My Life and Adventures
Integrating Biology and Technology

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Perhaps one of the most special and unexpected benefits of the Kyoto Prize has been thinking about the commemorative lecture. It allowed me to place my life and work in an integrated perspective for the first time—and I, as many others before me, marvel at how my early experiences shaped my subsequent life choices in science.

The Early Years (1938-1952)

I was born in October of 1938 in Missoula, Montana, a beautiful town split by a rapidly flowing river and lying at the convergence of two forested mountain ranges. My father, one course short of a B.S. in physics, was an electrical engineer for the Mountain States Bell Telephone Company. He rose in the company to become a high level engineer and manager—through his considerable natural talents and an incredible commitment to his work. I was always grateful that in spite of the fact my father was given several opportunities to move to Bell Laboratories in New Jersey, he chose to stay and raise his children in what he perceived to be a better environment—Montana. My mother, with a B.S. in home economics, remained at home committed to our family, including my two brothers, Glen and Myron, and my sister, Doral.

The early years of my life up through grade school gave rise to a variety of life interests.

My mother and father set very high standards of excellence—in school and in all other chosen endeavors. These standards emerged more from the way they lived their lives than explicit exhortations. Accordingly, I was a very good student, always at the top of my class.

My mother believed that children should be given freedom and independence. I was hiking in the surrounding mountains before I was five or six and camping out independently shortly after that. Thus emerged a life-long love of the outdoors and its beauty and an interest that eventually evolved into mountaineering and technical

climbing—and more recently, cross-country skiing and sea kayaking—wonderful means for recharging my intellectual batteries. But most important was my mother's encouragement to be and think independently from a very young age.

My mother also believed every child should learn to play a musical instrument. I, like many active children, objected. Yet, my mother was implacable. I learned to play the piano, then the clarinet, and finally spent most of my time in grade school and high school playing the oboe. I came to love many types of music and more recently have taken up a simpler and more forgiving (of little practice) instrument—the soprano recorder.

From my earliest years, I enjoyed school, especially science and mathematics. I loved fiction and read widely in science, science fiction, and adventure stories. I remember for five or so years being fascinated with planes and my fervent desire was to become a pilot, until a respected mathematics teacher in about the 5th grade, who had flown planes in World War II, told me that being a pilot was much like being a truck driver. My vocational interests quickly shifted toward science.

One other experience did greatly impact our family when I was eight. My youngest brother, Glen, was born with Down's Syndrome—with a chromosome 21 trisomy. My mother was 32 at Glen's birth, hence, in retrospect the risk was there. My father was in favor of sending Glen to a state home so that the family would not be faced with the many challenges of raising a Mongoloid child. I learned in later years how extremely difficult this decision was for my mother. She has made heroic and partially successful efforts to keep Glen a part of the family. Glen has been remarkable. He adapted well to the state school and as a man (he is still alive) lives independently in his own house and works steadily at several jobs. One wonders how subconsciously life experiences influence career paths. My career in genetics has certainly raised the possibilities of exciting future approaches to genetic disease (see below), although chromosome abnormalities such as Mongolism pose a special challenge.

Parenthetically, my brother Myron went on to be a mathematics professor at California State College, San Luis Obispo and my sister, Doral, a nurse and then a nursing supervisor at a number of different hospitals throughout Alaska and the West Coast. Myron and I collaborated on several projects concerned with mathematically modeling the evolution of gene families.

My grandfather occupied a very special place in my life. I was for him the

son he never had. I learned from him the power of love, commitment, and friendship－something all children need early, if they are to effectively respond later to friendship and love.

High School (1952-1956)

My family moved from Missoula to Shelby at the beginning of my high school years. Shelby, a small town of 3,000, was on the windswept plains of eastern Montana. The high school had 140 students (my graduating class had 40). For me, high school was a remarkably broadening experience. I had three of the best teachers ever－a math teacher, Paul Tschache; a science teacher, Cliff Olson; and a history/social studies teacher, Corlie Dunster. They taught me to be analytic and skeptical of the written word. Their love for their subjects was infectious. They were remarkable in treating me as an equal and in opening my mind to academic objectives far beyond anything I had previously encountered.

When in grade school, I had taken up running and football. I remained interested in these sports throughout my entire educational career, but at Shelby, I had a special opportunity. Life in Shelby revolved around high school sports, especially football and basketball. I went out for football. I made the team as a freshman. I played occasionally my first year and more frequently thereafter until I was starting quarterback my senior year. Our football team did not lose a single game after midway through the season of my first year. Playing on a team that was undefeated for three and a half years was one of the highlights of my high school career. Learning the importance of teamwork and meeting the challenges of a physically demanding sport were valuable lessons for the future.

Going to a small school was quite a remarkable experience. One had the opportunity to become involved in diverse activities－music, acting, sports, debate, writing－while still being challenged academically. I also had the opportunity to become a student leader in academics, sports, and student government, providing valuable lessons in leading organizations. This diversity of activities was wonderful preparation for academic life where one is asked to do many things well－teaching, research, administration, fund raising, community service, public and scientific speaking, etc.

I was on the debate team for four years, the last couple of which my team

went to the state finals. In debate, I learned to speak without notes, to think analytically on my feet, and to convey complex issues in a simple way. This was superb preparation for my future career in science and teaching.

One experience with my father foreshadowed my future scientific interests. Dad taught a course to qualify telephone company employees for a second-class operator's license by examination. He asked me whether I would like to attend this course my sophomore year. I did and for the first time, I struggled with the challenges and excitement of circuits and systems. I did very well. My father was as proud of me as I ever saw him.

As I mentioned earlier, my maternal grandfather was a special person for me. He had a ranch in the Beartooth Mountains of southwestern Montana where I spent much of my boyhood. There I learned to ride horses and to climb rugged mountains. I helped with the animals. And I was given enormous freedom to hike throughout the surrounding mountains. My grandfather also managed a summer geology camp for professors and students from Princeton, Columbia, Harvard, and Rutgers among others. I took several geology courses with these students during my junior and senior years in high school and was a field assistant for several geological mapping projects in the nearby mountain ranges. One of these course projects－the geological mapping of an oil-producing anticline in northern Wyoming－was the basis of my Westinghouse Science Talent submission. I was one of 40 winners nationally－the first ever from Montana－and the long train ride from Montana to Washington, D.C. was the first time I had ever been out of the state. I was awed by the other national winners, but really excited by the diversity of excellence in science, math, and engineering. The geology camp experiences and talking there with the professors and students, as well as the Westinghouse experience, gave me an exciting view of what science was really about.

