Human Genome news

Sponsored by the U.S. Department of Energy and the National Institutes of Health

ISSN: 1050-6101 Vol. 7, No. 5, January–March 1996

Collaborations Multiply Research, Commercial Benefits

Academic, National Laboratory, Industrial Innovations Yield Chromosome Painting, Merck Gene Index

Collaborations among researchers in academia, national laboratories, and industry are yielding important benefits for genomic research and the broader biomedical research community. Two outstanding examples, the chromosome painting technology and the Merck Gene Index Project, are described below.

Chromosome Painting Reveals Cancer, Other Diseases

In September 1995, a broad patent was awarded to the University of California (UC) for "chromosome painting," a technology that uses FISH to stain specific locations in cells and chromosomes. Chromosome painting was invented by Joe Gray and Dan Pinkel during their tenure at Lawrence Livermore National Laboratory (LLNL), which is managed for DOE by UC. Licensed exclusively to Vysis Inc., the technology will be made widely available through a nonexclusive sublicensing program.

The innovative approach uses specifically tailored, fluorescently labeled probes that hybridize (bind) with genes or whole chromosomes of interest. The patent covers the use of nonfluorescent "blocking DNA" that prevents nontargeted DNA from being fluorescently stained. After the probes are applied, the results can be seen in a standard fluorescence microscope. Gene amplifications, deletions, or abnormal rearrangements in individual cells are revealed so that missing or extra pieces of chromosomes can be identified. Such genetic abnormalities often provide the first signs of cancer and other diseases.

"We have used these techniques to elucidate genetic changes in a broad range of human diseases including breast, prostate, and colon cancers," said coinventor Gray. "They also appear to have substantial usefulness in prenatal and neonatal detection of genetic diseases such as Down's syndrome, as well as in detecting genetic damage after exposure to radiation and other toxic agents."

According to John Bishop, president of Vysis, the patent is a cornerstone in developing a new generation of tests

(continued next page)

DOE Assumes Full *HGN* Sponsorship

Web Site To Be Main NCHGR Gateway

By Leslie Fink, NCHGR Office of Communications (*leslief@od.nchgr.nih.gov*)

With this issue, NCHGR will say good-bye to our readers as copublisher of *Human Genome News*. We have enjoyed collaborating with our partners at DOE and the Human Genome Management Information System on this newsletter over these past several years. Feedback from *HGN* readers has indicated repeatedly that it fills a valuable niche in communicating information about human genome meetings, results, and resources to scientific readers. Our colleagues at DOE will continue to publish *HGN* as an important link to the working scientist. (See related article, p. 3.)

NCHGR will maintain information flow to the scientific community through the development of a state-of-the-art World Wide Web site, which we believe will provide researchers with a major gateway to research data, grant information, news, and policy information about the Human Genome Project and NCHGR programs. Cybernauts can already visit the NCHGR Web site (*http://www.nchgr.nih.gov*) to find results and accomplishments of the Human Genome Project. There you will find information about NCHGR programs and funding, as well as links to central databases and to each of the Genome Science and Technology Centers (GESTECs) around the country. GESTEC Web sites contain the latest data releases from work in their laboratories. NCHGR's Web site also contains information about laboratories in our Division of Intramural

(see NCHGR, p. 2)

In This Issue

that not only detect cancer and genetic diseases but provide valuable information regarding disease prognosis and predisposition. Larry Fox, vice president of Technology and Business Development, added, "The use of this technology for the detection of disease is currently in its infancy and will emerge in the next 10 years into a multibillion-dollar market."

Continued development in this area of technology is one of the major goals of The Resource for Molecular Cytogenetics, established in 1993 and funded by DOE, NIH, and Vysis. The Resource is a partnership between the University of California, San Francisco (UCSF), and Lawrence Berkeley National Laboratory (LBNL), which is also managed by UC. The Resource integrates the technical capabilities of the LBNL Human Genome Center with cancer genetics expertise at UCSF and the Life Sciences Division of LBNL. According to Gray, "The Resource serves as a source of new hybridization technologies, computer-aided fluorescence microscopy capabilities, and probes optimized for molecular cytogenetic studies."

The international molecular cytogenetics community has already begun to tap successfully into The Resource. A public database featuring available probes, along with a request form, can be accessed via WWW (*http://rmc-www.lbl.gov*). *[David Gilbert, LBNL, david_gilbert@macmail.lbl.gov]*

Merck Gene Index Project

In September 1994, Merck & Co. and Washington University announced plans for a publicly available collection of expressed human gene sequences based on high-quality cDNA clones from normalized libraries. Since then, the project has contributed over 220,000 sequences to the public database dbEST, amounting to over 75% of the reported human ESTs in that database. Merck plans to use these sequences to organize the characterized clones into a minimal set representing each unique identified human gene—an index to the genome—that will also be made available.

By promoting free data exchange, the project aims to reduce duplicated efforts and speed identification of disease-related genes. Increased accessibility of sequence data and cDNA clones provides starting points for research that will lead ultimately to new targets for drug design, expressed proteins with potential therapeutic value, and discovery of disease-related genes that may become the focus for gene-therapy regimens. Making these basic research tools broadly available to the biomedical community may lead to breakthrough discoveries that will benefit the public by providing opportunities and preserving incentives for gene-based product development.

Collaborators. The Merck-supported sequencing project is conducted at the NIH-sponsored Genome Sequencing Center at the Washington University School of Medicine, St. Louis. Successful large-scale sequencing efforts and demonstrated expertise in EST sequencing and informatics led Merck to select the sequencing center to generate ESTs from both ends of more than 150,000 cDNA clones. The center has contributed to genome sequencing efforts for the roundworm *Caenorhabditis elegans*, the yeast *Saccharomyces cerevisiae*, and human. Currently, the center's sequencing capacity is about 14 Mb per year of finished sequence.

For the EST sequencing project, clones are arrayed at LLNL and sent to the center through the Integrated Molecular Analysis of Gene Expression

(see Collaborations, p. 7)

☛ IMAGE, Other cDNA Clones Available

Because cDNA molecules represent coding areas of the genome, sets (libraries) of these cloned molecules provide the research community with ready access to biological materials for hunting disease and other human genes. The 250,000 cDNA clones arrayed by the IMAGE Consortium (*http://www-bio.llnl.gov/bbrp/image/image.html*), described in the article above, are publicly available from five distributors around the world:

United States

- American *Type Culture* Collection (ATCC): 301/816-4378, *http://www.atcc.org/*
- Genome Systems, St. Louis, Missouri: 800/430-0030, *http://www.genomesystems.com/*
- Research Genetics, Huntsville, Alabama: 800/533-4363, *http://www.resgen.com/*

United Kingdom

- Human Genome Mapping Project Resource Centre: +44-1223/494500, *http://www.hgmp.mrc.ac.uk/*

Germany

- Max Planck Institute, Berlin: +49-30/8413-1627, *http://rldb.rz-berlin.mpg.de/*

Other cDNA clones may also be obtained from these distributors. For example, The Institute for Genomic Research (*http://www.tigr.org/*) has made some 90,000 cDNA clones accessible through ATCC to registered users of the Human cDNA Database. Information about these materials was published in the *Nature Genome Directory* [*Nature* **377**(Supplement), 3–174 (1995)], which is accessible via WWW (*http://www.tigr.org/tdb/hcd/nature_paper/nature_paper.html*).◊

NCHGR *(from p. 1)*

Research, which applies genome technologies to the study of human inherited diseases.

In addition, we will expand our outreach efforts toward educating healthcare professionals about the impact of Human Genome Project technologies on the practice of medicine. This move will broaden Human Genome Project outreach programs specifically to include an audience critical to the successful translation of HGP technologies into opportunities for improved medical care. When the Human Genome Project began 5 years ago, it was immediately clear that the spin-offs of this enterprise would profoundly affect the way modern medicine is practiced.

