Present and Future Challenges, Far-Reaching Benefits

more efficient way. "The genome budget is devoted to very specific goals, and we make sure that projects contribute toward reaching them."

International Scope

Smith credited the international community with contributing to many project successes. "The initial planning was for a U.S. project, but the outcome, of course, is that it is truly international, and we would not be nearly as far as we are today without those contributions. Also, there's been a fair amount of money from private companies, and support from the Muscular Dystrophy Association in France and The Wellcome Trust in the United Kingdom has been extremely important."

Technology Advances

While noting enormous advances across the board, Smith cited automation progress and observed that tremendously powerful robots and automated processes are changing the way molecular biology is done. "A lot of novel technologies probably won't be useful for initial sequencing but will be very valuable for comparing sequences of different people and for polymorphism studies. One of the most gratifying recent successes is the DNA polymerase engineering project. Researchers made a fairly simple change, but it resulted in a thermosequenase that may answer a lot of problems, reduce the cost of sequencing, and give us better data."

Progress in genome research requires the use of maturing technologies in other fields. "The combination of technologies that are coming together has been fortuitous; for example, advances in informatics and data-handling technologies have had a tremendous impact on the genome project. We would be in deep trouble if they were at a less-mature stage of development. They have been an important DOE focus."

ELSI

Smith described tangible progress toward goals associated with programs on the ethical, legal, and social issues (ELSI) related to data produced by the genome project. "ELSI programs have done a lot to educate the thinkers, and this has produced a higher level of discourse in the country about these issues. DOE is spending a large fraction of its ELSI money on informing special populations who can reach others. Educating judges has been especially well received because they realize the potential impact of DNA technology on the courts."

According to Smith, more people and groups need to be involved in ELSI matters. "We have some ELSI products: the DOE-NIH Joint ELSI Working Group has an insurance task force report, and a DOE ELSI grantee has produced draft privacy legislation. Now it's time for others to come and translate ELSI efforts into policy. Perhaps the new National Bioethics Advisory Commission can do some of this."

New Model for Biological Research

Smith spoke of a changing paradigm guiding DOE-supported biology. "Some years ago, the central idea or dogma in molecular biology research was that information in DNA directs RNA, and RNA directs proteins. Today, I think there is a new paradigm to guide us: Sequence implies structure, and structure implies function. The word 'implies' in our new paradigm means there are rules," continued Smith, "but these are rules we don't understand today. With the aid of structural information, algorithms, and computers, we will be able to relate sequence to structure and eventually relate structure to function. Our effort focuses on developing the technologies and tools that will allow us to do this efficiently."

"That's how I think about what we do at DOE," he said. "We're working a lot on technology and projects aimed at human and microbial genome sequencing. For understanding sequence implications, we are making major, increasing investments in synchrotrons, synchrotron user facilities, neutron user facilities, and big nuclear magnetic resonance machines. These are all aimed at rapid structure determination." Smith explained that now we are seeing the beginnings of the biotechnology revolution implied by the sequence-to-structure-to-function paradigm. "If you really understand the relationship between sequence and function, you can begin to design sequences for particular purposes. We don't yet know that much about the world around us, but there are capabilities out there in the biological world, and if we can understand them, we can put those capabilities to use."

"Comparative genomics," he continued, "will teach us a tremendous amount about human evolution. The current phylogenetic tree is based on ribosomal RNA sequences, but when we have determined whole genomic sequences of different microbes, they will probably give us different ideas about relationships among archaebacteria, eukaryotes, and prokaryotes."

Feeling good about progress over the previous 5 years, Smith summed it up succinctly: "Genomics has come of age, and it is opening the door to entirely new approaches to biology."

David Smith retired at the end of January 1996. Taking responsibility for the DOE Human Genome Program is Aristides Patrinos, who is also Associate Director of the DOE Office of Biological and Environmental Research. Marvin Frazier is Director of the Health Effects and Life Sciences Research Division, which manages the Human Genome Program.