In high school, I was interested in science, and had a slight preference for biology, although I had really enjoyed my geology experience. One experience focused my passion on biology. Cliff Olson taught biology but as a chemist and meteorologist, he felt somewhat uncomfortable with it. He asked me as a senior to help with the sophomore biology course. So I taught a series of classes out of articles from *Scientific American*. I really enjoyed getting Montana sophomores excited about biology. More important, I learned enough to begin to see the enormous potential of biology in the future. For example, I remember being fascinated by one article on the structure of

DNA, discovered just three years earlier in 1953. I came away convinced I wanted to go into biology.

But the question was where. I had applied to a variety of liberal arts schools and had almost settled on an excellent one, Carleton in Minnesota. Cliff Olson then approached me and said I should think about going to Caltech. He had gone to Caltech during World War II and was convinced its small size, excellent students, elite faculty, and outstanding research record made it the ideal place for me. I was not so sure. I had never heard of Caltech. I was not certain I would like living in the Los Angeles area. I was also concerned it might not have enough humanities. In the end, I was persuaded and off to Caltech I went－one of a series of wonderful educational choices I was fortunate enough to make.

I met my future wife and life-long friend, Valerie Logan, at a speech meet during my junior year. She saw me win a gold medal for acting the part of a hen-pecked husband, but in spite of this, she agreed to my request for a dance at that evening's festivities. We dated on and off for the next seven years.

In retrospect, growing up in my family and in small towns in Montana was a wonderful experience to prepare me for my future career. I was independent-minded and had the confidence I could do virtually anything I chose. I acquired a life-long love of athletics, the outdoors, and exercise, which was a marvelous counterpart to my intellectually focused career. I was fascinated by teaching and had acquired the ability to communicate effectively. I enjoyed leadership and the challenge of choosing objectives and moving toward them. I enjoyed both reading and writing and had enormous confidence in my academic abilities. Finally, I was totally captivated by science in general and biology in particular.

Caltech－Undergraduate (1956-1960)

My first year at Caltech was my most challenging academic experience. Caltech is small－250 faculty, slightly more than 800 undergraduates and perhaps 1,000 postdoctoral fellows and staff. It was (is) perhaps the most competitive school for undergraduate admission in the United States. Many of my classmates came from big city science schools and private preparation schools that provided superb science and math training. For example, most of my classmates had calculus and even higher level

mathematics training, whereas Shelby High School did not even offer calculus. My first year was enormously challenging as I struggled to keep up with my extremely well prepared classmates in physics, chemistry, and mathematics－required courses for our first two years. This fundamental quantitative training was the core of my subsequent efforts to integrate biology and technology.

Caltech was an outstanding educational experience. Perhaps most exciting were my classmates－intelligent, accomplished, creative, and curious. I met there a life-long physicist friend, Eric Adelberger, and we together explored the exciting intellectual, scientific, and social opportunities of Caltech. Even more important, I helped him climb his first mountain and this led to a life-long series of mountaineering adventures in most of the mountain ranges of the West Coast.

As undergraduates, Caltech let us spend considerably more than 25% of our time in humanities－indeed, I believe I got an equal, if not superior, humanities experience to many of my friends going to liberal arts schools. I also participated in a variety of YMCA experiences focused around interesting social, ethical, and cultural opportunities－foreshadowing some of my future societal interests.

The Caltech faculty was exceptional and accessible. I had Richard Feynman for freshman physics; George Beadle for general biology; and even had a few chemistry lectures from Linus Pauling. But two biologists were especially inspiring teachers and valuable mentors－Ray Owen, an immunologist, and James Bonner, a plant biologist. Ray gave me my first exposure to immunology－a central theme in my subsequent biological career; and James Bonner was one of the best teachers I ever had.

Caltech, being small like Shelby High School, also presented the opportunity to participate in many extracurricular activities. I played football (halfback and defensive back) all four years. Our four home football games were played each year in Pasadena's Rose Bowl; hence, we Caltech players played in more Rose Bowl games than any professional football player! I sang in the choir and participated in a variety of student leadership activities. Indeed, my senior year, I was awarded the Outstanding Student Leadership Award. But what was really special about Caltech was the opportunity to experience the leading edge of molecular and cellular biology. I was even more convinced than ever that I wanted to go into biology, but for reasons I never fully understood. Perhaps in part due to my brother Glen, I was more attracted to human biology, a topic not well covered at Caltech. Hence, I decided to go to medical school

for two years to take courses like anatomy, histology, pathology, microbiology, and pharmacology to broaden my understanding of human biology before undertaking a Ph.D. I considered Harvard and Johns Hopkins medical schools and chose the latter, mostly because it had a special accelerated program where one could finish the M.D. degree in three years (going through summers) while receiving all the basic and clinical training.

The take-home lesson from my Caltech undergraduate experience was the exhilaration of being associated with exceptionally talented individuals at the student and faculty levels. They reset the standards and expectations for my future career.

Johns Hopkins Medical School (1960-1963)

Medical school was a shock after Caltech in several ways. First, most students were interested in medicine, not science, and in medical practice. This is not surprising in retrospect, but it created a different atmosphere than I had known at Caltech. Second, the sheer volume of material mandated a rote memorization approach that was quite different from my inquiry-based Caltech experiences. But I found learning human biology very exciting. I was staggered by how little we really understood about human biology. Indeed, I remember asking a pediatric intern, a resident, and then a visiting professor, in that order, what caused diarrhea. Each could list organisms and diseases that did so, but did not (could not) speak to the pathophysiological mechanisms－a view of biology that was completely descriptive and quite different from that which I learned at Caltech.

The microbiology course in my first year determined in part my future career path. I was fascinated by immunology and did a report on how the immune system is capable of responding to diverse pathogens (bacteria, viruses, etc.). The big issue was whether the immune system was instructed by the pathogen on how to fold the antibody molecules that were the body's first line of defense (instructionistic theory) or whether the immune system generated a diversity of antibody shapes so that pathogens could select and amplify those with appropriate molecular complementarity (selectionistic theory). I recognized that tumors of antibody-producing cells (myeloma tumors) probably gave one access to the homogeneous antibody molecules needed to explore these hypotheses, and I went on to carry out my Ph.D. and, indeed, spend my entire research career in this and related immunological areas.