Yet, in spite of the project's certain impact on medical care, surveys of various professional communities over the years have shown that few providers feel they are adequately trained to responsibly handle the increasing demand for genetic services by consumers. To help fill this knowledge gap, NCHGR is forging new partnerships with key players in health care—audiences that are critically important to the mission of our parent agency, the National Institutes of Health.

So, next time you are surfing the Net, please stop in. We are continuing to expand and polish our Web site, and hope to go on line with a new edition this spring. Cowabunga! ◊

HGN Expands Focus

Will Cover Human Genome Project's Impact on Other Fields

Now entering its seventh year of publication, *Human Genome News* will continue to serve as a prime source on all aspects of the Human Genome Project for the working scientist, the biomedical research community, medical professionals, bioethicists, educators, interested public, and disseminators of genetic information. Produced by the Human Genome Management Information System (HGMIS) at Oak Ridge National Laboratory for the DOE Office of Health and Environmental Research (OHER), *HGN* will be published 4 to 5 times a year in hard copy and on the HGMIS WWW site.

Human Genome News

*Domestic and Foreign Subscription Affiliations**

Academic or research	8175
Industry	1590
Government organizations	964
DOE laboratories	327
Press	273
Individuals/Miscellaneous	251
Libraries	235
Ethics	151
Genetic counseling	139
Scientific societies	106
Legal profession	93
Forensics	8
Law enforcement	5
Total	12,317

*Current rate of subscription requests is about 200/month.

HGN is broadening its focus to include other research sponsored by the Health Effects and Life Sciences Research Division, Medical Applications and Biophysical Research Division, and Environmental Sciences Division of OHER. These programs directly impact progress and the practical uses of Human Genome Project data—the "payoff" of research. They include the DOE Microbial Genome Initiative, which is a direct spin-off of the genome project, and programs in structural biology, computational structural biology, and molecular medicine.

As in past issues, *HGN* will feature technical and general-interest articles and features covering national and international project news; ethical, legal, and social implications of genome data; development and transfer of the growing body of genome technologies; available resources; genome meeting and training calendars; and funding opportunities.

HGMIS staff members continuously monitor changes in direction of the international project and search for ways to strengthen newsletter content relevancy and other HGMIS services. Suggestions are welcome.

WWW Sites

The three Web sites described below were selected recently by the McKinley Group's professional editorial team as "4-Star Sites," the highest rating achievable in the Magellan Internet directory.

HGMIS Site

Since November 1994 HGMIS has maintained the "Human Genome Project Information" Web site (*http://www.ornl.gov/hgmis/*). The site contains searchable versions of *HGN*, goals of the U.S. Human Genome Project, abstracts from the DOE Santa Fe Contractor-Grantee workshops, DOE Human Genome Program reports, topic-specific pages, and numerous links to other sites.

HGMIS is also collaborating with the Einstein Institute for Science, Health, and the Courts to establish and maintain a WWW site for the judicial genetics education project.

Virtual Library: Genetics

In June 1995 HGMIS staff assumed responsibility for maintaining and updating the Genetics section, Biosciences division, of the CERN Virtual Library. The site (*http://www.ornl.gov/TechResources/Human_Genome/genetics.html*) includes an organism index linking to other pertinent databases; information on the U.S. and international Human Genome Project; and links to research sites, human chromosome–specific sites, Genome Database, and Online *Mendelian Inheritance in Man*. Each month, about 8000 host computers access one or both HGMIS Web sites, and about 70,000 requests for information are received. According to the Alta Vista index of WWW links, more than 800 links connect to the HGMIS pages. (HGMIS contact: Sheryl Martin, *martinsa@ornl.gov*)

Primer in Adobe Acrobat

The 1992 DOE *Primer on Molecular Genetics*, which has been accessible on several WWW sites for about 2 years, is now available as an Adobe Acrobat (pdf) file on the HGMIS site (*http://www.ornl.gov/hgmis/publicat/primer/primer.pdf*). An Acrobat reader that retains original formatting and allows high-quality printing of graphics and text can be obtained via *http://www.adobe.com/* under Free Software.

More than 33,000 hard copies of the primer have been distributed as a handout for genome centers; a resource for interdisciplinary staff training by companies that make products for researchers and consumers; and an educational tool for teachers and genetic counselors. Such organizations as high schools, universities, and medical schools use the primer for their first-year medical students and continuing-education curriculum. The hard-copy version is out of print, but a single photocopy is available from HGMIS. This primer is being revised, and HGMIS staff would appreciate suggestions for updates. (HGMIS contact: Denise Casey, *caseydk@ornl.gov*)

Newsgroup Moderation

Betty Mansfield, Managing Editor of *HGN*, also moderates the BIOSCI Human Genome newsgroup. The newsgroup's purpose is to promote scientific discussion and distribution of information about the international Human Genome Project and to provide scientists with easy access to program administrators. (To post a message: *gnome-pr@net.bio.net* or *gnome-pr@daresbury.ac.uk*)

BIOSCI is a set of electronic communication forums—the bionet USENET newsgroups and parallel e-mail lists—that promote communication among professionals in the biological sciences (*http://www.bio.net/*). Users can access the various BIOSCI newsgroups through this WWW address.◊

Genome Program Director Smith Retires from DOE OHER

Multidisciplinary OHER Research Programs Study Energy Consequences, Solve Scientific Problems

After a DOE career spanning 19 years, David A. Smith retired on February 3 as director of the Health Effects and Life Sciences Research Division (HELSRD) of the DOE Office of Health and Environmental Research (OHER). As director, Smith managed the division's diverse programs including the Human Genome Program, which he was instrumental in initiating in 1986. He is succeeded as director of the Human Genome Program and chair of the Human Genome Task Group by OHER Associate Director Aristides Patrinos. Marvin Frazier is now acting director of HELSRD.

OHER Research Programs

Based on mandates from Congress, DOE OHER's principal mission is to (1) develop the knowledge necessary to identify, understand, and anticipate long-term health and environmental consequences of energy use and development and (2) employ DOE's unique scientific and technological capabilities in solving major scientific problems in medicine, biology, and the environment.

Because of its multidisciplinary nature, OHER's programs are organized and managed in three divisions: HELSRD, Medical Applications and Biophysical Research (MABRD), and Environmental Sciences (ESD). Some programs are administered jointly by the staffs of two or all three divisions. OHER organization and program areas are depicted at right.

Current HELSRD priorities emphasize the use of unique resources and tools developed in the human genome, structural biology, and cellular and molecular biology programs. MABRD has a long history of support for medical imaging and diagnostic modalities. HELSRD and MABRD have recently initiated a new program in computational structural biology.

ESD supports basic research in aspects of global climate change, including the fate of increased carbon dioxide in the atmosphere, ecological effects, and climate modeling. ESD also supports research in the fundamental sciences that will underpin the development of new technologies for cleanup of the nation's nuclear weapons processing and production sites.

Headquartered in Germantown, Maryland, OHER technical staff is responsible for managing, planning, and developing programs for the organization, whose FY 1996 budget totals $419.5 million. [See p. 19 for DOE Human Genome Program funding announcements.] The staff establishes strategy, priorities, and schedules; defines resource allocations; coordinates peer reviews of research proposals, program reviews, and evaluations; and maintains close liaison with other DOE programs, federal agencies, Congress, and the scientific community. (OHER contacts: 301/903-6488, Fax: -8521, *genome@oer.doe.gov, http://www.er.doe.gov/production/oher/oher_top.html*) ◊

Marvin Frazier (left), new acting director of OHER's Health Effects and Life Sciences Division, and David Smith, retiring director, at the recent DOE Human Genome Program Contractor- Grantee Meeting in Santa Fe, New Mexico. An article on this meeting will appear in the next issue of *HGN*.

