

EXCEPTIONAL SERVICE AWARD for Exploring Genomes

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DOE initiated the world's first genome program in 1986 after concluding that the most useful approach for detecting inherited mutations—an important DOE health mission—is to obtain a complete DNA reference sequence. In addition, the analytical power developed in pursuit of that goal will lead to myriad applications in widely disparate fields including bioremediation, medicine, agriculture, and renewable energy.

Many are surprised to learn that the longest-running federally funded genome research effort is the 12-year-old DOE Human Genome Program. Its goal is to analyze the genetic material—the genome—that determines an individual's characteristics at the most fundamental level. In fact, the Office of Biological and Environmental Research and DOE's predecessor agencies have long sponsored genetic research in both microbial and higher biological systems, studies that include explorations into population genetics; genome structure, maintenance, replication, damage, and repair; and the consequences of genetic mutations.

The DOE program quickly proved visionary, gaining support and momentum to grow rapidly into the U.S. Human Genome Project (in partnership with the National Institutes of Health) in 1990. Today, international support is a critical component of the project as well. DOE continues to play a major scientific and leadership role through its

development of biological resources; cost-effective, automated technologies for mapping and sequencing; and tools for genome-data analysis. The project currently is on track to deliver the sequence of 3 billion human base pairs by 2005.

Vital to the project's continued success is DOE's consistent and focused commitment to disseminating information about the progress, resources, and other results generated in the Human Genome Project. These communication efforts also inform researchers across the broader scientific community, who are beginning to apply the project's data and analytical power to fundamental research problems. Outreach specifically geared to nonscientists promotes public literacy in genetics and helps lay a foundation for informed discourse and responsible decision making by policymakers and the general public.

An important component of the Human Genome Project is a firm resolution to address its societal impact, including ethical, legal, and social issues that arise as a result of new tools and the increased availability of genetic data. Rapid worldwide progress in the project has heightened the urgency of this challenge.

Taking advantage of new capabilities developed by project researchers, DOE initiated the Microbial Genome Initiative in 1994 with the objective of sequencing the

genomes of bacteria having potential economic, industrial, and environmental uses. In a major scientific breakthrough in 1996, researchers sequenced the first entire genome of a microorganism—the methane-producing *Methanococcus jannaschii*—that confirmed the existence of the third major branch of life on earth, the archaea. This feat helped usher in the age of “comparative genomics,” allowing extensive and detailed comparisons of entire genomes. In addition to helping researchers understand the evolution of prokaryotes, eukaryotes, and archaea, practical payoffs include the identification of genes and gene products that underlie unique microbial capabilities. These capabilities may pave the way for development of new and improved energy sources, tools for bioremediation, and a variety of industrial applications.

BER Accomplishments

Clone Resources

- DOE chromosome-specific clone libraries, which are collections containing pieces of human chromosomes maintained in bacterial and yeast cells, have been used as raw material for numerous mapping and sequencing projects around the world. The libraries have led to the isolation of a number of disease genes, including those for breast cancer, myotonic dystrophy, Huntington’s disease, and colon cancer. DOE now supports a new generation of clone resources that are critical for large-scale DNA sequencing in the Human Genome Project.

Gene Finding and Mapping Resources

- A DOE cDNA initiative in 1990 led to greatly improved technologies for reading cDNA end sequences, which were shown to be a valuable resource for categorizing genes utilized in various tissues. The technologies provided the first clues to the

functions of the genes from which they were derived, an approach that has attracted millions of dollars in commercial investment. cDNA molecules also are being used to identify the location of corresponding genes on chromosomes, involving laboratories worldwide in the ongoing task to map the estimated 80,000 human genes.

- The Gene Recognition and Analysis Internet Link (GRAIL) processes tens of millions of bases of DNA sequence each month for researchers around the world, making GRAIL the most widely used “gene-finding” system available.

Structural Studies

- Using information about the 3-D structure of DNA polymerases (enzymes needed for DNA replication) and how they function, researchers engineered an improved polymerase, now produced commercially, that reduces the amount of expensive sequencing reagents required. More recent, highly detailed structural studies partially funded by BER are expected to lead to a further reduction in costs. The structure also will be of interest to researchers using drugs that target DNA replication, such as the antiviral AIDS drug AZT.