At Johns Hopkins, I had several wonderful teachers－Barry Wood and Robert Wagner (microbiology), Jerome Frank (psychiatry), Al Lenninger (biochemistry), and Charlie Thomas (physical biochemistry). I enjoyed my clinical experiences as much as the basic science experiences and learned a great deal about how to deal with many diverse types of people.

One experience was quite special. With classmates Paul Kohnen and Steve Rosenberg, I attempted to teach hands-on science to students in a local high school (approximately 95 percent African Americans). We obtained equipment, designed experiments, and taught classes. A few students were incredibly receptive and I was imprinted for life with a commitment to K-12 science teaching.

At the end of my three years at medical school, several of my professors argued that I should continue my career in medicine with the classical path of an internship and residency. But I wanted to be one of the best in my chosen career path and I was certain I could not achieve this with a dual commitment to clinical medicine and basic science. Johns Hopkins had given me a broad background in human biology and had pointed me clearly in the direction of immunology－I was determined to follow that path.

Caltech－Ph.D. (1963-1967)

I chose Caltech for graduate school because of my future mentor, Bill Dreyer. Bill had just moved to Caltech from the National Institutes of Health. He was interested in a variety of problems, including myeloma or antibody proteins of plasma cell tumors in mice and humans and what they might tell us about theories of antibody diversity－precisely the area I wanted to explore. My first year of graduate school, I remember arguing with a professor of medicine at the University of California Los Angeles (UCLA) about whether myeloma proteins would tell us about cancer (his position) or about immunology (my position). I was right. Bill promised me the myeloma project would be a “Saturday afternoon project”－one that I could work on independently and at my own pace. It was anything but a Saturday afternoon project. It turned out by my second year of graduate school to be one of the most exciting areas in then contemporary molecular biology. I had learned how to sequence proteins (determine the order of the 20 subunits in their linear chains) and applied this technique to a variety of

myeloma proteins－and immediately fascinating insights were provided concerning the theories of antibody diversity. With Bill leading, I had the pleasure of participating in the formulation of one of the most radical theories ever proposed in biology－the idea that antibody chains were actually encoded by two distinct genes－a variable gene for recognition of the foreign molecular patterns, and a constant gene for facilitating the killing responses of antibody molecules. The idea was that these two genes would be physically rearranged and joined together during the maturation of the antibody-producing cells. The general reaction of the scientific community to the two gene-one polypeptide hypothesis was skepticism and even approbation. I realized for the first time how threatening new ideas are to many scientists. My work propelled me into the leading edge of this exciting debate and by my second year of graduate school, I was giving lectures at universities (Berkeley, San Diego, etc.) and national meetings. Thus, I had a wonderful introduction to the exhilaration of rapidly paced molecular immunology.

Bill Dreyer was a remarkable mentor. I learned from him to think conceptually. He was always willing to explore any problem. He was incredibly creative. Bill also had a deep interest in technology. He helped Beckman Instruments develop their very successful amino acid analyzer. He thought deeply about how to develop an effective protein sequencer－a project I later collaborated with him on. He realized long before most scientists the power of fluorescent antibodies as reagents for biological discovery. Indeed, Bill gave me the two dictums that have guided my subsequent scientific career. First, “Always practice biology at the leading edge.” It is more fun－always exciting and challenging. Second, “If you really want to change biology, develop a new technology for pushing back the frontiers of biological knowledge.”

I enjoyed my Caltech graduate experience thoroughly. I took courses in philosophy, literature, and advanced organic chemistry. I began to give science lectures in the local high schools. I learned technical rock climbing with my mountaineering partner Eric Adelberger and continued my mountaineering experiences in the Sierra Nevada mountains of California and the many canyons of the Grand Canyon. I found mountaineering a wonderful, renewing experience, both for the mind and the body.

Most important of all, I married Valerie Logan during my first year of graduate school. She has been my companion for virtually all my life’s activities.

Valerie participated in all of the outdoors aspects of my life－mountaineering, climbing, skiing, as well as partnering with me later in a series of very exciting K-12 science education opportunities.

My graduate career was transformational. I had a clear idea that my immediate future would be focused on solving the still unresolved problem of antibody diversity－the question was where to go next. I considered postdoctoral positions at a number of locations － Europe seemed particularly attractive. The Vietnam War intervened. As an M.D. susceptible to the draft, I decided to join the Public Health Service at the National Institutes of Health (NIH).

National Cancer Institute－NIH (1967-1970)

I was given an independent research position as Senior Investigator in the Immunology Branch of the National Cancer Institute (NCI) in return for establishing a protein chemistry laboratory. I continued to pursue molecular immunology and started some technology development. I gave courses in molecular immunology and molecular evolution. I had three wonderful years to think about where to go next scientifically and to continue being engaged in the exciting experiments and debates about theories of antibody diversity. The future leaders of American medicine were all at NIH－for the same reasons I was－and getting to know them was one of the major benefits of my three years at NIH.

Perhaps the most memorable experiences at NIH were the birth of my son, Eran, and my daughter, Marqui. I was in the delivery room for both births. These were among the most moving experiences of my life. Thus, Valerie and I embarked on another of life's great adventures－parenting.

I had decided to continue with my interests in molecular immunology and was increasingly interested in technology development. The question was, where could I do both best. I explored positions at Harvard Medical School, Colorado, Stanford Medical School, Caltech, and others. Caltech clearly offered the best opportunities for the integration of biology and technology.

Caltech－Faculty (1970-1992)

I went to Caltech with a commitment to split my time between biology (then molecular immunology) and technology. The idea was that biology should drive the choice of the

technology developed and that the technology should lift barriers to the deciphering of important biological information.