Office of Health and Environmental Research

Ari Patrinos, Associate Director
Michael Riches, Executive Assistant
Ben Barnhart, Program Coordinator

Health Effects and Life Sciences Research Division

Marvin Frazier, Acting Director
301/903-5468

- Structural Biology
- Molecular and Cellular Biology
- Human Genome/Microbial Genome
- Health Effects
  - Biological Research

Medical Applications and Biophysical Research Division

Roland Hirsch, Acting Director
301/903-3213

- Medical Applications
  - Radioisotope Development
  - Radiopharmaceuticals
  - Instrumentation
  - Clinical Feasibility
  - Boron Neutron Capture Therapy
  - Molecular Nuclear Medicine
- Measurement Science and Dosimetry Research
- Structural Biology Facilities
- Human Genome Instrumentation
- Computational Structural Biology

Environmental Sciences Division

Michelle Broido, Acting Director
301/903-3281

- Climate and Hydrology
  - Climate Modeling and Computer Hardware Advanced Mathematics and Model Physics (CHAMMP)
  - Atmospheric Radiation Measurement (ARM)
  - Unmanned Air Vehicle
- Atmospheric Chemistry and Carbon Cycle
  - Atmospheric Science
  - Marine Transport
  - Carbon Cycle
  - Oceans Research
- Ecological Processes
  - Ecosystem Function and Response
  - Vegetation
- National Institute of Global Environmental Change (NIGEC)
- Environmental Restoration [including Natural and Accelerated Bioremediation Research (NABIR) and Microbial Genome]

Detailed Human Physical Map Published by Whitehead-MIT

STS-Based Map Represents Halfway Point to 100-kb Human Genome Project Goal

In December 1995, a team led by scientists at the Whitehead Institute–Massachusetts Instituteof Technology (MIT) Center for Genome Research and Généthon presented the most detailed physical map of the human genome yet published. The new map, which contains more than 15,000 STS DNA markers spaced an average of 199 kb apart, covers almost 95% of the entire genome. Previously, the highest-resolution whole-genome physical map, a clone-based effort reported last fall in a special supplement to *Nature*, covered about 75% of the genome and involved about 2500 STSs.

Reported in the December 22, 1995, issue of *Science* (**270**, 1945–54), this latest achievement brings within close range the short-term Human Genome Project goal of a 100-kb whole-genome map requiring about 30,000 STSs. The map project required 2.5 years and involved a Whitehead-MIT team averaging 16 researchers in mapping, 3 in sequencing, and 5 in data management and computational analysis. Although originally slated for 1998, map completion by Whitehead-MIT and other groups is expected by the end of this year.

Detailed genome maps and improved technology will drastically reduce the time needed to localize and clone disease genes and also enable researchers to determine the complete sequence of all human DNA—the ultimate goal of the Human Genome Project.

Faster Technology

The new map is based on STSs—DNA markers that can be used in various physical and genetic mapping techniques to provide a common link for integrating and comparing different types of genome maps. Another advantage of STS-based maps is their accessibility. Stored electronically in publicly available databases, STSs are easily accessible to researchers, who can obtain any mapped chromosomal region by PCR-based clone screening for particular STS markers.

Detecting and placing STSs on the 3 maps required over 15 million PCR analyses. Eric Lander, director of the Whitehead-MIT genome center, and Thomas Hudson, leader of the mapping team, credit their success to a strong, early commitment to laboratory automation. The team spent the first 1.5 years of the project developing automated robots, designing mathematical pooling schemes to reduce the number of tests required to localize markers, and generating a bar-coding system like that used in supermarkets to accurately identify and track samples. The researchers also adapted camera technologies from the aerospace industry to read PCR test results directly into the computer database and created computer programs to check data automatically and design new sets of experiments based on existing results.

The resulting Genomatron, built in collaboration with Intelligent Automation Systems, enabled scientists to run 300,000 PCR reactions/day compared with 6000/day in 1993.

Data and Resource Availability

Data corresponding to the integrated map are available as flat files via ftp (*ftp://ftp-genome.wi.mit.edu/pub/human_STS_releases/dec95/*) and in an interactive, browsable form via WWW (*http://www-genome.wi.mit.edu/*). Random genome-wide STSs and YACs as well as RH cell lines used for creating the maps are available commercially from Research Genetics in Huntsville, Alabama (800/533-4363, Fax: 205/536-9016, *http://www.resgen.com*).

Combined Genome View

The new map is a combination of three independent maps that were joined to produce an integrated map with different levels of detail. Efforts by the Whitehead-MIT team included (1) construction of an STS-content map consisting of 10,000 STSs screened in the CEPH YAC library and depicting marker order over a range of about 1 Mb; (2) assembly of a radiation hybrid (RH) map consisting of roughly 6200 markers enabling STSs to be mapped up to about 10 Mb; and (3) incorporation of the 5200-loci Généthon genetic linkage map allowing STS mapping over distances up to 30 Mb (Dib et al., *Nature* **380**, 149–54 (March 14, 1996).

Each type of map has advantages. Genetic and RH maps help determine the long-range order of STS landmarks, and STS-content maps are best suited for estimates of fine-structure order. "Integration of the three strategies allowed us to check and recheck the accuracy of our data, producing a detailed product with a high level of precision," said Hudson, who coauthored the *Science* article with Lander, Lincoln D. Stein, and others.

Community-Wide Access

The combined map makes much of the human genome accessible to the entire community, Hudson continued. "The wonderful feature of an STS-based map is that any scientist can find a specific location in the human genome by setting up the appropriate PCR assay," he said. "All the information necessary to locate an STS from our map is freely available by computer through our World Wide Web site. In one recent week we had 67,000 accesses to that site."

Scaffold for Sequencing

The *Science* article authors state that this STS-based map also presents a practical scaffold for initiating large-scale sequencing. STS maps are useful for production sequencing, they note, because the markers are anchored in the genome. Improved libraries can be substituted easily as they become available, and efforts can focus on regions of any size, instead of entire chromosomes.

"Generating the complete sequence of human DNA is the most exciting adventure in modern science," says Lander. "In the 19th century, chemists defined the periodic table of elements, and it forever changed the practice of chemistry. Sequencing the human genome will have the same impact on human biology and medicine. It will give us a new understanding of human development and a broad array of new tools for fighting human disease."◊

OMIM Catalogs Human Genes and Genetic Disorders

Online *Mendelian Inheritance in Man (OMIM)* is a comprehensive, authoritative, and up-to-date human gene and genetic disorder catalog that supports medical genetics and the Human Genome Project. The print version, *Mendelian Inheritance in Man (MIM)*, was started in the early 1960s by physician Victor McKusick [Johns Hopkins University (JHU)] as a catalog of X-linked traits. The first edition of *MIM* was printed in 1966 and the 11th in 1994.

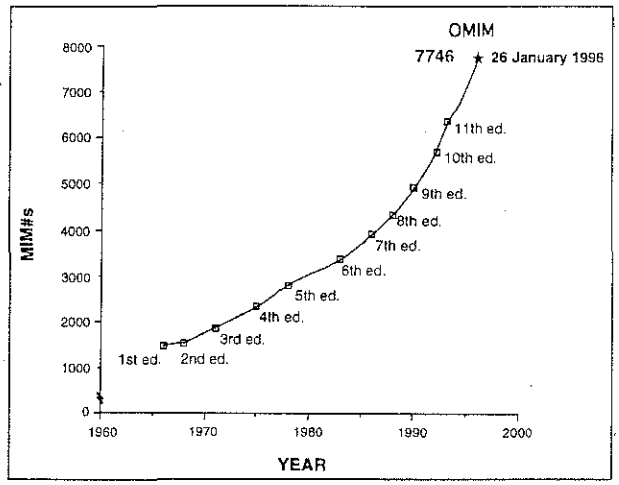
In the early 1980s, *MIM* was used by an informatics group at the National Library of Medicine (NLM) Lister Hill Center as the testbed in developing the Information Retrieval Experiment (IRx), a system for maintaining and searching full-text knowledge bases. The *MIM* online version, established in 1985 at the JHU Welch Medical Library, was made publicly available in September 1987 under funding from the Howard Hughes Medical Institute (HHMI). In 1989 HHMI moved the Human Gene Mapping Library, which it also was funding, from New Haven to Baltimore for management and distribution along with *OMIM*. In 1990 DOE and NIH assumed funding of OMIM and the new entity (Genome Database) as part of the Human Genome Project.

