration and the Congress to provide support. If the economy were tight, the project would very likely not be complete today; and the politics would no doubt have been much more complicated and unpleasant. So perseverance during the initial years—when we didn’t know the economic forecast, and when we were being roundly criticized, was essential. That leads to the second message: perseverance is crucial to success.

Let me give you a briefer and perhaps more dramatic example of perseverance. It’s the story of a man who’s familiar to all of us, and it goes something like this.

Age 23 He runs for state legislature, and is defeated.
Age 24 He fails in business, but later that year is elected to the state legislature.
Age 26 He’s devastated by the premature death of his fiancé, and a year later has a nervous breakdown.
Age 29 He’s defeated for speaker of the State House
Age 34 He’s defeated for nomination to the US Congress
Age 39 He’s elected to Congress, only to lose his seat when he runs for reelection two years later
Age 45 He’s defeated in his bid for the US Senate.
Age 47 He seeks nomination for the Vice President, unsuccessfully.
Age 49 He’s again defeated for the Senate.

Then finally, in 1860, at the age of 51, Abraham Lincoln is elected the 16th president of the US

There are many stories of this sort—of persistence in the face of setbacks; of advocacy for what you know is right in the face of criticism; of perseverance when the odds are stacked against you. They can be told of some of the greatest scientists in history. In the early 20th C an astronomer
Alfred Wegener proposed a theory that the land mass of the Earth was entirely continuous until the late carboniferous period, about 300 million years ago, and that it subsequently fragmented into the continents, which float on a liquid mantel. For 5 decades the theory was ridiculed—but it’s now accepted as one of the most fundamental scientific breakthroughs of the 20th C. Then there was Charles Darwin, whose deeply beloved wife, a highly devout Episcopalian, was severely depressed by her husband’s theory—which verged on heresy. And Galileo’s battles with the Church. But those are stories for another time, and I think the message is in any case clear.

During the later years of the Genome Project thousands of researchers were involved. But even in the early years—like everything else in science and engineering—many people contributed. It required cooperation between people often having different views. In short, politics—compromise—was at play from the beginning. The third message, therefore, is to be mindful that technology is always only a small part of the mix—a mix that has, political, economic, psychological and moral dimensions.

I’d like to leave you with two quotes that provide perspective on the moral dimension. They’re from men who lived four centuries ago—at about the same time. In fact they were fellow countryman, both from England. One of them was a very famous philosopher, the other a poet, moderately known, but not a major figure in his time. I’ll first quote the eminent philosopher, who was knighted—Sir Francis Bacon—as he extols technology in his major work, Novum Organum.

"Printing, gunpowder, and the magnet," wrote Sir Francis, "have changed the whole face and state of things throughout the world,... no empire, no sect, no star seems to have exerted greater power and influence in human affairs."

Now hear the words of the poet and playwright, from one of the greatest romantic tragedies of all time. The place is Northern Italy, in the foothills of the Appenini’s in the town of Verona.

It's Act V scene 3. Romeo and Juliet are both dead and Friar Laurence, who had secretly married them, is recounting the events leading to the tragedy. He's explaining that Juliet was distraught over pressure from her father to marry Count Paris and was searching for a way to avoid the second marriage. Friar Laurence proposed that she take a potion that would induce the appearance of death, and that Romeo rescue her. However, unforeseen circumstances prevent word of the plan from reaching Romeo, and upon seeing her asleep in a coffin he believes she actually is dead, and kills himself. When she wakes seeing him dead, she kills herself.

Here are the words of Friar Laurence⁴:

...then comes she to me
And, with wild looks bid me devise some mean
To rid her from the second marriage,
or in my cell there would she kill herself.
Then I gave her, so tutored by my art,
A sleeping potion which so took effect
As I intended, for it wrought on her
the form of death...

This is the kind of stunning insight so characteristic of Shakespeare—it captures a timeless metaphor for the unanticipated effects of technology. It was chance that
prevented Romeo from learning of Friar Lawrence's plan--unforeseen events conspired with the well intentioned and knowledgeable use of the technology of the day, with tragic consequences. Put in a modern context, the passage reminds us that superimposed on that complex mix of engineering principles, economics, sociology and politics that shape technology, is stochasticity—the vagaries of chance.

Anyone who thinks that the circumstances in Shakespeare's tragedy seem contrived, need only recall such modern technological disasters as Challenger and Chernobyl: they too were caused by a confluence of errors in human judgment and random events.

As you embark upon careers in a profession that will continue to change the conduct of human affairs, do so with the passion and optimism expressed so eloquently by Bacon. But let that passion and optimism be informed by the knowledge that technology can affect and be affected by every other component in the complicated web of life.

Congratulations once again, and the very best of luck to all of you.