Let me provide a brief tutorial for the discussion to come. There are three major types of biological information [Fig. 1]. First, DNA is a linear or digital string composed of letters from a four-letter alphabet: G, C, A, and T. The long strings of DNA in the cells of living organisms are called chromosomes. One type of information present in the chromosome strings is its genes. Each gene is copied into RNA—a second type of digital string with a four-letter alphabet very similar to that of DNA. These so-called messenger RNAs (mRNAs) are then translated into a final product—proteins. Thus, each gene encodes a second major type of biological information—the protein. Proteins are strings composed of subunits from a 20-letter alphabet. Each protein string folds into particular three-dimensional structure capable of performing a function. Proteins are the molecular machines of life, which give the body shape and form, and catalyze the chemistry of life. The third major type of information is the biological system. Each biological system is composed of many different informational elements (e.g., proteins, cells). The nervous system and the immune system are examples. Biological systems have emergent or systems properties arising from the coordinated interactions of the many elements in the system. Emergent properties of the immune system are the immune response (reactions against foreign infectious agents) and tolerance (the inability to react against self). As we will see subsequently, my laboratory developed instruments to decipher each of these three types of biological information. For example, I was initially a protein chemist, so a natural biological barrier was the fact many interesting proteins were available in very low quantities. The most powerful approach to the initial characterization of proteins is to determine their sequence; that is, the order of their amino acid subunits. Hence, the first instrument my laboratory focused on developing was a protein sequencer that was 100 times more sensitive than its predecessors. Once developed, the protein sequencer was used to sequence many proteins that had heretofore been inaccessible because they were only available in small quantities. The analysis of these sequences opened up many new horizons in biology for exploration [Table 1]. Hence, there is an intimate interrelationship where biology dictates the choice of technology and the technology in turn opens up new frontiers in biology. Hopefully, this is an iterative cycle as new technologies emerge. Clearly this approach integrates technology with biology.

My interest in molecular immunology led me to the realization that the true key for understanding theories of antibody diversity and proving the two gene-one polypeptide hypothesis required learning molecular biology. So my laboratory did. One of my fundamental rules is that biological research must be driven by the biology. A biologist should go wherever the biology takes him and always learn whatever new technologies are necessary for solving an unfolding biological problem. However, in the course of moving in this direction, I came to realize, once again, that there were striking technological limitations. And this, in part, prompted my laboratory to consider the development of three additional instruments: the DNA synthesizer, an instrument for synthesizing DNA (gene) fragments; the protein synthesizer, an instrument for synthesizing protein fragments; and the DNA sequencer, an instrument for sequencing DNA fragments. These three instruments, along with the protein sequencer, created an integrated facility that allowed scientists to readily move from a protein sequence to its gene sequence or vice versa. Moreover, genes or fragments of proteins could be readily synthesized. These instruments also opened up the possibility of many new powerful strategies for molecular biology. For example, the ready synthesis of DNA fragments was necessary for the development of the powerful polymerase chain reaction (PCR), a widely used technique for amplifying DNA fragments one million-fold or more. This suite of four instruments forms the technological foundation of modern molecular biology. Finally, our work on the automation of DNA sequencing contributed to the emergence of an exciting new direction in biology, the Human Genome Project, a subject we will return to in a moment.

My interest in molecular immunology, as noted earlier, moved me from an analysis of antibody molecules (proteins) to an analysis of antibody genes. The question of how the body can synthesize millions of different types of antibody molecules focused on two theories. The somatic mutation theory said there were few antibody genes and they diversified by extensive mutation during the lifetime of the individual. Alternatively, the germline theory said there were many antibody genes, most were present in our DNA and somatic mutation was unimportant. Together with the laboratories of Susumu Tonegawa and Phil Leder, our laboratory established 1) that the two gene-one polypeptide chain theory was correct, and 2) that both theories were partially correct and partially incorrect about antibody diversification－there were lots of antibody genes in our DNA and they were capable of somatic mutation. These efforts

led to a Nobel Prize for Dr. Tonegawa. My laboratory became excited about characterizing the gene families that encoded two other classes of immune receptors, the T-cell receptors and the MHC receptors, and over the next 15 years used all four of the instruments we had developed for the characterization sequence analyses of these receptor genes in mouse and human. These data, together with a new approach, systems biology, to be discussed later, have given us the potential to understand in a deep manner some of the most important properties of the immune system－the immune response (how to generate vaccines), and tolerance (why the body's immune system does not react to self-components or, alternatively, why the immune system does in disease conditions react against self in autoimmune diseases).

In the late 1970s, a friend approached me and said it was certainly unfortunate that only my group had the highly sensitive protein sequencer. Why didn't I commercialize it and make it available to the scientific community. I was intrigued and went to the then President of Caltech, Murph Goldberger, with this proposition. Goldberger said Caltech has no interest in commercializing anything, but if I wished, I could attempt to commercialize it myself. I went to 19 companies with the fully developed protein sequencer and a vision of the three other instruments (the DNA and protein synthesizers and the DNA sequencer) and how collectively they would transform biology. Not one of the 19 companies I visited was interested and after three visits to the one company I thought would be an ideal partner, Beckman Instruments, I was told not to come back. To say I was discouraged is an understatement. However, I then got a call from Bill Bowes, a venture capitalist in San Francisco. Bill said he had heard I was shopping my instruments unsuccessfully and that he would give me $2 million to start a company. I was ecstatic. I went back to Murph Goldberger but he was extremely reluctant to "get in bed with venture capital." At the time, Harvard had been struggling with its relationship to a biotechnology company founded by two of its faculty, and I believe Murph was reluctant to face the same problems. However, it became obvious that Bowes' offer was the only offer on the table, so with reluctance, Goldberger agreed to accept the venture capital. But the story was not over. Shortly thereafter, I gave a lecture to the Caltech trustees on the vision of how our four instruments would change the world of biology. One of the Trustees, Arnold Beckman, came up to me afterwards and said, "This is fascinating. It is just what my company

needs." I pointed out that his company had already turned me down three times. After some additional hesitation, Murph Goldberger finally agreed we could use the venture money to start the company that became Applied Biosystems. Today, Applied Biosystems is world leader in molecular instrumentation.

I learned two lessons from my first venture into commercialization. First, always approach the CEOs or leaders of companies about opportunities and not the middle level managers, who are more interested in short-term profit and loss than long-term vision and potential. Second, it was extremely fortunate that all 19 companies turned me down, because I believe none of them could (or would) have attracted the talent, had the focus, nor committed the resources necessary to commercialize these technically challenging instruments effectively. In general, it is often true that radical new opportunities can progress more effectively as new start-ups rather than through the licensing to preexisting companies. I have gone on to co-found ten additional companies, including Amgen, Systemix, Darwin, Rosetta, and MacroGenics－all with very different approaches to biology and all using technologies and biology emerging, at least in part, from my laboratory. I believe every scientist has an obligation to transfer his or her knowledge to society, and creating companies (and licensing intellectual property) is one effective way to do so.

