2002 Paul Ehrlich and Ludwig Darmstaedter Prize

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March 14, 2002

Distinguished guests, it is an honor and a privilege to be here with you today to accept the 2002 Paul Ehrlich and Ludwig Darmstaedter Prize. I am humbled and awed to be a part of such a distinguished list of previous recipients as they represent some of the greatest minds in science. I have had the privilege of collaborating with some Ehrlich prize winners including Bert Vogelstein on new DNA mismatch repair enzymes in colon cancer and with Rino Rappuoli on a new meningitis vaccine based on bacterial genomics. I am indeed honored to be introduced by a previous prize winner, Dr. Abner Notkins who I first met during my time at the National Institutes of Health in Bethesda.

I am grateful that I am being recognized for my work that led up to the sequencing of the human genome. The methods and concepts that came out of the Expressed Sequence Tag method for gene discovery; the sequencing of the first microbial genomes and the fruit fly genome were essential steps on the path toward completion of the human genome sequence by my team and the public consortium. I am proud that my contributions have lead to the world having the human and mouse genome sequences years ahead of time.

I accept this award with the understanding that I represent teams of exceptional scientists from The Institute for Genomic Research and Celera Genomics. Genomics requires a multidisciplinary team effort with experts from molecular biology, biochemistry, physiology, genetics, algorithm and software development, and high-end computing. I have been extremely lucky to be associated with such eminent scientists throughout my scientific career.

I would also like to acknowledge the scientists who have gone before me in the quest to better understand life at its most basic level. Without the earlier work of those scientists, my team could not have achieved the decoding of any of the organisms we have done including the human genome. The beauty of science is that important discoveries are made by building on the discoveries of others. I continue to be humbled by the work of those pioneering individuals in the broad array of disciplines.

My scientific/medical education began in 1965, when I was drafted into the military. Up until that time I had been a poor student with little interest in school. I was bored and unchallenged. I ended up in the US Navy Medical Corps. The harsh realities of war triggered a keen awareness of how fragile life was and how quickly it can be taken from us. Suddenly I could not learn fast enough. I was fascinated by every aspect of medicine and disease. I soon found myself in charge of one of the largest infectious disease wards in the world at Balboa Navy Hospital in San Diego. I was learning about and helping to treat diseases such as malaria, tuberculosis, cholera, meningitis, and syphilis. Little did I

know that thirty years later I would decode the genomes of these historic killers. Due to my acquired skill set in infectious disease and emergency medicine, I volunteered to go to Vietnam where I thought my knowledge could help. I was sent to Danang, Vietnam from August 1967 to August 1968. During my first six months I helped run the intensive care ward and in the second half of my tour I worked in an infectious disease clinic dealing again with malaria and other tropical diseases. I was also a medic for a small village and an orphanage. I witnessed the best and worst of humanity. I had to learn to deal with death on a daily basis and the limits of medical knowledge. I was also extremely frustrated with the political justification for the war. On leaving Vietnam I was highly motivated to return to school.

My work and ideas have been considered controversial and widely covered in the press. I often get asked how I had the audacity to do what I've done particularly in the face of strong criticism. I never considered what I was doing or proposing to be risky or controversial. I have always been guided by what I call my inner compass and have never doubted the direction I was headed was the right one. A key element of my success has been my willingness to take risks in the pursuit of truth. There are many events that have shaped my life, including one of the most profound--my tour of duty in Vietnam where I learned that we are more than just the sum total of our genes and that the human spirit and will power often played a role in whether men lived or died.

After three years and a degree in Biochemistry from the University of California at San Diego (UCSD), I started graduate studies there with my mentor, the late Nathan O. Kaplan. I had the fortune to be a part of one of the best science lineages. Kaplan had trained with Fritz Lipmann and had co-discovered coenzyme A with him. Lipmann in turn had worked with Otto Myerhoff. Lipmann and Myerhoff are both Nobel Laureates. Kaplan was in the Chemistry Department at UCSD and I was in a Physiology/Pharmacology graduate program. It was in both chemistry and pharmacology where I first learned of Paul Ehrlich and his many contributions. His work on receptors and his "side chain" hypothesis had important impact on my early work which was devoted to proving that adrenaline worked on a specific cell surface receptor. I devoted the next 10 years to the isolation and purification of that receptor protein, and to finally sequencing the gene. The adrenaline receptor gene was one of the first neurotransmitter receptors isolated from the human brain.