Contents. Early versions of *MIM* listed Mendelian phenotypes (mainly disorders) classified according to the inheritance mode: autosomal dominant, autosomal recessive, and X-linked. The objective was to create one entry per gene locus. Based mainly on heavily referenced periodical literature, entries described the disorder as well as genetic peculiarities. When phenotype distinctness and inheritance mode were considered quite certain, the entry was honored with an asterisk. The absence of an asterisk indicated uncertainty.

In the 1960s, Mendelian inheritance of a phenotype was almost the only way to define an entry for *MIM*. In the 1970s, interspecific somatic cell hybrids permitted mapping of genes for which no Mendelian variation had been identified (e.g., thymidine kinase on chromosome 17). These genes of known function but no Mendelian variation were also given entries in *MIM*.

Since 1980, molecular genetics has permitted the isolation, sequencing, and mapping of many genes and the identification of disease-associated mutations; many have been given entries in *OMIM* even though no Mendelian phenotype was known.

This evolution was responsible for a change in *MIM*'s subtitle from *Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes* (used in the first 10 editions) to *Catalogs of Human Genes and Genetic Disorders* (used in the 11th edition). The accompanying graph illustrates the growth of entries in *MIM* (and *OMIM*) over the more than 30 years of its existence.



Total number of entries in *Mendelian Inheritance in Man* and the online version, *OMIM*.

Organization. All entries are given a unique six-digit number. Catalogs of Y-linked loci, with ID numbers beginning with 4, and of mitochondrial genes and phenotypes, with ID numbers beginning with 5, were started in 1992. Up until May 15, 1994, separate catalogs were maintained for autosomal dominant, autosomal recessive, and X-linked entries, with ID numbers beginning with 1, 2, and 3, respectively. Any autosomal gene of known function that had been characterized by mapping, cloning, or sequencing but had no known associated Mendelian phenotype or variation was placed in the autosomal dominant catalog.

Autosomal entries created after May 15, 1994, are assigned an arbitrary, consecutive ID number beginning with 6. Thus, in addition to the three chromosome-specific catalogs—X, Y, and mitochondrial—autosomal loci are now represented also by entries having numbers beginning with 6.

A number sign (#) is used to distinguish some entries that describe a particular phenotype caused by mutations in two or more different genes represented by separate entries.

Special Features. *OMIM* has two features important to both the science and practice of medical genetics: (1) listing of the mutations (allelic variants) that constitute the molecular basis of genetic diseases and (2) synopsis of the human gene map, with particular attention to the morbid map (i.e., chromosomal sites of genetic disorders).

Accessing *OMIM*

Responsibility for distributing *OMIM* was transferred on December 1, 1995, to the National Center for Biotechnology Information (NCBI) of NLM. *OMIM* editorial offices and functions will remain at Johns Hopkins Hospital in Baltimore. *OMIM* formerly was distributed by GDB, which is also at JHU. Moyra Smith, scientific director since March 1, coordinates the distributed multiauthorship. Editorial functions are funded by the NIH National Center for Human Genome Research under a grant to JHU, with David Valle the principal investigator.

GDB will continue to maintain its WWW links to *OMIM*. NCBI provides WWW, telnet, and dialup access to the IRx version; an e-mail server; and anonymous ftp for downloading files. New *OMIM* enhancements include direct links to DNA and protein sequence databases and to the Medline database. Most references in *OMIM* are linked to an abstract in Medline.

Allelic variants are identified uniquely by a ten-digit number consisting of the six digits of the primary entry number followed by a dot and four digits beginning with .0001. Thus, the unique entry number for the beta-globin locus (HBB) is 141900 and that for the sickle hemoglobin mutation (HBS) is 141900.0243.

A synopsis of the human gene map has been maintained in the front matter of the print *MIM* beginning with the third (1971) edition. Users of the online version can move directly from the entry concerning a particular gene or phenotype to the appropriate place in the chromosome-by-chromosome listing of mapped genes, and vice versa. Information on methods and certainty of mapping, disorders due to mutation in the given gene, and mapping of the mouse homolog is also given in tabular form.

Timeliness. *OMIM* staff members attempt to incorporate journal information as soon as possible. Two-thirds of *OMIM* references come from 20 "high-impact" journals, some of which distribute embargoed prepublication copies of articles to the lay media.

[NCBI *OMIM* browser: *http://www3.ncbi.nlm.nih.gov/Omim/*. NCBI services: *info@ncbi.nlm.nih.gov* or 301/496-2475. *OMIM* editorial offices: 410/955-6641, Fax: -4999, *mimadm@ncbi.nlm.nih.gov*] ◊

Collaborations *(from p.2)*

(IMAGE) Consortium [*HGN* **6**(6), 3 (March–April 1995)]. All the arrayed clones have preassigned GDB accession numbers. This standardizing feature helps integrate mapping data obtained from IMAGE clones used in such other projects as the gene map described near the end of this article (see box on clones, p. 2).

The sequencing center sizes the clones by restriction digestion and imaging of agarose gels, after which sequencing is attempted from the 5′ and 3′ ends of each clone. Resulting EST sequences are subjected to quality-control procedures that include removing all vector and nonnuclear RNA sequences as well as any contaminating bacterial or yeast sequences. Sequences are annotated with similarity information, clone source, read orientation, and range of high-quality data and then submitted directly to dbEST. The sequencing center currently processes about 5000 sequences/week and has submitted sequences from more than 131,000 clones, making it the largest public EST sequencing effort.

Other cDNA sequencing collaborators include the NIH National Center for Biotechnology Information, which is publicly distributing sequence data through GenBank and dbEST. The Computational Biology and Informatics Laboratory (University of Pennsylvania School of Medicine) is integrating and checking data for consistency.

Immediate Data Release. Immediate distribution of sequence data to public databases allows all interested parties to access, analyze, and use the information as it is generated. No one has advance access, nor can any of the sequence data from the center be delayed or restricted. In the months following the first data release, dbEST usage increased over 1000%.

The data-release policy already is facilitating downstream projects. A Human Genome Organisation (HUGO) consortium is using the data to generate a high-resolution transcript (gene) map. The HUGO consortium includes the Stanford Human Genome Center and Whitehead–MIT Genome Center in the United States; Oxford University, University of Cambridge, and Sanger Centre in the United Kingdom; and Généthon in France. This collaboration will facilitate the candidate-gene approach for mapping disease genes [*HGN* **6**(6), 1–2 (March–April 1995)]. The EST sequencing initiative thus promises to help change the way gene expression is addressed and understood.

Unique Gene Index. A set of high-quality EST sequences and associated clones representing each unique gene is being generated by thoroughly analyzing the 3′ untranslated regions from IMAGE clones. These efforts will eliminate low-quality sequences and generate a confidence assessment of each clone's validity as a unique human gene tag. Merck expects a coordinate release of the Merck Gene Index data set and associated cDNA clones as individual clones, clone sets, and high-density gridded filters. All cDNA clones incorporated into the index will be resequenced to verify their identities. *[Keith Elliston, Merck & Co., keith_elliston@merck.com]* ◊

LLNL Publishes Chromosome 19 Metric Physical Map

Researchers at the Human Genome Center of Lawrence Livermore National Laboratory have completed an integrated metric physical map of human chromosome 19 that spans over 95% of the euchromatin (about 50 Mb).