I must stress that the work I am discussing here was done largely by incredibly talented young colleagues, many of whom have gone on to be leaders in biotechnology－Mike Hunkapiller, Lloyd Smith, Steve Kent, Ruedi Aebersold, Alan Blanchard, Ulf Landegren, and many others. Perhaps this has been my greatest pleasure in science－working with talented and energetic young scientists－undergraduate and graduate students, as well as postdoctoral fellows. Let me say a word about mentoring. I have had the privileged opportunity to work with outstanding graduate students and postdoctoral fellows. For exceptional young scientists, a mentor should provide a rich scientific/intellectual environment, adequate technical and financial resources, and an interesting problem. The mentor provides a powerful model for the student of how he or she goes about the various aspects of his or her science. The mentor must be freely available, but in the end, young scientists learn science by working through the challenges themselves. Students must be given the freedom and time to figure out how to solve their particular problem. Once the data are gathered, the mentor again plays an important role in modeling the way in which data is analyzed and, ultimately, the way

papers are written. The better the student, the less explicit input is required from the mentor. Students will often come up with solutions to problems that the mentor would neither have the time nor, in some cases, the specialized skills necessary to solve. This was often the case with my students.

While a faculty member at Caltech, Valerie finally persuaded me to quit playing touch football after multiple trips to the hospital with repeated knee injuries (recurrences of my old college football injuries). I then started running three to six miles many mornings. I have found that my best scientific ideas have often come while running. I run alone. It is one time during the day when I can think in an uninterrupted manner on a focused topic for an hour or more. It is wonderful to be able to explore a problem from many different angles.

In the spring of 1985, I was invited along with 11 other scientists to Santa Cruz, California to the first meeting ever held on the Human Genome Project. (The human genome is the 23 pairs of chromosomes present in each of our cells that collectively contain 3 billion letters of the DNA language.) Robert Sinsheimer, Chancellor of the University of California at Santa Cruz, was considering creating an institute to sequence the human genome and he sought expert advice. The 12 of us debated for one and a half days and came to two conclusions. First, it would be feasible, although technically challenging, to sequence the human genome; and second, we were evenly split on whether it would be a good idea. I was intrigued by three aspects of this project. First, it brought to biology an entirely new approach to science, which I have since termed "discovery science." The idea is that all of the elements of a biological system can be defined and placed in a database, thus enriching the infrastructure of biology and potentially changing how science is done by raising the possibility of global analyses. For example, sequencing the human genome and placing the sequences of the 23 pairs of human chromosomes in a database is pure discovery science, which raises the possibility of globally analyzing the behavior of all human genes, for example, in normal and cancer cells (which we now routinely can do). Discovery science stands in contrast to hypothesis-driven science, where a hypothesis is formulated and experiments are designed to test the hypothesis. Second, the Human Genome Project would push the development of high-speed DNA sequencing, a central project of my laboratory at the time, and equally important, it raised the possibility of developing other

high-throughput tools for measuring the behaviors of genes, mRNAs, and proteins－the informational building blocks of biology. Finally, I was excited by the enormous promise the Human Genome Project held for human health, for it was a tool for discovering genetically defective genes, the first step toward understanding their roles in disease and how to overcome their defective functioning－moving us toward what I have come to call predictive and preventive medicine. I will return to this topic.

In spite of all this promise, most biologists vehemently opposed the Human Genome Project from 1985-1990. I remember giving many lectures on the Human Genome Project's enormous potential and responding throughout this time to many hostile questions. Most biologists felt that since only 2 percent of the genome was presumably genes, it was a waste of time and money to sequence the entire genome. Moreover, since the Human Genome Project was not hypothesis-driven, most biologists felt it was not real science. It was pejoratively termed stamp collecting or a fishing expedition. The opponents totally failed to understand the power of discovery science. Finally, since the Human Genome Project would cost approximately $3 billion, it was labeled as big science and, hence, was automatically bad. I was struck during this five-year debate by how closed-minded most of the opponents were－not that they did not have valid points, but that they could (would) not admit to the valid points from those supporting the Human Genome Project. The turning point in the debate came when the National Academy of Sciences appointed a committee, chaired by Bruce Alberts, its current president, made up equally of proponents and opponents of the project. This committee unanimously endorsed the Human Genome Project, which started in 1990 with a projected 15-year timeline. The first draft of the human genome was finished in 2001 and it will be completely finished in April 2003－just in time to celebrate the 50th anniversary of the discovery of the structure of DNA. The Human Genome Project has, as I will discuss later, transformed the landscapes of biology and medicine. But the major early imperative coming directly from the Human Genome Project was to drive forward the automation of large-scale DNA sequencing－and this objective pushed my laboratory toward the idea of cross-disciplinary science in biology.

The development of the automated DNA sequencer required a blend of technical expertise: biology, chemistry, engineering, and computer science. By the 1980s, my laboratory had developed a then unique (for biology) cross-disciplinary culture where the biologists and technologists communicated effectively with one

another. In 1987, we applied for and received a newly initiated National Science Foundation (NSF) program named the Science and Technology Centers (STCs). The purpose of the these centers was three-fold: 1) to integrate science and technology (in our case molecular biotechnology), 2) to establish meaningful scientific partnerships with industry, and 3) to support educational outreach programs, which we defined as K-12 science education. The key to making this program work was 11 years of flexible funding at the level of $3 million per year (with competitive reviews). I believe the STC program was one of the most outstanding ever funded by the federal government. Our STC was exceptionally successful－we, together with others, pioneered the DNA oligonucleotide array (chip) technology and virtually started the field of proteomics. Our STC spawned 2 of the 16 Genome Centers that worked on the Human Genome Project. It also spawned a myriad of industrial collaborations and started one of the most successful K-12 science education programs in the United States, which I will discuss later.

I was surprised that only one of my biologist colleagues at Caltech, Eric Davidson, was interested in participating in this center. Yet, in retrospect, I realize now how resistant even outstanding biologists were to the integration of technology into biology. For example, I remember one surprising episode in 1973 with the then Chairman of Biology, Robert Sinsheimer, where he warned me about spending too much of my time on technology. I pointed out that I had originally told him of my intention to split my efforts between biology and technology, and that I was still committed to doing so. I got tenure later that year, quite early for Caltech, so the warning was unrelated to my tenure evaluation. Years later, Sinsheimer told me his warning was merely a reflection of how the majority of the senior faculty felt. And I saw this attitude once again as I realized from the STC success that I could not create alone the appropriate cross-disciplinary environment entirely within my laboratory, but rather we needed other cross-disciplinary faculty, and especially graduate students with an interest in cross-disciplinary science. I initially proposed within the Division of Biology that there be a molecular biotechnology option with the recruitment of appropriate faculty. The leaders in Biology turned this down. I then went to the President of Caltech, Tom Everhart, with the suggestion of a new Division of Molecular Biotechnology. He said, “Fine, if you can convince your biologist colleagues.” The divisions of Chemistry and Engineering were supportive of the idea, but Biology was

opposed. By this time, I had become convinced this cross-disciplinary vision of science was essential to where I thought biology should move. So it was with considerable reluctance I made the decision in 1992 to move from Caltech to the University of Washington School of Medicine, where I founded the cross-disciplinary Department of Molecular Biotechnology.

