The 2002 Paul Ehrlich-Ludwig Darmstaedter Prize
Awarded to J. Craig Venter, Ph.D.

Laudatio by Abner Louis Notkins, M.D.

They have been called the "books of life", the "blueprints of biology", the "road maps of living organisms". Dozens of volumes now have been written and hundreds more are in process. They have been analyzed and read over and over again, perhaps millions of times, but by robots and computers. Recorded in these books is the complete genetic information or genomes of different living organisms.

From a literary point of view, these books will never win a prize because their alphabet consists of only four letters - - A, T, G, C - - repeated over and over again in various combinations. These four letters are the alphabet of the genetic code and they stand for the nucleotides or building blocks of DNA. The order in which these letters appear within a strand of DNA provides the instructions for making proteins, the key structural and functional components of all living cells.

A number of years ago, by a process known as DNA sequencing, it became possible to determine the order of these letters in a strand of DNA and thereby identify the genes and the encoded proteins. But the process of decoding genes was painfully slow. This was a serious problem for scientists, since the DNA of even the simplest organism contains millions of these four letters in various combinations, encoding thousands of different proteins. Scientists wanted to speed up the process of identifying and decoding genes. In fact, they wanted to identify not just a handful of important genes, but the entire genetic composition, the genome, of living organisms.

In the early 1990's, Craig Venter, then at the National Institutes of Health in Bethesda, Maryland, thought he might know how to do this. The approach used by most scientists at that time was to decode long pieces of DNA, one at a time, by a step-by-step manual approach. Venter's approach was radically different. He asked, why work on just one piece of DNA at a time? Instead, why not decode the entire genome of an organism by chopping up all of its DNA into small pieces? Each of these small pieces then could be sequenced quickly and the pieces put together by looking for areas where the letters of the code overlapped with each other.

But to accomplish this, new technology was needed: automation in the form of robotics to select and sequence the individual pieces of DNA; powerful computers to organize and store the vast amount of data; and new software programs to analyze and sort the data. No laboratory was set up to do this, including those at the NIH, at least at the scale visualized by Craig Venter. In 1992, Venter left NIH and, with true entrepreneurial spirit, established The Institute for Genomic Research (TIGR) and several years later, Celera. His new laboratories were not state of the art; they were futuristic with row-upon-row of robots and computers.

Most scientists thought the Venter approach would not work and as a result he was not able to obtain public funds to test his ideas. Perhaps to tweak the more conservative scientific community which used the orderly, step-by-step manual sequencing approach, Venter called his automated approach "shotgun" sequencing. Proof of principle that this "shotgun" approach would work came in 1995 with the publication of the first complete genomic sequence of an entire living organism, the bacterium haemophilus influenza which is a major cause of respiratory infections in children.

As often happens with the publication of a startling new approach, a spectrum of responses was obtained ranging from sheer disbelief to raves. But before the scientific community could catch its

breath, in quick succession, Craig Venter published the complete genomes of more than a half-dozen important human pathogens including those that cause tuberculosis, gastric ulcers, pneumonia, meningitis, cholera, syphilis, malaria and Lyme's disease. In a period of just several years, the automated "shotgun" approach provided more information about the genes and proteins of these organisms than existed in the entire scientific literature. Almost overnight "small biology" was transformed into "big science" and the genomic data provided new insight into how microbes produced disease and what proteins and enzymes should be targeted to make better vaccines and antibiotics. Craig Venter's shotgun approach opened up the field of microbial genomics.

From single cell microbes, Venter moved on to test the feasibility of using the "shotgun" approach to sequence the genome of a more complex multicellular organism. He chose Drosophila, commonly known as the fruit fly, because the fruit fly had been studied as a genetic model for more than 100 years. In March of 2000, Venter and co-workers, in collaboration with the Berkley Drosophila Genome Project, published the first complete genomic sequence of the fruit fly and identified 14,000 genes, the largest number ever looked at in a complex organism.

