The Los Alamos Center for Human Genome Studies

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It is a pleasure to introduce an issue of *Los Alamos Science* about what we feel is one of the most exciting and challenging research programs in the history of science, the Human Genome Project. This project will have unprecedented impact on our country and the world. The understanding gained through the project will have profound effects on the quality of both medicine and our technological competitiveness, not in a century, but in our lifetime. We hope this volume portrays our enthusiasm for the project and the critical role Los Alamos National Laboratory has played in its inception and progress.

The Los Alamos Center for Human Genome Studies was established in June 1988, but the Laboratory's interest in genetics and DNA dates from its very early days. Health Research Units were established in the wartime laboratories by the Atomic Energy Commission because radiation was known to cause cell injury and genetic mutation. The early biological research was devoted primarily to whole-animal studies to better understand the physiologic and genetic consequences of radiation exposure and to set rational dose limitations for workers. As the knowledge base expanded, studies became increasingly sophisticated and included investigations at the cellular and subcellular levels.

At Los Alamos the transition from whole-animal studies to studies at the cellular and molecular levels came during the early 1960s. During that time a group of chemists led by F. Newton Hayes was attempting to decipher the genetic code, and D. F. Peterson recruited the Laboratory's first group of cell biologists. The excitement generated by discoveries in the life sciences in those years also attracted the attention of Los Alamos physicists and mathematicians. During the 1950s George Gamow and Nick Metropolis used the MANIAC computer to attempt to understand how sequences of the four different DNA elements (nucleotides) are used to generate sequences of the twenty different protein elements (amino acids). In the early 1960s a seminar series was organized that included Stanislaw Ulam, Walter Goad, George Bell, and James Tuck as regular attendees. It was during those seminars, which continued through the sixties and early seventies, that the basic methods for computer manipulation and analysis of DNA sequences were developed. Those efforts ultimately led to the establishment at Los Alamos of GenBank, the national genetic-sequence databank.

By 1970 scientists in the Laboratory's Biomedical Research Group had become leaders in the area of cell synchronization, especially in studies of the major biochemical events that occur during the cell cycle. Their work included the development of instruments that could rapidly measure the volume of each cell in a large cell population. Improvements led to an instrument that could sort cells with a preselected volume from larger or smaller cells. When those instruments were modified to detect the fluorescence emitted by stained cells, they were called flow microfluorometers. By 1975 such instruments had been renamed flow cytometers or flow sorters and were being used to analyze chromosomes as well as intact cells.

In the late seventies and early eighties a considerable amount of research in the Life Sciences Division was redirected to address health problems associated with non-nuclear sources of energy. The work focused on fundamental investigations of the structure and function of mammalian chromosomes, including the mechanisms involved in the differential regulation of gene expression. Those efforts brought together a small group of molecular biologists, cell biologists, and cytogeneticists interested in human-genome organization. The flow-cytometry resources at Los Alamos and the newly developed recombinant-DNA technology were directed toward construction of chromosome-specific DNA libraries. The success of that work led in 1983 to initiation of the National Laboratory Gene Library Project, which put Los Alamos in contact with hundreds of human-genetics laboratories throughout the world.

The presence at the Laboratory of GenBank, the National Laboratory Gene Library Project, and related individual research projects all contributed to its selection as a center for human genome research when the first such centers were designated by the DOE in 1988. The centers were charged with organizing research units to lead a national effort to map, sequence, and analyze the human genome. Initial emphasis was to be given to (a) improving the technology for physical mapping of chromosomes, (b) improving and automating sequencing

technology, and (c) designing databases and related computational tools for accommodating and making easily accessible the mapping and sequencing data. In addition, the Los Alamos center was asked to explore the possibility of cooperative research programs with the private sector for developing commercial applications of human-genome research.

George Bell served as acting director of the center for approximately one year. An international search for a permanent director led to the appointment of Robert K. Moyzis in August 1989. Monica Fink joined the center in 1990 as Administrative Assistant, and Larry L. Deaven was appointed as Deputy Director in 1991. Deaven had been instrumental in the initiation and success of the Laboratory's Gene Library Project. The Center is located in the Health Research Laboratory; research activities are conducted at a number of Laboratory sites.

The Center serves as an administrative unit and supports research in the Laboratory's Life Sciences, Theoretical, Computing and Communications, Physics, Chemical and Laser Sciences, and Mechanical and Electronic Engineering divisions. The strong and versatile base of support available at the Laboratory makes the Los Alamos center unique among the other designated centers—no other center is as richly diversified in projects that link the physical and biological sciences.

A significant percentage of the Center's activities involve participation in the DOE's Human Genome Coordinating Committee and the Joint NIH/DOE Human Genome Advisory Committee as well as direct communication with other Genome Centers. The major technical subdivisions of the Center are physical mapping, technology development, and information management. Progress and accomplishments in these areas are described in detail in this issue.

Briefly, the technical achievements include the following. (1) Construction and distribution of various types of DNA libraries. The libraries provide the materials used by genome-research laboratories throughout the world to construct detailed maps of human DNA. (2) Construction of a physical map for over 90 percent of human chromosome 16. This achievement required the integration of molecular biological, biophysical, and computational approaches pioneered at Los Alamos. (3) Identification and characterization of the DNA that terminates each human chromosome in a structure called the telomere. This achievement, by supplying the "end pieces" of the human-genome "jigsaw puzzle," allowed the mapping of human chromosomes to proceed at an accelerated pace. (4) Construction of a robot that can reliably handle the millions of DNA clones necessary to complete the Genome Project. The robot allows Los Alamos to be a major distribution center for cloned DNA. (5) Detection of single fluorescent molecules with advanced laser and computational techniques. This achievement led to the first Cooperative Research and Development Agreement associated with the Human Genome Project.

Now that the physical map of human chromosome 16 is almost complete, we can begin to concentrate on the future. Three areas of research will be aggressively pursued. First, it is our goal to help ensure that a physical map of each human chromosome is completed as rapidly as possible. We have already begun to work with other Genome Centers on constructing maps of additional human chromosomes. The successes in physical mapping at Los Alamos and around the world suggest that a complete genetic and physical map for every human chromosome will be obtained in the next few years.

Second, rapid advances in DNA-sequencing technology in the last few years suggest that the amount of DNA that can be sequenced per day by a single investigator can soon be increased from the current level of 1000 nucleotides to between 100,000 and 1,000,000 nucleotides. Although further technology development is needed, the higher rate can achieve most of the immediate goals of the Genome Project. Therefore, a major shift in the Los Alamos effort to production-level sequencing is anticipated. The problems that remain no longer involve sequencing itself, but "front-end" sample preparation and "back-end" analysis. Exploration of a variety of physical and computational solutions to these problems will be integrated into a major sequencing effort.

Finally, a major challenge for the future will be the dissemination of new genetic information and diagnostic techniques to the medical community to help accomplish the goal of rapid, personalized genetic diagnostics. The explosion of genetic information generated by the project will revolutionize medicine only if the dream of technology transfer becomes a reality. Some aspects of technology development and transfer are likely to be pursued in the context of other programs, but the Center for Human Genome Studies will continue to aim our basic research toward this ultimate application.

As scientists, we are responsible to society to be "productively creative." Publicly funded scientific research should eventually lead to benefits for humankind. No project in our lifetime will have as tangible an impact on medicine, biotechnology, and eventually society as the Human Genome Project. We feel honored and privileged to be part of this endeavor and to be surrounded by colleagues who share our vision for the future.