University of Washington, Department of Molecular Biotechnology (1992-1999)

When I first went to the University of Washington to discuss my vision for a cross-disciplinary department, the Dean of the School of Medicine, Philip Fialkow, felt my vision was inappropriate and far too sophisticated for a medical school. I went home disappointed. However, Fialkow called me a week later and said he had reconsidered－he flew down and spent a day with me and convinced me we should explore the possibilities. I found it quite remarkable that a busy medical school dean could actually change his mind on a major topic like this and see a vision of the future most biologists failed to appreciate. I was invited to give three Danz Lectures at the University of Washington, where I encapsulated my views on cross-disciplinary technologies and the impact they would have on the future of biology and medicine. Bill Gates attended these lectures and subsequently at a fascinating four-hour dinner agreed to help support the creation of the Department of Molecular Biotechnology. I moved the NSF Science and Technology Center from Caltech and succeeded over the next four years in creating the first ever cross-disciplinary department of molecular biotechnology (with biologists, engineers, computer scientists, and chemists) and a novel graduate program. I believe this department was extremely successful. John Yates and Ruedi Aebersold together started the field of proteomics. Maynard Olson and I each ran independent Human Genome Centers. My laboratory developed the new ink-jet printer technology for synthesizing oligonucleotide arrays (now licensed by Rosetta and Agilant), yet another example of a global technology that permits the study of the expression patterns of all genes. For example, one could synthesize an array with DNA fragments representing all human genes and use this array to compare the patterns of gene expression in a normal cell and a cancer cell. The changes in the patterns of gene expression provide clues to the nature of the cancer mechanism. Ger van den Engh developed the world's most powerful fluorescent-activated cell sorting machine. Phil Green pioneered the critical software programs for assembly and quality control in the Human Genome Project.

Thus, the department was successful beyond my wildest expectations, but a striking new opportunity that I had been thinking about since 1990 or so began to emerge－systems biology. Systems biology advocates studying all the elements in a system rather than studying systems one gene or one protein at a time as biologists have done for the past 30 years. I will return to systems biology.

The School of Medicine was a wonderful environment for extending my research interests into human biology and disease. With Paul Lange, Chairman of the Department of Urology, and a remarkable M.D. fellow, Pete Nelson, I got interested in systems approaches to prostate cancer using various global technologies (e.g., DNA sequencing, DNA arrays, proteomics, etc.). With Elaine Ostrander and Janet Stanford of the Fred Hutchinson Cancer Research Center, we started to study the genetics of prostate cancer. Both of these efforts were supported by Michael Milken and his CaP CURE Foundation. To illustrate the power of television, Michael suggested that he, General Schwartzkof, and I go on Larry King Live and make an appeal to families with two or more cases of prostate cancer and urge them to participate in our genetic family studies. I was skeptical, but I agreed. Within weeks after the program, we had more than 200 families signed up. Over the past eight years, the study of these families has yielded fascinating insights into potential chromosomal regions predisposing to prostate cancer. My laboratory also began to study bone marrow stem cells and autoimmune disease. All of these studies were enormously facilitated by the genomics and proteomics technologies and strategies that we and others had developed. Thus, the integration of advanced technologies, biology, and medicine continued. However, a new opportunity for doing biology and medicine was beginning to emerge from the confluence of cross-disciplinary science, the internet, and the Human Genome Project－systems biology.

In 1996, I went to the President of the University of Washington, Richard McCormick, with a proposal to raise the money for a new building to house our rapidly growing (and space-limited) department with the intent of creating a new thrust in systems biology. I was told that there were ten approved buildings in front of mine and that the process could take up to ten years. I then proposed to the President and the Dean of the School of Medicine, Paul Ramsey, that we start an Institute for Systems Biology modeled after the successful Whitehead Institute at MIT. This institute was independent but closely associated with MIT. Dean Ramsey said that the institute must

be entirely contained within the School of Medicine. We continued to explore this possibility for the next three years or so before it became obvious that systems biology was very different from the classical hypothesis-driven small group research that is the essence of traditional academic science in biology. The academic administrative structure, particularly of a state university, appeared incapable of responding to the new requirements of systems biology (see below) and, in December of 1999, again after much agonizing, I resigned from the University of Washington to co-found, along with faculty colleagues Alan Aderem and Ruedi Aebersold, the non-profit Institute for Systems Biology.

Institute for Systems Biology (2000-present)

The Institute for Systems Biology was created with the mission to create, apply, and disseminate systems biology. Cross-disciplinary science created many of the global tools necessary for systems biology (e.g., DNA sequencer, oligonucleotide or DNA arrays, the many strategies and tools of proteomics, etc.). The internet provided us with the means for instant global communication and the ability to store and transmit large amounts of data.

The Human Genome Project changed how biologists view and practice biology.

· Discovery science introduced the possibility of global informational analyses.

· A genetics parts list of all human genes and their control region sequences emerged.

· The idea emerged that biology is an informational science with three major types of information: the digital or one-dimensional structure of DNA and genes; the three-dimensional structures of proteins, the molecular machines of life; and biological systems with their emergent behaviors.

· Tools for high-throughput quantitative measurements of biological information were developed (e.g., DNA sequencer, DNA arrays, proteomics, etc.).

· Computer science, mathematics, and statistics were employed to handle, store, analyze, integrate, and disseminate biological information.

· Model organisms (yeast, worm, fly, mouse) were used as Rosetta Stones for deciphering complex biological systems in humans. This is possible because all of life

arose from a common ancestor and the basic mechanisms for life's most fundamental processes－metabolism, information storage, and expression, etc. －are shared by all living organisms.

· We will soon be able to decipher the logic of life from a genome. We can then compare how this logic has changed in living organisms through comparative genomics. Comparative genomics will be one of the keys to deciphering human biological complexity.