Appearing in the December 1995 issue of *Nature Genetics* (**11**, 422–27), the map is based on sets of overlapping cosmid clones (contigs); gaps between contigs were filled using various types of larger-insert clones. A "metric" scaffold was generated by using FISH in sperm pronuclei to estimate distances between selected cosmids. This FISH scaffold was integrated with other partial-order data generated by hybridization, STS screening, and restriction mapping using automated map assembly software.

The map, which is depicted in a special 4-page pull-out section, contains 51 "islands" of multiple clone types, with size, order, and relative distance known. Markers include more than 450 genes, polymorphic markers, STSs, and ESTs that are localized on average every 230 kb across the noncentromeric chromosome portion. Complete digest *Eco*R I cosmid restriction maps, also generated across 41 Mb, can be used to create subclone libraries for DNA sequencing. [More map data: *http://www-bio.llnl.gov/bbrp/genome/genome.html*] ◊

MEETING REPORTS

Second Meeting Held on Interconnection of Molecular Biology Databases

The Second Meeting on Interconnection of Molecular Biology Databases (MIMBD-95) was held at Cambridge University on July 20–22, 1995, in conjunction with ISMB-95 (see next page). The workshop was organized by Peter Karp of the SRI International Artificial Intelligence Center, Victor M. Markowitz of Lawrence Berkeley National Laboratory, and Tom Flores of the European Bioinformatics Institute. The premise of this meeting was that the roughly 100 existing molecular biology databases (MBDs) will be of much greater value to molecular biologists when interconnected than in their current isolated states. Scientists will be able to integrate diverse sources of information to answer questions that are laborious or impossible to tackle today.

Research in this area is proceeding along three main lines: interconnecting databases via WWW, the data-warehousing approach, and the distributed-query approach. Central to all three approaches is the concept of creating dfatabase links—recording information about relationships between objects in various MBDs (such as linking a protein sequence in one to the corresponding DNA sequence in another).

The WWW-based approach to interoperation combines WWW access to entries of individual MBDs with electronic links to allow user navigation among entries of related databases. The distributed-query approach allows the expression of complex queries over multiple MBDs and addresses the problems of splitting such queries into component subqueries for individual MBDs and assembling the results. The data-warehousing approach also supports the expression of complex queries over multiple databases. Such queries are simplified by physically integrating multiple MBDs into a centralized data warehouse.

Other topics discussed at the meeting included the automatic inference of links among MBDs, maintenance of link integrity as objects are updated, similarities of notations (data-definition languages) employed for specifying structure (schema), and development of new MBDs.

Two panels were held at the workshop. The first panel discussed the role of standards and componentry in achieving database interoperation and reuse of bioinformatics software. The second panel discussed the current state of systems developed for supporting interoperability, including their architectures, approaches, assumptions, limitations, and costs; and explored future directions. Position papers presented during the second panel were published in *Journal of Computational Biology* 2(4), 1995.

As a result of the growing maturity of MBD interoperability work, next year's MIMBD meeting will be merged into the ISMB-96 meeting in St. Louis. A one-day follow-up MIMBD workshop will also be held in conjunction with ISMB-96 to discuss advances in this area. [MIMBD-95 abstracts: *http://www.ai.sri.com/~pkarp/mimbd.html*] *[Peter D. Karp, SRI International (pkarp@ai.sri.com)]* ◊

Conference Examines Biotechnological Innovation

A conference on Promoting and Managing Genome Innovation was presented at the Franklin Pierce Law Center (FPLC) in Concord, New Hampshire, on October 13–14, 1995. It was organized by Thomas Field (FPLC) and Gianna Julian-Arnold (formerly of Nixon, Hargrave, Devans, and Doyle) and funded in part by the Ethical, Legal, and Social Issues component of the DOE Human Genome Program.

This conference, building upon the July 1993 conference on Maximizing the Return from Genome Research, [*HGN* 5(6), 6 (March 1994)], examined relationships among regulation, risk, reward, and innovation in the field of biotechnology. Presentation topics included societal issues raised through the application of genomic research; the role of intellectual property in promoting research and development; the interaction and effects of rules and regulations relating to pre- and postmarket testing of biotechnological innovations; and the intersection of patent law and U.S. Food and Drug Administration regulation. Case studies furthering these discussions related to vaccine development, bioremediation, and databases of genome sequence information. The full program, listing speakers and their topics, is available on the FPLC Web site (*http://www.fplc.edu/tfield/genPro.htm*).

A future issue of *Risk: Health Safety & Environment* will be devoted to papers from this conference. [Contact: Carol Ruh; *Risk*; Franklin Pierce Law Center; 2 White Street; Concord, NH 03301 (603/228-1541, Fax: /224-3342, *cruh@fplc.edu*)] ◊

☛ *EcoCyc Version 2.7*

The Encyclopedia of *E. coli* Genes and Metabolism (EcoCyc) is a collaboration of Peter D. Karp (SRI International), Monica Riley (Marine Biological Laboratory), and Kenneth Rudd [National Library of Medicine (NLM)]. Its short-term goal is to compile a large knowledge base (KB) of *Escherichia coli* genes and intermediary metabolism to describe each pathway, bioreaction, and enzyme of *E. coli* metabolism, including the enzyme's cofactors, activators, inhibitors, and subunit structure. When known, genes encoding enzyme subunits will be listed with their chromosomal map positions. Version 2.7 contains more data than previous versions and generates metabolic-pathway diagrams, genomic maps, and other graphics through WWW (*http://www.ai.sri.com/ecocyc/browser.html*).

In addition, the KB will characterize every chemical compound involved in each bioreaction and list molecular weight, chemical structure in many cases, and synonyms for the compound name. Some 2956 *E. coli* genes, 397 enzymes, 627 bioreactions in 100 pathways, and 1180 chemical compounds are depicted in EcoCyc, which links to such other databases as GenBank, SWISS-PROT, PDB, Prosite, and Medline. EcoCyc is supported by grants from the NIH National Center for Research Resources and NLM. [Installation instructions, EcoCyc publications, and links to the EcoCyc WWW server (*http://www.ai.sri.com/ecocyc/ecocyc.html*). Contact: Peter Karp, Fax: 415/859-3735, *pkarp@ai.sri.com*] ◊

ISMB-95* Addresses Computational Issues

Some 270 delegates attended the Third International Conference on Intelligent Systems for Molecular Biology (ISMB-95) held in Cambridge, England, on July 16–19, 1995. The conference brought together scientists who are using advanced computational methods to address problems in molecular biology. These methods include data modeling, machine learning, artificial intelligence, cognitive science, robotics, combinatorial and stochastic optimization, adaptive computing, string and graph algorithms, linguistic methods, and parallel computer technologies.

The conference was preceded by 8 introductory and advanced tutorials attended by 187 delegates. The best-attended tutorials were (1) Protein Structure Prediction and (2) Statistical Foundations of Multiple Sequence Alignments and Structure Prediction.

The conference consisted of 8 sessions and 26 oral papers on key bioinformatics issues: protein structure and docking, sequence alignment, protein sequence and structure, understanding sequence function, RNA sequence and structure, genome information systems, gene finding and gene structure, and database searching.

Topics of particular interest included methods for automatically identifying different structural and functional domains within protein structures and the use of advanced statistical methods (e.g., hidden Markov models and stochastic context-free grammars) for identifying complex protein sequence patterns and sequence relationships. Recurring themes were (1) genome-information integration and presentation and (2) methods for rapidly searching DNA and protein sequence and structure databases for related molecules.

Throughout the meeting, two general trends could be discerned: (1) the need to compare new approaches to existing methods, with the associated complexities of selecting appropriate data sets, and (2) the desire to make predictions of biological function that could be validated properly. This raises the general question of how to represent biological function in molecular biology databases. More complete databases of biological processes and pathways that can be linked to sequence and structure data sets are clearly needed.