Microbial Genomes

- In the DOE Microbial Genome Project, nine microbes had been sequenced completely as of April 1999 and over a dozen more were in progress.

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Charles DeLisi

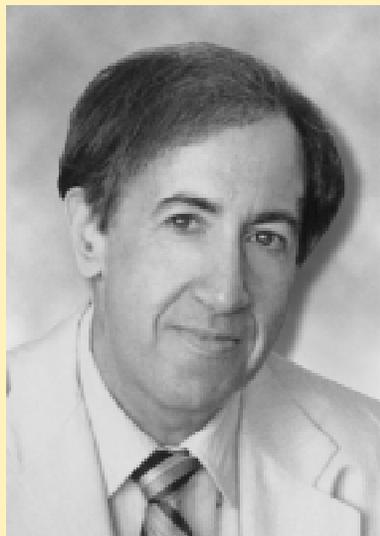
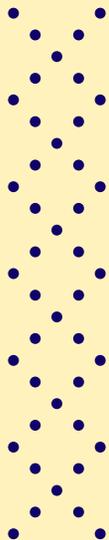
“In recognition of the seminal role you played while Associate Director for Health and Environmental Research in proposing and initiating the Department’s, the nation’s, and the world’s first Human Genome Program in 1986.”

Human Genome Program

Charles DeLisi made the statement, “The Human Genome Program did not happen at the Department of Energy by accident. It happened at DOE because it could not have happened at another agency.”

By the early 1980s, he noted, the rate of DNA sequencing exceeded the rate at which the biochemical function of the encoded proteins could be determined. Sequencing rate no longer limited progress, as it had just a few years earlier. More interesting, even a conservative extrapolation indicated that the gap between data generation and conversion to knowledge would continue to widen rapidly. When Dr. DeLisi was working at the National Institutes of Health (NIH), the question of whether experimental progress was rapid enough to yield a complete human genome sequence in a current lifetime was discussed briefly on one or two occasions, but the NIH intramural atmosphere was not conducive to thinking about high-technology projects of the magnitude that would be required by such a venture.