What exactly is systems biology? Let me use the example of a systems approach towards analyzing how a car functions. First, one would use discovery science to identify all the different types of elements in a car－mechanical, electrical, and control. Second, one would formulate a preliminary model of how the car functions from prior knowledge. Third, one would drive, accelerate, brake, etc., the car and use global technologies to measure how all of the elements behaved with respect to one another under these various conditions. The behaviors of the different kinds of elements －mechanical, electrical, and control－would be integrated and compared to the model predictions. Hypotheses would be generated to explain the discrepancies between model predictions and experimental data, a second round of hypothesis-driven, global analyses would be carried out, and the results would be used to reformulate the model. This process would be repeated until the experimental data and the model were in agreement with one another. At the Institute for Systems Biology, we have used this approach to successfully begin studies on several different biological systems in bacteria, yeast, sea urchins, and mice.

What does it take to carry out systems biology? It takes a cross-disciplinary faculty－biologists, computer scientists, chemists, engineers, mathematicians, and physicists－who speak and understand the languages of these different disciplines to facilitate the development of new global technologies and to integrate these with the data acquisition, storage, integration, and analysis tools of computational biology and mathematics. A major challenge is to give the technologists a deep understanding of biology and vise versa. In addition, technologists and biologists must share a common language. This requires new approaches to teaching. Together these technologies must be integrated with biology and medicine. High-throughput facilities for genomics and proteomics technology must be available, as well as the expertise to keep these facilities

at the leading edge of technology development. There must be an integration of effort with academia, primarily to encompass intriguing new areas of biology and medicine, and with industry for new technologies and support. The cross-disciplinary faculty must use integrated teamwork to execute the iterative and integrative cycles of systems biology. Discovery science must be integrated with hypothesis-driven science for the global analysis of systems. One must deal efficiently and appropriately with issues of competitive salary scales and the acquisition and licensing of intellectual property. Our view of how to carry out systems biology poses serious challenges, both for academia and industry. I believe non-profit institutes like ours, if appropriately supported, represent the ideal organizational structure for approaching systems biology.

Predictive and Preventive Medicine

The Human Genome Project has catalyzed two paradigm changes in contemporary biology and medicine－systems biology and predictive and preventive medicine. The Human Genome Project has provided access to the extensive human genome variability (polymorphisms) that distinguishes each of us from one another (apart from identical twins). On average, 1 letter in 500 differs between your DNA and mine. This means, on average, we differ from one another by approximately 6 million variations. Most of these variations have no influence on our appearance or behavior. However, a few make some of us tall or short and others thin or fat. An additional few predispose to diseases such as cancer, cardiovascular disease, neurologic disease, or metabolic diseases. My prediction is that in 10-15 years, we will have identified hundreds of genes that predispose to disease. We will be able to analyze the relevant DNA sequences from these genes from a small amount of blood and use these to predict a probabilistic future health history for each individual. This is *predictive medicine*. Since it is an anathema in medicine to predict without being able to cure or prevent, we will use systems approaches over the next 15-25 years to place these defective genes in the context of their biological systems and learn how to circumvent their limitations. This is *preventive medicine*. The agents for preventive medicine will include drugs, embryonic stem cell therapy, engineered proteins, genetically-engineered cells, and many others. Because each of us will have different potential disease combinations, medicine will become highly personalized. My prediction is that preventive medicine will extend the average lifespan by 10-30 years. The efforts to move us toward predictive and preventive

medicine are a major focus of the Institute for Systems Biology. I believe the Institute for Systems Biology is in a unique position to integrate the emerging technological opportunities, e.g., nanotechnology, with the imperatives of predictive and preventive medicine.

Social and Ethical Issues

This predictive and preventive medicine will pose striking social, ethical, and legal challenges for society. How will society treat 70-90-year-olds who are still vital, productive, and creative? How will medical schools train physicians who in 15-25 years will be practicing predictive and preventive medicine? How can society itself respond effectively to the opportunities of predictive and preventive medicine? How will we deal with issues of genetic privacy? The engineer will soon be able to engineer himself or herself through germline genetic engineering. The germline is the DNA passed on to future generations. Hence, engineering of the fertilized human egg, for example, means that the germline genetic changes will become a permanent part of human heredity. Is it appropriate to use germline genetic engineering to avoid disease or to improve the human condition (e.g., increase intelligence)? This debate will be a major societal issue for the future. How will society balance the narrow religious dictates of the few against the virtually unlimited potential medical opportunities for the many presented by controversial areas (in the United States) such as embryonic stem cells? As we attack the problems of mental disease, we will identify genes that predispose to particular behaviors such as aggression. How will we deal with this knowledge? To block this type of research means that perhaps 2 percent of humans will remain psychologically impaired—locked in the prisons of mental illness. The most reasonable approach to dealing with most of these issues is to have a thoughtful, informed, and rational public. Once again, the Institute for Systems Biology sees real opportunities for bringing these issues to society through education.

Education

My interest in education has moved in several directions. My fascination with K-12 science education started in Shelby, Montana and was reinforced by my medical school and graduate school experiences. The NSF Science and Technology Center mandated a K-12 science education commitment. While in Pasadena, California, we created and

supported a novel high school science teacher summer institute, supported by the Keck Foundation, for advanced technologies－molecular separations, the use of DNA-cutting enzymes for genetic engineering, and the use of electric frying pans to carry out the polymerase chain reaction (PCR)－the ability to amplify segments of DNA one million-fold. Over the four years we had the STC at Caltech, we trained about 60 teachers and they in turn brought the excitement of relatively sophisticated experimental biological science to several thousands of students. We also discussed with the teachers some of the ethical issues raised in the preceding section. Upon moving to Seattle, the K-12 science outreach program changed markedly. We partnered with the Seattle Public School District to carry out systemic science reform. We elected to start with an elementary program (K-5) and subsequently created a middle school program (6-8) and currently we are developing a high school program (9-12). For example, Seattle has 72 elementary schools, 1,100 teachers, and 23,000 students. As part of our commitment to systemic reform, our science program reached all elementary schools, most teachers, and many students. Special lead teachers were trained in hands-on, inquiry-based science. Scientist volunteers assisted the lead teachers. The focus was on professional teacher training, and this was done through summer workshops and in-service training. We partnered with the school district to write a "local systemic initiative" grant to the National Science Foundation, which supported this program for five years－with matching funds from local businesses and the school district. From this experience emerged a distinct K-12 science education philosophy.