A new topic was the search for efficient and accurate methods of finding the best fit between macromolecular structures (docking), with both protein-protein and protein-ligand interactions being considered. Several papers and a tutorial covered the challenges of protein structure prediction and the refinements to methods for threading sequences through known protein structures. Applications for machine-learning methods (e.g., neural networks, hidden Markov models, and genetic algorithms) were well represented, and a new approach based on a simulation of the immune system was presented. RNA structure prediction was addressed by several different techniques, including the use of linguistics and graph theory.

Conference proceedings (ISBN 0-929280-83-0), including 26 oral papers and 22 posters featured in the formal poster session, can be obtained directly from AAAI/MIT Press (*info@aaai.org*). Proceedings of ISMB-93 (ISBN 0-929280-47-4) and ISMB-94 (ISBN 0-929280-68-7) are also available from AAAI.

ISMB-96, being organized by David States, will be held June 12–15 at Washington University, St. Louis. [ISMB-96 electronic mailing list: *mail ismb96@ibc.wustl.edu* with the word *subscribe* in the message body. Information: *http://ibc.wustl.edu/ismb96*] *[Chris Rawlings (Chris_Rawlings-1@sbphrd.com) and Evelyn Boyle (Evelyn_Boyle-1@sbphrd.com), SmithKline Beecham]* ◊

*ISMB-95 was supported by the Commission of European Communities Euroconferences program, Medical Research Council, Biotechnology and Biological Science Research Council, Imperial Cancer Research Fund, Glaxo Wellcome, and Oxford Molecular Group in the United Kingdom; and the National Science Foundation, DOE, and NIH in the United States.◊

Automation Conference Held at LBNL

The Third International Conference on Automation in Mapping and Sequencing, held November 3–5, 1995, at Lawrence Berkeley National Laboratory (LBNL), focused on instrumentation and automation issues associated with large-scale genomic research. Although driven by specific needs of genome projects worldwide, these technologies also have broad implications for biotechnology in general because of the large scale of genomic operations for which they are designed.

The capacity audience of 230 represented an international community of specialists from major mapping and sequencing centers, university and government laboratories, and the private sector. In addition to the 78 presentations, 20 manufacturers exhibited leading-edge technology. DOE and NIH managers gave overviews of various genome programs and their expectations for continued automation and instrumentation development.

Researchers reported significant progress in both conventional and new technologies. Several talks described gains in sequencing speed and throughput using capillary electrophoresis and new methods based on revolutionary chip-microfabrication technologies. Representatives from genome research centers described efforts to increase productivity through large-scale system integration; data handling in large-scale applications and expert-system analysis were also addressed.

Although the conference program was tightly scheduled for the 3-day event, social occasions provided time for individual interactions at the welcoming reception, exhibitors' display reception, and conference banquet. The Engineering R&D area displayed technology development and fabrication efforts at LBNL, and human genome laboratory tours showed a wide range of custom-built and custom-adapted equipment in actual use.

Copies of the scientific program and abstracts are available via the Internet (*http://www.lbl.gov/Conferences/AMS/*). The next meeting is scheduled for March 1997 at the European Molecular Biology Laboratory in Heidelberg, Germany. *[Joseph Jaklevic, Lawrence Berkeley National Laboratory, jmjaklevic@lbl.gov]* ◊

MEETING REPORTS

Toward Understanding Genome Function: Workshop in France Focuses on Transcribed Sequences

The Fifth International Workshop on the Identification of Transcribed Sequences was held November 5–8, 1995, on Ile Les Embiez, an island off the coast of France. The meeting was sponsored by the Association Française contre les Myopathies, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Medicale (INSERM), La Région Provence-Côte-d'Azur-Corse, and DOE. More than 50 speakers discussed topics including the generation of regional and chromosomal transcriptional maps, functional analysis of gene expression, techniques for isolating and analyzing genes, the use of model organisms, and informatics.

This year's workshop showed clearly that the robust techniques of cDNA selection, exon trapping, and software trapping of genomic sequences are being applied rigorously and successfully to numerous large regions of the human genome. The great successes of transcriptional mapping have located large numbers of novel genes for which function must now be determined. This new challenge promises to be particularly formidable, perhaps even more difficult than transcriptional mapping has been. However, exciting progress and important ideas in several relevant areas were demonstrated at the workshop. These included methods for determining differential expression and tissue-specific expression of large numbers of genes, use of model organisms— from yeast to mouse—for functional and mutational analysis, and expanded (and generally more accessible) informatics tools.

Selected Presentation Summaries

Transcriptional Mapping. Considerable progress is being made in transcriptional mapping of entire chromosomes and of selected chromosomal regions. Exon trapping, cDNA selection, and genomic sequencing followed by GRAIL analysis remain the most popular approaches, but improvements to these techniques and some alternative approaches were also discussed.

Particularly detailed discussions were presented for chromosomes 19 and 21, where emerging patterns in gene families and overall gene distribution can be related to genome organizational features. Chromosome 19 appears to be very GC rich and gene rich [Anthony Carrano, Lawrence Livermore National Laboratory (LLNL)]. Chromosome 21 shows regional variation in gene density based on the results of exon trapping and cDNA selection (Marie-Laure Yaspo, Max Planck Institute for Molecular Genetics, Germany; Katheleen Gardiner, Eleanor Roosevelt Institute).

Significant numbers of transcribed sequences have also been isolated from chromosome 7 and correlated with physical maps [Stephen Scherer, The Hospital for Sick Children (THSC), Toronto; Eric Green, NIH National Center for Human Genome Research].

An alternative approach to whole-chromosome mapping used reciprocal screening of arrayed cosmid and cDNA libraries (Cheng Chi Lee, Baylor College of Medicine) and yielded close to 100 new genes for each chromosome surveyed (human chromosomes 7 and X).

Results of regional mapping efforts also show variability in gene density based on the number of genes obtained. The Giemsa band 3p12-13 is CpG-island poor and has proved difficult to map transcriptionally [Vasi Sundarasen, Medical Research Council (MRC), Cambridge]. On the other hand, the reverse band 3q21 is GC rich and rather gene rich, although low levels of expression have hampered detailed analysis of cDNAs obtained through cDNA selection (Alla Rynditch, Institute of Molecular Biology and Genetics, Ukraine). Similarly, mapping within chromosome 14q32.1 yielded few genes, but several local clusters of genes were defined within 14q24 (Anne-Francoise Roux, THSC).

Transcriptional mapping efforts on the X chromosome have yielded 15 new genes within Xqcen-q21, including one for Menkes Disease and one for an alpha thalassemia (Michel Fontes, INSERM). Jozef Gecz (Women's and Children's Hospital, North Adelaide, Australia) reported on two genes isolated from Xq28, near FRAXE. They identified one gene in this region and a second, potential gene in a large (>100-kb) exon of the first gene, presumably transcribed in the opposite direction. A combination of exon trapping and cDNA selection has yielded more than 12 genes within another 300-kb region of Xq28 (Nina Heiss, German Cancer Research Center, Heidelberg).

Other Transcriptional Analyses. Gene-specific transcriptional analyses included use of exon trapping and cDNA selection to isolate the gene for motor-endplate disease in mouse (David Kohrman, University of Michigan Medical School). Sample sequencing of nested deletions was used to define gene orientation and repeat content in the HLA C region (B. Rajendra Krishnan, Washington University School of Medicine). Analysis of a cytokine receptor family in 21q22.1 demonstrated complex patterns of alternative processing of some members and gave clues to the evolutionary origin of the 300-kb cluster (Georges Lutfalla, Institut de Génétique Moléculaire, Montpellier, France).

Marcia Budarf (Children's Hospital of Philadelphia) compared sequence-based methods for gene discovery using the rapidly growing EST resources and computational prediction of coding regions using GRAIL. In the intensively studied Di George and velocardiofacial syndrome (DGCR) region of human chromosome 22q11.2, 40% of the 12 previously identified genes were represented in the EST database. GRAIL predicted exons for 75% of the genes known to be in this region. As expected, GRAIL did less well on intron-less genes and small transcripts, whereas EST-based methods were less sensitive for genes with low or restricted modes of expression.

