Rede Vogelstein

Ladies and Gentleman:

It is both an honor and a privilege to accept the Paul Ehrlich and Ludwig Darmstaedter Prize. I am particularly glad to receive it together with Professors Lane and Levine. If not for their pioneering basic research and their discovery of the p53 gene, our work would not
have been possible.

As all of the scientists in this room know, the experiments that advance biomedical research are now largely done by doctoral students and post-doctoral fellows rather than by more senior scientists. This award is therefore a tribute to their work, and I accept it on their behalf.

The p53 story illustrates many of the most important lessons learned in science, and particularly in cancer, over the past two decades. As you*ve heard from Drs. Levine and Lane, the p53 gene product was originally identified through its interaction with tumor viruses. Our interest in this gene began almost ten years after their discovery. We were searching for a tumor suppressor gene on chromosome 17. We thought such a gene existed because this chromosome was often altered during the process of colorectal tumorigenesis. But initially we had no idea of the nature of this gene, and in fact at the time, tumor suppressor genes were only hypothetical beasts, as none had ever been isolated. We finely mapped chromosome 17 with numerous markers, and determined that a small region of this chromosome likely harbored the putative tumor suppressor. Interestingly, this small region also contained p53. But at the time, p53 was thought to be an

oncogene, the opposite of a tumor suppressor, so we initially didn*t think p53 was a good candidate. The more we mapped, however, the more sure we became that p53 was in our target area and we simply couldn*t exclude it on the basis of genetic criteria. Finally, a graduate student in our lab, Suzie Baker, agreed to definitively test the hypothesis that p53 was the culprit we were hunting, employing a test based on concepts originated by Al Knudson. She chose a single, well studied colorectal cancer for these studies, and to our initial amazement, found a mutation in p53 in this cancer. She and a fellow graduate student, Janice Nigro, quickly extended this observation with additional studies showing that p53 was mutated in virtually all colorectal tumors with alterations of chromosome 17, proving beyond doubt that p53 was the gene for which we were searching. Subsequent studies in our lab by Scott Kern, Wafik El-Deiry, and Nelly Polyak have shown how p53 exerts its tumor suppressive ability, principally by binding to specific DNA sequences and causing the activation of genes which stop the cell cycle or cause cells to die.

The p53 gene is now the most widely studied gene in science. The reason is that it appears to behave as a common denominator, underlying many different types of cancers. Study of this single gene has unified several areas of cancer research, including viral and chemical carcinogenesis. It seems that virtually all tumor types must eliminate p53 function if they are to become fully malignant. Most importantly, studies of this gene have created new optimism for future therapeutics. If a single gene underlies the development of many types of malignancy, then therapies based on an understanding of ththe p53 pathway are likely to apply to many patients.

Again, I feel privileged to have participated in the revolution begun in 1979 by Drs. Lane and Levine, and thank the Committee for selecting me to share in this prestigious award.