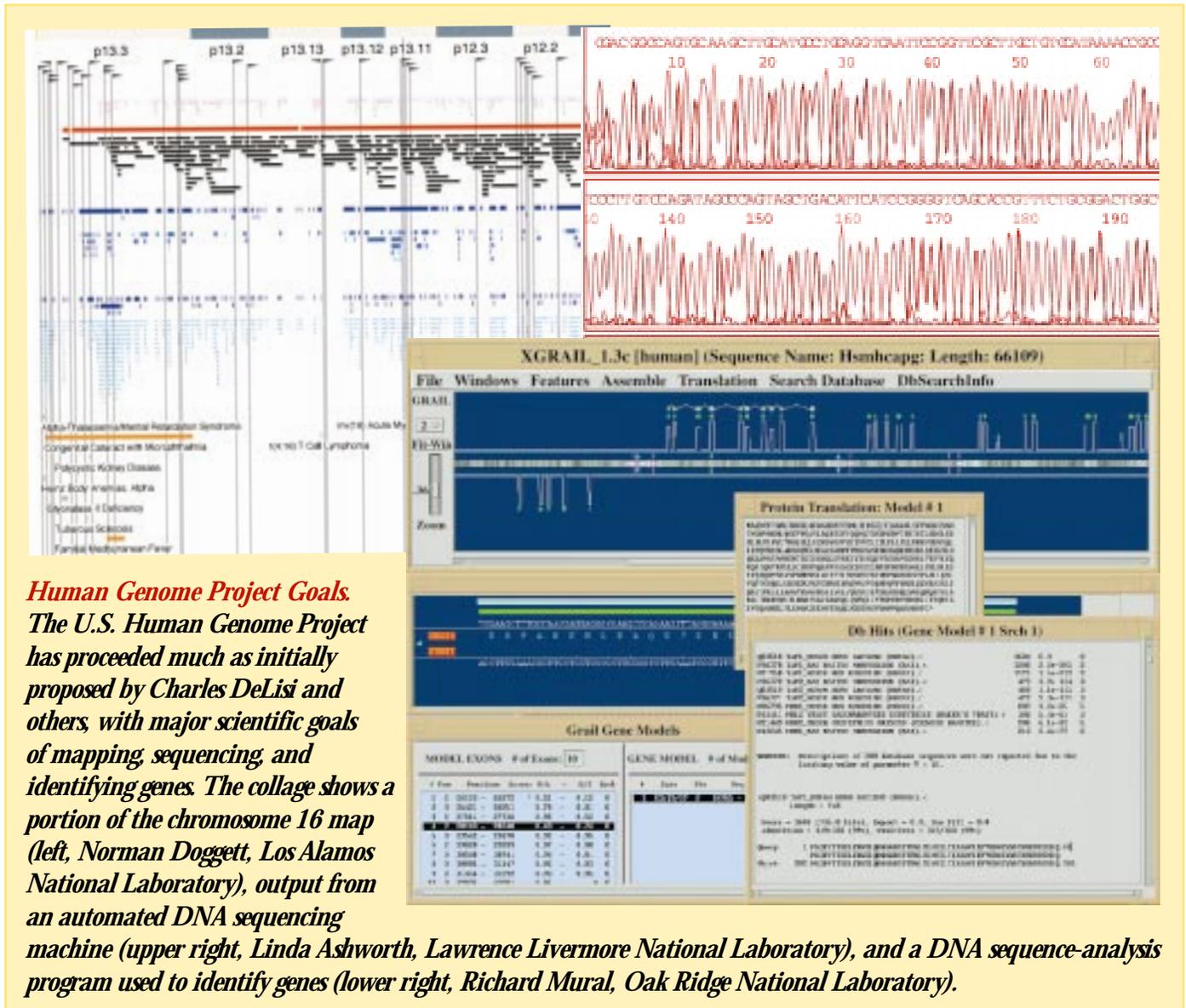
In 1985 Dr. DeLisi was offered the pivotal opportunity of his career as head of DOE’s Office of Health and Environmental Research (OHER), where large, high-technology projects were commonplace. He was, therefore, in a receptive environment when he read the Office of Technology Assessment’s report on heritable mutations, which was based largely on the research of OHER investigators and which considered the possibility of full genomic sequencing.



Charles DeLisi, Ph.D.
Boston University
Boston, Massachusetts

After receiving a B.A. in physics from City College of New York and a Ph.D. in physics from New York University, Charles DeLisi held a postdoctoral appointment for 3 years at Yale University, where he worked on nucleic acid structure. For the next decade, he worked in cellular and systems-level immunology and membrane biophysics, first at Los Alamos National Laboratory and then, from 1977 to 1985, at the National Cancer Institute, where he was a Section Chief. From 1985 to 1987, he was Associate Director of Energy Research for Health and Environmental Research (later renamed Biological and Environmental Research) at DOE. After serving for 3 years as a professor and department chair at the Mount Sinai School of Medicine, in 1990 he joined Boston University, where he is now a professor and Dean of the College of Engineering.

Author of some 200 articles and books, Dr. DeLisi has served on a number of editorial and advisory boards. He holds four patents, with two others pending.



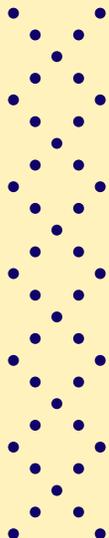
Dr. Mortimer Mendelsohn, who was then Associate Director for Health and Environmental Research at Lawrence Livermore National Laboratory and chair of the OHER Health and Environmental Research Advisory Committee (HERAC), had already given some thought to a massive mapping and sequencing project. He provided the essential critical evaluation of what would be required. Continuous discussions with Dr. David Smith and Dr. Benjamin Barnhart of OHER helped sort out a number of political complexities and led to the first Santa Fe workshop, chaired by Dr. Mark Bitensky, then Life Sciences Director at Los Alamos National Laboratory.