Improvements to Exon Trapping and cDNA Selection. A historic problem with exon trapping has been the limitations imposed by having only a single, usually small, exon as the only product of a given experiment. Esther van de Vosse (Leiden University, Netherlands) discussed new cosmid-based vectors for exon trapping that allow simultaneous trapping of a number of exons. This system should greatly facilitate the

scanning of large genomic DNA regions for the presence of genes.

Anthony Brooks (MRC, Edinburgh) discussed improvements and enhancements to coincident sequence-cloning methods that improve the method's efficiency and reduce background problems. These procedures isolate different products from those obtained by direct cDNA selection, thus providing a useful complementary method.

Expression Patterns. David Beier (Harvard Medical School) discussed ongoing work to map more than 1000 mouse ESTs using single-strand conformational polymorphism. Of more than 600 sequences tested, 89% were polymorphic and thus could be mapped by this method. Mapping these ESTs will help to integrate genetic and physical maps of the mouse genome.

Several groups are exploring procedures for isolating tissue-specific genes and determining broad patterns of differential expression by constructing and screening tissue-specific libraries. Tissues included 10.5-day mouse embryo (Stephen Kingsmore, University of Florida), human heart and testes (Chris Lau, University of California, San Francisco), and fetal kidney (Cecile Jeanpierre, INSERM, Paris). A second approach uses colony screening of arrayed cDNA libraries with RNA from different tissues, cell lines, or induction states. System calibration and sensitivity definition have been carried out (Karine Bernard, CIML, Marseille), and expression data for muscle (Genevieve Peitu, CNRS, Villejuif) and thymus (Dominique Rocha, CIML, Marseille) gene expression have been examined.

Functional Analysis. A new and very useful session on functional analysis of gene expression considered a potpourri of approaches and results. Alexandre Reymond (Massachusetts General Hospital) discussed the use of interaction-mating technologies to make testable "guesses" about the function of unknown proteins and to examine protein-protein interactions.

James Eberwine (University of Pennsylvania Medical School) presented elegant work on the subcellular localization of mRNA in neurons. Different parts of neurons harbor different populations of mRNAs. One interesting observation was that alternatively spliced forms of the same mRNA could be found in the same cell. Synaptic activity was also shown to influence locally the translation of various mRNAs.

Three presentations discussed use of differential display. Shermann Weissman (Yale University School of Medicine) showed data on changes in expression for a large number of transcripts from activated Jurkit cells. Michael McClelland (Sidney Kimmel Cancer Center, La Jolla, California) discussed how changes in the "fingerprint" generated by differential display can be used to monitor changes in expression of a large number of genes following various treatments (with drugs or hormones, for example). J. Gregor Sutcliffe (Scripps Research Institute, La Jolla, California) described a method for uniquely tagging mRNA molecules to allow comparisons of different tissues or of the same tissue or cell line following different treatments.

Particularly important for cDNA library construction and RT-PCR analyses was a presentation by Wai-Choi Leung (Tulane University School of Medicine) on methods for studying the 3-D structure ("architecture") of mRNA molecules. His results showed that "rarity" of transcripts may sometimes be more an artifact of reverse-transcriptase inhibition by secondary mRNA structure than a true reflection of mRNA abundance.

Model Organisms. Understanding human gene function requires the development of surrogate genetic systems in model organisms. Appreciation is growing not only for the power of model organism systems in studying gene function but also for the role of comparative genomics in understanding the broader biological implications of data generated by the Human Genome Project. A number of workshop speakers addressed the role of model organisms in elucidating gene function.

Petra Ross-Macdonald (Yale University) described the generation of yeast strains harboring *lacZ* fusions that can be used to study intercellular localization and pattern of expression. In some cases, these experiments can suggest functions for previously uncharacterized genes and may give clues to the role of uncharacterized human genes with homologs in yeast.

Donna Albertson (University of California, San Francisco) discussed a method for visualizing the pattern of mRNA expression in whole animals. The method uses high-resolution FISH to study the expression pattern of uncharacterized genes in the nematode *Caenorhabditis elegans*. This technique has been applied to 30 predicted genes of unknown function, only 4 of which failed to give a hybridization signal.

Melody Clark (Addenbrookes Hospital, Cambridge, U.K.) reviewed the advantages of using genomic sequencing of the Pufferfish (*Fugu*) for gene identification. Although the *Fugu* genome is about one-eighth the size of the human genome, it is thought to contain essentially the same complement of genes. Therefore, gene density is high in *Fugu*, introns are small, and genes are easier to identify.

Determining gene function, even in such experimentally tractable model organisms as the mouse, is not a trivial undertaking. Miles Brennan (NIH National Institute of Mental Health) described using Cre/lox, the site-specific recombination system of bacteriophage P1, to generate transgenic mice with precisely engineered deletions or duplications. This allows the simultaneous manipulation of ploidy of multiple genes and will be critical for understanding complex multigene disorders. Richard Woychik [Oak Ridge National Laboratory (ORNL)] expanded on the use of engineered deletions in transgenic mice by explaining a strategy for making point mutations in genes made hemizygous by the deletion. Such procedures hold promise for establishing models of various human diseases in mice.

Informatics. Two workshop sessions dealt with informatics and the role of computational science in gene discovery and analysis. Richard Mural (ORNL) discussed new enhancements to the GRAIL system, including improved sensitivity for identifying protein-coding exons from genomic DNA with high A+T content. He also described tools like BatchGRAIL that

Human Genome news

This newsletter is intended to facilitate communication among genome researchers and to inform persons interested in genome research. Suggestions are invited.

Human Genome Management Information System
Oak Ridge National Laboratory
1060 Commerce Park, MS 6480
Oak Ridge,TN 37830
423/576-6669, Fax: /574-9888
http://www.ornl.gov/hgmis

Managing Editor
Betty K. Mansfield *bkq@ornl.gov*

Editors/Writers/Designers
Anne E. Adamson
Denise K. Casey
Judy M. Wyrick

Production Assistants
Murray Browne
Larry W. Davis
Sheryl A. Martin
Marissa D. Mills
Laura N. Yust

MEETING REPORTS

were designed to facilitate the analysis of large numbers of such single-pass sequences as might be generated in a cDNA or cosmid-skimming project. "Software trapping" can be an important method for gene identification when used in a judicious manner. Jean-Michel Claverie (CNRS, Marseille) stressed the importance of filtering out repetitive and other low-entropy sequences before using database-searching methods to identify relationships between sequences.

Philippe Bucher (ISREC, Lausanne) described a new approach that combines both computational and experimental methods to identify sequences bound by regulatory DNA-binding proteins. The approach, which has been applied to several eukaryotic transcription factors, provides a more reliable predictor of protein-binding sites than methods based on conventional multiple alignments. Kerstin Quandt (Institut fuer Saeugetiergenetik, Germany) discussed a new software package that finds correlations within promoter regions and between promoter elements and ORFs. The software XFACtoR provides a graphical user interface, allowing the user to view higher-order structures of promoter regions.

James Fickett (Los Alamos National Laboratory) discussed a method for assigning function to newly identified genes by examining their regulatory context. Preliminary studies have focused on cataloguing the features characteristic of skeletal muscle–specific enhancers and promoters. Being able to determine the time and place of gene expression would be a useful step toward understanding its function. Laurent Duret (Geneva University Hospital) presented data on the importance of 3′ UTRs in the post-transcriptional processing of mRNAs. He indicated that 3′ UTRs are more conserved than 5′ UTRs and that, among vertebrates, 30% of genes have large (100- to 400-bp) parts of their UTRs conserved across 300 million years of evolution. These regions may play a role in translational control and messenger stability.