In the mid 1980's I became excited about the early discussions about sequencing the entire human genome. After spending a full decade on the isolation of one single gene, the notion of having all human genes sequenced over a 20 year period seemed to me a wonderful goal. My NIH laboratory was the initial test site for the first version of a semi-automated DNA sequencer, and in 1987 I published the first paper on genes sequenced with this machine.

I decided to make a complete change in research fields, leaving neurotransmitter-receptors for the new genomics field. In 1988 I began the first human genome sequencing test project for NIH, from chromosomes 4 and 19. Instead of searching the genome for a specific gene based on protein sequence as I and many others had done, we now had raw

genomic sequence without a clear way to interpret it. Approaches to biology were turned upside down. It became clear to me that without the sequence of genes derived from messenger RNA (cDNA sequences) as a guide, the human genetic code would be impossible to interpret. Necessity being the mother of invention, I developed a new method that I named "Expressed Sequence Tags" or EST's that utilized rapid DNA sequencing to partially sequence hundreds to thousands of human genes quickly and efficiently. This technique, published in the journal Science in 1991, rapidly changed the world of gene discovery. The EST method is the main gene discovery tool currently used with over 10 million EST sequences in GenBank from hundreds of species. Discoveries driven by the EST method include the new colon cancer genes.

It was from new mathematical tools that we developed to deal with hundred's of thousands of EST sequences that led us to the new methods we created for whole genome sequencing. In 1995 the field of genomics truly began when we published the first complete sequence from a living species, *Haemophilus influenzae*, a key human pathogen that causes meningitis and chronic ear infections in children. Over the next years we decoded the genomes of some of the most notorious human pathogens including, *Plasmodium falciparum* which causes malaria, the common killers *Staphylococcus aureus*, *Streptococcus pneumoniae, Helicobacter pylori* which causes ulcers, *Mycobacterium tubercuolosis*, and *Treponema pallidum*, the cause of syphilis and the target of Ehrlich's "Salvarsan". Progressive success with multiple genomes gave us clear confidence in the whole genome shotgun method.

With public funds not available to try my approach on larger genomes, I accepted funding from the manufacturer of DNA sequencing instruments to form a company with the goal of rapidly sequencing the human genome.

Applying whole genome shotgun sequencing at a scale over 100 times greater than we had before, we sequenced the Drosophila genome in less than one year. The method was proving to be effective considering the next largest genome completed to date had required over a decade to sequence.

One year later we announced the first assembly of the human genome sequence. This work validated the techniques established with the sequencing of the first genome *Haemophilus influenzae* six years earlier, and then with Drosophila.

I believe that we will see major changes in the way medicine is practiced due to genomics. There have already been breakthroughs based on our work sequencing viruses, bacteria, parasites, insects, and mammalian genomes. Our work on pathogens is leading to new vaccines, antibiotics and methods for diagnosing disease.

It is hard to believe that it has been one year since my team and I published the sequence and first analysis of the human genome in the journal, Science. One of the best findings from this work supports the fundamental unity of all of us. We share 99.9% of our genetic code with each other, 98.7% with chimpanzees, as well as many genes with every

species sequenced to date. It is a wondrous world in which we live, a world where the 3 billion letters of the human genetic code, the mouse genome, the fruit fly genome and more than 100 microbial genomes are immediately available via desktop computer as a resource for scientific discovery. This is indeed the genomics era. But as with all new areas of science it is imperative that we consider all the ramifications and implications of these breakthroughs. We as scientists on the forefront on this field have an obligation to educate the public about the social and ethical issues surrounding these breakthroughs in genomics. One of my goals is that my work on the genetic code and human variations can dispel many of the myths and pseudo-science that have been used as tools for political oppression and discrimination. We cannot determine anyone's actual ethnicity on the basis of the genetic code as race and ethnicity are not based on science but on social concepts. We must all work toward higher science literacy and the wise use of our common heritage.

I entered science to find understanding and perhaps change the world in some small way. As I've said many times, sequencing the genomes was only a beginning. I, along with my team, continue to work ceaselessly hoping to turn our new ideas and discoveries into potential treatments and cures for human disease. As John Dewey said, "Every great advance in science has issued from a new audacity of imagination." In this sense I hope I am thought to be audacious. Thank you again for this award for which I am profoundly grateful.