Dr. Bitensky attracted the leading molecular biologists to Santa Fe, and, within a few weeks, he was

able to solicit written evaluations of the meeting from almost all of them. Those reports provided the basis for Dr. DeLisi's memos of May 1986 to Dr. Alvin Trivelpiece, then Director of the Office of Energy Research, proposing the project and outlining its scope. In retrospect, the recommendations by HERAC and workshop attendees were prescient: the project in broad outline has proceeded much as initially proposed and scheduled.

It was evident from the beginning that the genome project would substantially exacerbate the already-pressing ethical issues raised by genetic engineering. In 1987, shortly before Dr. DeLisi left DOE, he set aside 3% of its Human Genome Program funds for the ethical and legal studies that have become an important component of the project.

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Betty Mansfield, M.S.
Oak Ridge National Laboratory
Oak Ridge, Tennessee

After receiving both the B.S. and M.S. degrees in biology with honors from James Madison University in Virginia, Betty Mansfield began work at Oak Ridge National Laboratory (ORNL) in 1977. In this position, she studied metabolic activation of carcinogens, DNA adduct formation, and gene expression following carcinogen exposure.

Collaborating with Reinhold Mann of ORNL and James Selkirk [now at the National Institute of Environmental Sciences (NIEHS)], she established and validated a two-dimensional gel electrophoresis laboratory and data-analysis system, which she used both at ORNL and during a 1-year assignment at NIEHS. These resources were useful for understanding qualitative and quantitative differences in gene expression following carcinogen treatment of normal cells and chemical treatment of malignant Friend Erythroleukemia cells as they entered a more normal state.

In 1989, Ms. Mansfield became founding editor of the *Human Genome News* newsletter and Task Leader of the Human Genome Management Information System (HGMIS), both sponsored by DOE at ORNL. HGMIS is dedicated to communication about the Human Genome Project.

Betty Mansfield

“To recognize you as founding and managing editor of *Human Genome News* and for outstanding success in communicating scientific information to the U.S. and international communities about the Department’s BER Program.”

Communicating Genomic Research

The Human Genome Management Information System (HGMIS) was initiated by DOE in 1989 to advance knowledge, promote the awareness of progress and applications, reduce duplicative efforts, and foster collaborations in the Human Genome Project. Because the project and now its spinoff programs require the contributions and understanding of many different types of professionals, DOE management felt that it was important to have a dedicated publication and an organization to provide extensive sources of information regarding the generation and use of genomic data and resources.

HGMIS serves the many groups that are being heavily impacted by increased genetic knowledge. These groups include the public, allied health professionals, educators, lawyers and judges, ethicists, sociologists, and multidisciplinary scientists who are either contributing to the project or applying its data and resources in their own research or in related programs. Innovative spinoff programs are attacking fundamental biological problems in new ways, creating new classes of pharmaceuticals, and using microorganisms to help solve environmental problems.

HGMIS employs an array of vehicles to accomplish its communication goals:

- *Human Genome News* newsletter. With nearly 14,000 U.S. and foreign print subscribers, *HGN* is available to many others via the World Wide Web.

The Human Genome Program of the U.S.
Department of Energy funds this suite of Web sites.



Human Genome Project Information



www.ornl.gov/hgmis

The Human Genome Project Information suite of Web sites, designed for both general and scientific audiences, offers thousands of text files and links for comprehensive coverage of

genome research and its biological applications. The Web site includes all issues of Human Genome News, which is available free via print subscription from HGMIS, as well as a number of other publications.

HGN offers a collection of articles and information not found in any other single source, including the more discipline-specific scientific publications.

- Comprehensive text-based *Human Genome Project Information* Web site. HGMIS expends about half of its total efforts on this heavily used resource, which is visited by some 70,000 users each month. Its 2600 text files are accessed over 3 million times annually. The newly designed site includes most HGMIS and DOE Human Genome Program publications, research in progress, frequently asked questions, meeting proceedings, funding and resource announcements, calendars of genome events, and many links to related Web sites.
- DOE *Primer on Molecular Genetics*. The primer is widely used by researchers in many fields, students and teachers, genetic counselors, and biotechnology companies.
- Other resources. These include DOE Human Genome Program reports, related documents,

proceedings of contractor-grantee meetings, topical handouts, informational exhibits and brochures, and program flyers.