Most people would have been satisfied with these achievements, but not Craig Venter. Since the automated "shotgun" approach worked on single cell microbes and the multicell fruit fly, why not apply it to the most complex of all organisms, the human? There were two problems: first, the vastness of the project and second, a Public Consortium involving twenty different laboratories around the world had been working on the project for several years. Completion, however, was not expected until 2005. When Venter took the challenge it was only 1998. Venter went with his automated "shotgun" sequencing approach while the Public Consortium continued primarily with the manual sequencing approach, later both groups used a combination of the two approaches in varying degrees. The two groups pushed each other, the tension and controversies were widely reported in the press, but the end result was that both groups succeeded, and at a much earlier date than anyone had anticipated. The winners were the scientific community and humankind.

In the spring of 2001, at the invitation of President Bill Clinton and Prime Minister Tony Blair, at a White House ceremony, Craig Venter representing Celera and Francis Collins representing the Public Consortium announced the near-completed blueprint of the human genome. The accomplishment was reported in newspapers and on television around the world. It was hailed as the biological equivalent of the landing on the moon. The findings from both groups showed that the human genome consists of close to 3.0 billion letters encoding 30,000 to 40,000 different genes. Craig Venter vividly expressed the vastness of the accomplishment when he estimated that if you tried to read the 3.0 billion letters of the human genome, at the rate of one letter per second, it would take 100 years.

Studies on the human genome now have entered a new phase and a variety of refinements are being pursued. The subtle differences in the genes that make each of us unique are being examined. Some of these differences, called polymorphisms, often involving just a single letter, can determine if an individual will develop cancer, sickle cell anemia or certain types of diabetes. Other differences may determine whether a particular drug will be therapeutically effective in one individual, but ineffective or produce side effects in another individual. Pharmaceutical companies are talking about making designer drugs to counter-act these genetically-controlled side effects. Futurists are talking about the possibility of sequencing the genome of each individual at birth to tell what disease or profile of diseases that individual is likely to confront during life. And super-futurists think that it may even be possible to identify behavioral characteristics.

Equally astonishing is what genomics is teaching us about evolution and how closely we are related not only to each other, but to other species. The genes of chimpanzees do not differ from those of humans by more than 1.0 %; mice have genes that are 95% similar to our own; and even worms, so small that they can only be seen with a microscope, have many genes in common with our own. There is a commonality of life, and how we view ourselves in relation to other creatures has forever changed.

Although much still remains to be done, some scientists have decided to move on from genomics to the next big challenge. That challenge is to determine the function, in health and disease, of each of the hundred thousand or more proteins encoded by the human genome, and in particular how these proteins interact with each other. This new field of exploration is called proteomics. Over the last couple of years this field has moved so fast that many scientists refer to the period in which we are now living as the post-genomic era.

Scientific issues, however, are just one part of the genomic and post-genomic era. To deal with some of these other issues, Dr. Venter has accepted a new challenge. He has just become president of the newly created TIGR Center for the Advancement of Genomics - a non-profit public policy forum for the social and ethical implications of genomics.

Dr. Craig Venter was born in 1946 in Salt Lake City, Utah. During the Vietnam War he served in the US Navy Medical Corp in Danang. This experience changed, forever, his view of life. Upon returning to the United States he studied at the University of California and earned a Ph.D in physiology and pharmacology. He spent the next 6 years at the University of Buffalo and then 8 years at the NIH where he began his gene discovery career. Today Dr. Venter is one of the most sought after speakers in the scientific community and is known for his imagination and vision. Dr. Venter is married to his long-time scientific collaborator, Dr. Claire Fraser, who is the president and CEO of the Institute of Genomic Research. When not decoding genes, Dr. Venter can be found on his 95-foot ocean-going sailboat with his three dogs.

Dr. Venter, on behalf of the Paul Ehrlich Foundation I extend to you our congratulations and our indebtedness for your magnificent contributions in providing an approach and elucidating the genomic blueprints of organisms as small as a microbe and as complex as a human.