Rede Levine

First, let me express my gratitude to the Paul Ehrlich Foundation and to the selection committee for the honor of sharing the Paul Ehrlich and Ludwig Darmstaedter Prize with Drs. David Lane and Bert Vogelstein. Each of this year's recipients have had the pleasure of sharing our lifetimes in science together and contributing to the field of cancer research at the very moment when the basis of this disease has become understood at a fundamental level. Starting in the mid 1970's the field of oncology uncovered several classes of genes which when altered via mutation contribute to the origins of cancer in humans. These came to be called the oncogenes, tumor suppressor genes and mutator genes. The oncogenes act in a dominant fashion to promote cell division. The tumor suppressor genes play a broad role in negatively regulating cell growth and are the checks and balances for the cycle of cell division. Third, the mutator genes are a set of genes involved in the repair and integrity of the genetic information and must function properly or cancer cells arise. Defects in these gene products will result in high mutation rates and genomic instability, which predispose to higher rates of cancer.

Inherited defects in either tumor suppressor genes or mutator genes will lead to inherited predispositions of cancer in a family. We now recognize some 60-100 genes in these three categories that will, in various combinations, result in human cancers of a wide variety of cell and tissue types.

While we have uncovered these genes and their effects over a twenty-year search, we do not know how many more genes there are that play a role in cancer or can contribute to the abnormal growth of cells. Recent advances in technology point the way to asking these questions for the first time. Small chips, much like computer chips, that carry 60,000 different sequences of genetic information have been used to probe the expression of some 6,200 genes simultaneously in normal and tumor cells of humans. Patterns of gene expression emerge that permit us to not only distinguish between normal and cancer cells, but also the different grades of cancer cells. Correlations have emerged that suggest the hypothesis that gene A regulates the levels of genes B, C, D in a tumor. From these correlations we can formulate an hypothesis and experiments can be designed to directly test these ideas in the laboratory, where cells grown in culture permit questions that bear on causality, not only correlation. Remarkably, these experiments reverse the normal process of developing an hypothesis using model systems in the laboratory and then testing one's ideas in "the real world" of cancer in humans. Rather the "DNA chips" permit one to go directly to a tumor removed from the patient and examine the relationship between patterns of gene expression in the cells of the tumor. Our experiments test ideas in a real world setting outside the laboratory.

The DNA chips can also be used to determine the DNA sequence differences between us. We will shortly have the ability to measure 6,000 different positions in our chromosomes and correlate the place on our chromosomes with a disease process in people. This resolution of gene mapping will speed up the discovery of new genes that cause disease, and uncover new insights about our genetic endowment. The technology will revolutionize the speed with which human genetics provides answers and validates genes that play a role in cancer. Validated genes provide targets for a rational approach to diagnosis, prognosis and treatment.

We are now seeing the first generation of drugs to treat cancer that are not the usual toxins or radiation, but target known molecules derived from oncogenes or cell type specific proteins. Monoclonal antibodies that permit the treatment of chronic B cell lymphoma are now approved and spare the depletion of bone marrow so common with the old, toxic chemotherapy. Antibodies directed against the oncogene product, Her2/ neu have finished phase III clinical trials and save the lives of women with metastatic otherwise terminal breast cancer. Inhibitors of protein kinases, in phase I trials, promise to block the key oncogene responsible for chronic myelogenous leukemia and inhibitors of critical enzymes that modify

the ras oncogene activated in 90% of pancreatic cancers will enter clinical trials shortly. All of these agents have in common that they target the very proteins produced by the mutated or altered genes discovered over the past 25 years of research. We have entered a new age of cancer treatment where toxicity is reduced and specificity is increased.

In 1979 the discovery of the p53 protein, followed by the cloning of the p53 gene in 1982-83, added one more gene to the list of oncogenes, tumor suppressor genes and mutator genes, with little or no fanfare. Using a monkey virus that causes tumors in hamsters, David Lane's group, and my own research team, uncovered the existence of this protein. Ten years later, I was at a meeting at Cold Spring Harbor when Burt Vogelstein announced that three colon carcinomas from humans carried mutations in both alleles of the p53 gene. What began as a question in basic or fundamental research led to the analysis of tumors, and p53 developed into one of the central players in human cancer. Today we know that some 50-55% of all cancers carry mutations in the p53 gene. An additional percentage of cancers inactivate the p53 protein function by elevating oncogene products or altering cellular processes. A defect in p53 function appears to be the most common event that results in the development of cancer in humans.

The practice of science often takes scientists through unusual twists and turns and into areas of research that can not always be planned. The twenty-year history that has lead to our present understanding of the p53 gene and protein has taken us all into new territory, into a new understanding of life processes and cancer biology. This history is the best justification of the reason why the Federal governments of the United States, Great Britain and Germany support basic research. That justification began in the nineteenth century with scientists like Paul Ehrlich. I am honored to win this award with David Lane and Bert Vogelstein and stand in the line of scientists behind Paul Ehrlich.