In addition to supplying educators and meeting and workshop organizers with multiple copies of documents and other resources, HGMIS works directly with those who make inquiries by e-mail, fax, or telephone. HGMIS staff members also represent the project at selected scientific conferences and meetings and make presentations to educational, judicial, and other groups.

Ms. Mansfield noted: "Recognizing HGMIS work shows that OBER is committed to communication and openness and to informing scientists, policymakers, and the public about how OBER is spending research dollars. Not only does this commitment help set the stage for informed public discourse and input, it increases science literacy and should lead ultimately to policy decisions that better reflect societal needs."

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J. Craig Venter

“In recognition of your . . . research . . . for determining the first three complete microbial genome sequences, discovering and cataloging new human and microbial genes, and exemplifying the private sector’s collaborative role in federal programs.”



J. Craig Venter, Ph.D.
Celera Genomics Corporation
The Institute for Genomic Research
Rockville, Maryland

J. Craig Venter is President and Chief Scientific Officer of Celera Genomics Corporation and founder, Chairman, Chief Scientist, and former President of The Institute for Genomic Research (TIGR), a not-for-profit research institution. At Celera, Dr. Venter is leading the company’s human genome sequencing efforts.

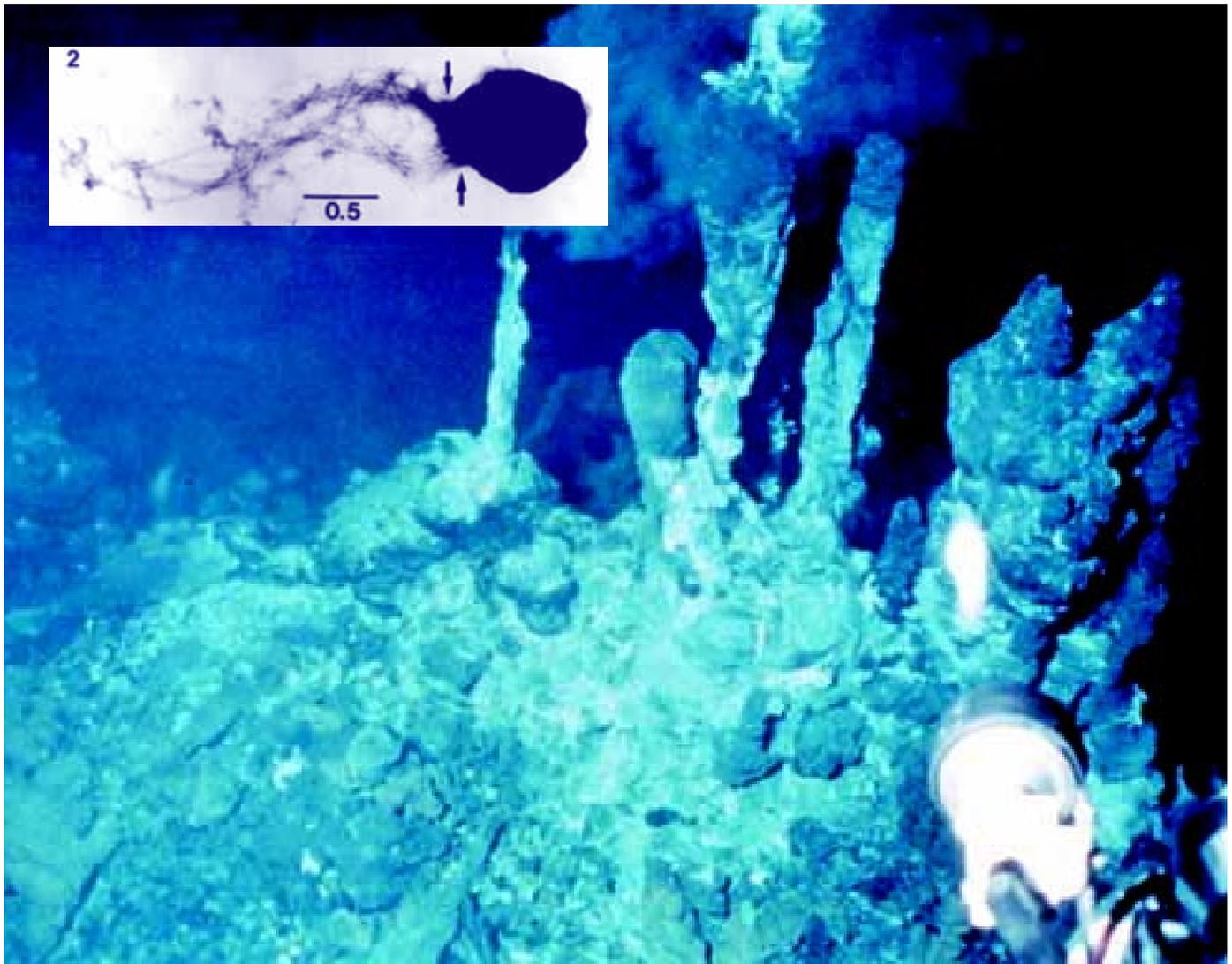
Between 1984 and the formation of TIGR in 1992, he was a Section and a Laboratory Chief in the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. During his genomics and biomedical research career, Dr. Venter has revolutionized the methods by which genomes are sequenced and analyzed. In 1990, he developed expressed sequence tags (ESTs), an innovative strategy for gene discovery that has transformed the biological sciences. Over 72% of all accessions in the public database GenBank are ESTs from a wide range of species including humans, plants, and microbes. Using the EST method, Dr. Venter and the scientists at TIGR have discovered and published more than half of all human genes. New algorithms for dealing with hundreds of thousands of sequences led to the whole-genome shotgun sequencing method with which TIGR completed the first three genomes in history and a total of ten through 1998.