· K-12 science education must be systemic－encompassing entire units of education (e.g., school districts). This is to insure that all students are reached.
· These programs must be sustainable after the federal grant support disappears, as it inevitably does. This requires the community to buy into the program, both for support, and to persuade new leaders (from frequent turnover) in the school district to support and maintain the program.
· The programs must be sequential and articulated throughout the K-12 spectrum. Elementary science must transit into middle school science, and that in turn must merge into high school science.
· One must be strategic. Professional teacher development focused on inquiry-based investigations and deep content knowledge are critical elements of K-12 science

education. Public support must be engendered. Partnerships between academic centers, the school districts, and the community are critical.

· Finally, K-12 science education starts with leadership at all levels: the school districts, the academic partners, the community, and the teaching staff. Perhaps leadership is the most critical and challenging of these dictums.

Where do we stand today? The Institute for Systems Biology and the Seattle School District support one of the most outstanding elementary science programs in the United States. We have put in place a middle school science program for Seattle and four surrounding school districts. We are in the process of putting in place a similar high school program. In these programs, I have had the pleasure of working together with my wife Valerie and a number of wonderful educators, such as Elaine Woo, Caroline Kiehle, Pat Ehrman, Ethan Allen and many other colleagues. And I have had the enormous pleasure of seeing kids become infected with the spirit of inquiry-based thinking. K-12 science education is a forever vocation. Its most important objective is to produce citizens who are thoughtful, informed, and capable of inquiry-based thinking.

I have also been interested in talking with public groups about the social and ethical challenges and opportunities of the new biology. This has included speeches to churches, business groups, academic groups, and the lay public. The challenge always is how to help individuals understand the opportunities while facing squarely the challenges of modern science. It all begins with a very basic understanding of science－something very difficult to bring to adults.

Finally, I have co-authored textbooks on many of the subjects I taught academically－immunology, biochemistry, molecular biology, and most recently, genetics. I co-edited along with Dan Kevles a book entitled the *Code of Codes*, which is concerned with the social, ethical, medical, scientific, and legal implications of the Human Genome Project. With each of these books has come a marvelous clarification and deepening of my understanding of these topics. But it is the book that I am currently working on that excites me the most. Together with David Galas, Greg Dewey, and Ruth Veres, I am writing *The Living Code: Biology as an Informational Science*. This book is about a new view of biology emerging from much of what has been discussed above. Our hope is that it will reach out not only to biologists, but also to chemists, computer scientists, engineers, mathematicians, and physicists. It is conceptual rather than

descriptive. Our hope also is that it will change the way we teach biology. It is the first new book that will be published by a new publishing company, Roberts & Company Publishers, started by Ben Roberts, a superb editor with a passion for high quality books. Four of my six books have been written at writing centers that provide authors with the luxury of being able to think and write, undisturbed by outside responsibilities for a month or more at a time.

Coda

As I look back over my life, I have been extremely fortunate. I grew up in Montana and, hence, was exposed to the wonders of the outdoors and sports — marvelous counterpoints to the intellectual intensity of science. I came from a family that encouraged independence and high standards. I made fortunate educational choices, associating with quality institutions and individuals. I came into biology when it was ripe for integration with technology. My explorations of the mammalian immune system and the human genome have opened a myriad of fascinating doors. I have had the opportunity to create new academic entities to enable cross-disciplinary science, systems biology, and the development of technologies for predictive and preventive medicine. I have long been aware of the ethical and social challenges the new biology brings and the corresponding need to bring science to society. This is critical to science itself, for society ultimately dictates the resources available to science and the rules by which science is governed. Our K-12 science programs are one answer to how scientists must deal with the opportunities and challenges of new technologies.

What are the responsibilities of academic scientists in this complex world? I would say we have four obligations. First is scholarship—carrying out our science and technology with the highest standards. Second is education. We must train students to use inquiry-based analyses. We must give students a deep view of their discipline, but this must be enriched with a broad cross-disciplinary training. Third is a responsibility to transfer knowledge to society. For example, this can be K-12 science education, communication of the scientific opportunities and ethical challenges of the new biology to the lay public or starting new biotechnology companies. Finally, academics should be willing to play a leadership role in their communities by helping to create an environment that would be ideal for their children and their grandchildren. Academics should contribute to these obligations in varying ways, depending on their skills,

interests, and opportunities. I believe this view is quite congruent with the powerful philosophy of the Inamori Foundation－to use science, technology, and the arts and humanities for the benefit of humankind.

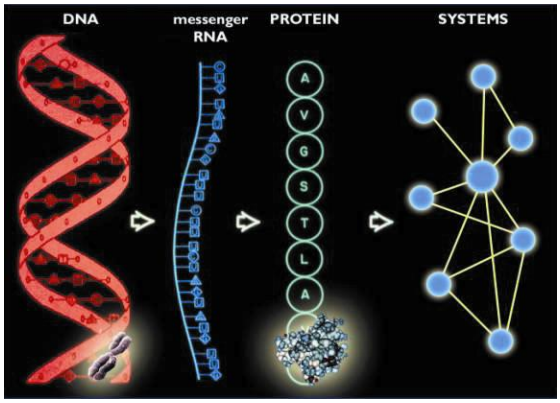

図 1　DNAがメッセンジャーRNAと蛋白質により生体システムとなる

Fig. 1 DNA to mRNA to Protein to Systems

表1　生物学と科学技術の統合── 高感度蛋白質配列解析機が扉を開いた生物学の研究分野

蛋白質配列	生物学上の可能性
1. 血小板由来成長因子	腫瘍遺伝子が癌を起こすメカニズムの解明
2. エリスロポエチン	バイオ関連薬で初の年間売上10億ドルを記録
3. プリオン蛋白質	BSE（狂牛病）の原因となる蛋白質の解明
4. コロニー刺激因子	血球の発生過程で重要な役割を果たすホルモンの解明
5. インターフェロン	一部の癌に対するバイオ関連薬、免疫反応の誘引
6. アセチルコリン受容体	神経受容体の研究に道を拓く

Table 1. Integrating Biology and Technology: Examples of New Areas in Biology Opened by the Highly Sensitive Protein Sequencer

Protein Sequences	Biological Opportunities
1. Platelet-derived growth factor	An understanding of how oncogenes cause cancer.
2. Erythropoietin	Biotechnology's first billion dollar a year drug.
3. Prion protein	An understanding of the protein causing Mad Cow disease.
4. Colony stimulating factors	An understanding of key hormones in the development of blood cells.
5. Interferons	Key biotechnology drugs for certain cancers and triggers to immune reactions.
6. Acetycholine receptors	Opened up the way for studying important neural receptors.