Author of more than 160 research articles, Dr. Venter is one of the most cited scientists in biology and medicine. He has received numerous awards and honorary degrees for his pioneering work and has been elected a fellow of several societies including the American Association for the Advancement of Science and the American Academy of Microbiology. He received his Ph.D. in physiology and pharmacology from the University of California, San Diego.

“Shotgun Sequencing”

The Institute for Genomic Research (TIGR) has interests in structural, functional, and comparative analysis of genomes and gene products in viruses, eubacteria, pathogenic bacteria, archaea, and both plant and animal eukaryotes. The whole-genome sequencing strategy used by TIGR is called a “shotgun” method, in which the genome is sheared randomly into small pieces that are then cloned, sequenced, and reassembled to form a whole genomic sequence. With this approach, there is no need to develop a genetic or physical map of the genome before sequencing it; the sequence itself serves as the ultimate map.

In large shotgun-sequencing projects, DNA fragments are assembled into a consensus sequence. Key to the shotgun method’s success is the availability of a truly random genomic DNA clone library and a powerful, accurate algorithm for reassembling the fragments into a complete genome. The basic approach for genome assembly is to compare all individual sequences to find overlaps and use this information to build a consensus sequence. Using software they developed for large-scale genome sequencing projects, TIGR investigators have assembled the



***Methanococcus jannaschii* and Hydrothermal Vent.** The microbe *M. jannaschii*, whose complete DNA sequence confirmed a third major branch of life on earth, was isolated in 1983 in the area of the above "smoker," a hydrothermal vent on the floor of the Pacific Ocean (photograph: Woods Hole Oceanographic Institution). Inset (scale = 0.5 μm): Electron micrograph of *M. jannaschii*, stained with uranyl acetate to show the two bundles of polar flagella, indicated by arrows (micrograph: Dr. W. Jack Jones).

complete genomes of *Haemophilus influenzae*, *Mycoplasma genitalium*, *Methanococcus jannaschii*, *Archaeoglobus fulgidus*, *Helicobacter pylori*, *Borrelia burgdorferi*, *Treponema pallidum*, *Thermotoga maritima*, and *Deinococcus radiodurans*. TIGR is sequencing other microbes, including *Shewanella putrefaciens*.

The next step in whole-genome analysis is to identify all the predicted genes and search the translated protein sequences against protein sequences available in public databases. Because of the tremendous conservation in protein sequence among organisms throughout evolution, putative genes can be identified by sequence similarities.