The Gene Expression Database, a relational database for gene expression during mouse development, was described by Martin Ringwald (Jackson Laboratory). Included in this database will be a 3-D atlas of mouse development being assembled in Edinburgh. Currently, data are being entered into this database from existing literature and by electronic submission. Chris Fields (National Center for Genome Resources, Santa Fe, New Mexico) discussed modifications to the Genome Sequence Data Base schema that will facilitate the inclusion of gene-expression data. This restructuring will allow for direct querying of expression data and provide links to external expression databases.

The Sixth International Workshop on the Identification of Transcribed Sequences is planned for October 3–5, 1996, in Edinburgh, Scotland. *[Richard Mural, Oak Ridge National Laboratory (muralrj@ornl.gov) and Katheleen Gardiner, Eleanor Roosevelt Institute (gardiner@eri.uchsc.edu)]* ◊

A report on the third cDNA/EST mapping workshop that preceded this meeting appears in HUGO's *Genome Digest* [3(1), 11–13 (January 1996)]. Contact: Editorial office (+44-171/935-8085, Fax: -8341)

☛ Quantitative Traits Mapping Program

MIM v1.2 implements the Multipoint IBD method (Goldgar, 1990; Goldgar and Oniki, 1992) for partitioning genetic variance of quantitative traits to specific chromosomal regions using data on nuclear families. More complex pedigrees must be decomposed into groups of nuclear families to enable use of this program. MIM allows multiple analyses from the same input file and has an enhanced error-checking routine and user-friendly file format. The program is written in C for a UNIX workstation but should be readily portable to a wide variety of computer systems. [Program copies: Edward Kort, University of Utah (*edward@episun2.med.utah.ed* or via ftp to *morgan.med.utah.edu* in the directory */pub/mim*)] ◊

Notre Dame Conference Explores ELSI Issues

An international, interdisciplinary conference on Controlling Our Destinies: Historical, Social, Philosophical, and Ethical Perspectives on the Human Genome Project was held at the University of Notre Dame (UND) on October 5–8, 1995. Sponsored by the John J. Reilly Center for Science, Technology, and Values with assistance from DOE, the conference was designed to create a dialogue on specific and general issues as related to the Human Genome Project. Invitations were extended widely to the scientific, clinical, and humanistic communities.

Following an opening address by science writer Horace Freeland Judson [George Washington University (GWU)], Raymond F. Gesteland (University of Utah) reviewed his large-scale sequencing project. Clinical molecular geneticist Thaddeus Dryja (Harvard Medical School) followed with a specific examination of the genetics of retinoblastoma, with discussion points raised by geneticist David Hyde (UND).

Later sessions dealt with historical issues [John Beatty (University of Minnesota); Lily Kay (Massachusetts Institute of Technology (MIT)); Evelyn Fox Keller (MIT)] with commentaries by Hans-Joerg Rheinberger (University of Salzburg, Austria), Jean Gayon (Université de Bourgogne, France), and Timothy Lenoir (Stanford University). Vigorous floor discussions concerned the notions of "code" and the language and metaphors used in the Human Genome Project. Beatty presented a historical perspective as it related to DOE's atomic energy work and the national laboratories. The interaction of humanistic and clinical concerns was explored in papers by John M. Opitz (Shodair Children's Hospital, Helena, Montana) and Harvey Bender (UND), with commentary by Jessica Davis (Cornell Medical Center). Opitz raised concerns about the growing "geneticization" of society, in which human beings increasingly are being seen as "readouts" of their genes. This theme recurred in later sessions.

Topics related to the sociology and anthropology of knowledge were addressed in papers by Stephen Hilgartner (Cornell University) and French sociologist and science anthropologist Jean-Paul Gaudillière (Institut National de la Santé et de la Recherche Medicale, Paris), with commentaries by Michael Fortun (Hampshire College) and Robert Bud (Science Museum, London). These papers generated discussions concerning the sociology of intercommunicating networks within human genomics and clinical decision-making as seen from a French perspective.

Other sessions offered insights into issues of reductionism, concern about new forms of eugenics, and science-religion questions. Main papers were presented by Kenneth Schaffner (GWU), Arthur Caplan (University of Pennsylvania), Philip Kitcher (University of California, San Diego), Arthur Peacocke (University of Oxford, England), and Kevin Fitzgerald (Georgetown University).

Commentaries were made by Edward Manier (UND), Timothy Murphy (University of Illinois College of Medicine), Diane Paul (University of Massachusetts, Boston), J. Robert Nelson (Texas Medical Center), Ernan McMullin (UND), and John Staudenmaier (University of Detroit).

Caplan's concern with a new form of "homemade eugenics" that might result from the genome project and Kitcher's development of distributive-justice issues surrounding the project's future sparked an active discussion about social applications of genetic knowledge.

Five parallel contributed-paper sessions were organized around the philosophy of science, medical ethics, distributive justice and the genome project, and the use of metaphor and imagery in human genetics.

An address by UND President Emeritus Theodore M. Hesburgh was followed by the showing of a short DOE-sponsored interactive teaching program. A final round-table of the participants and a commentary by UND medical ethicist Richard McCormick closed the conference.

Edited conference papers will be issued by UND Press in the series *Contributions from the Reilly Center in Science, Technology, and Values*. Publication is expected in late 1996. *[Phillip R. Sloan, University of Notre Dame, phillip.r.sloan.1@nd.edu]* ◊

¶ Nomenclature Recommendations Update

ISCN 1995: An International System for Human Cytogenetic Nomenclature, edited by Felix Mitelman (University of Lund, Sweden), was finalized in October 1994 and published in 1995. The report combines and extends the system of human cytogenetic nomenclature prepared by expert committees and published since 1963 in or with *Cytogenetics and Cell Genetics*. All previous human cytogenetic nomenclature recommendations are updated, corrected, and combined into one systematically organized publication. A foldout composite is included of the normal human karyotype, consisting of photographs of G-banded and R-banded chromosomes at the commonly examined 550-band resolution stage; foldouts are also sold separately in sets of 5. Soft cover, 114 pp. [S. Karger Publishers; Farmington, CT (800/828-5479 or 860/675-7834, Fax: -7302)] ◊

HUGO Pacific Newsletter

HUGO Pacific Genome Newsletter recently began publication in Tokyo. Written in English, this Human Genome Organisation newsletter aims to foster communication and cooperation among Pacific area genome scientists and to familiarize others with Human Genome Project activities in the Far East. HUGO also sponsors *Genome Digest*, which is published in the United Kingdom. [HUGO Pacific Office; Human Genome Center; Institute of Medical Science; Tokyo 108, Japan (+81-3/5449-5623, Fax: -5445, *shobu@ims.u-tokyo.ac.jp*)] ◊

RESOURCES

HuGEM Educational Videos

A set of five videos on the Human Genome Project and its ethical, legal, and social implications (ELSI) is now available. In personal interviews and panel discussions, such ELSI topics as insurance and employment discrimination, genetic testing of children, and the impact of diagnoses on family lifestyles and relationships are explored by people who have experienced the issues firsthand. Scientific information is provided by Francis Collins, Director of the NIH National Center for Human Genome Research (NCHGR).

The videos are produced by HuGEM, now in its third year as a collaborative education model for consumers of genetic services and health professionals who work in university-affiliated programs across the country. A project of Georgetown University Child Development Center and the Alliance of Genetic Support Groups, HuGEM is supported by NCHGR.

Running times are between 19 and 45 min, and videos can be purchased individually or as a set. Individual videos, $15; set, $50.[HuGEM Project; Georgetown University; Child Development Center; 3307 M Street NW, Suite 401; Washington, DC 20007-3935 (202/687-8635, Fax: -8899)] ◊

Discovery Channel School

Discovery Channel School (*http://www.discovery.com/school/*), an innovative educational service for K–12 teachers, debuted online on March 4. The site describes more than 50 hours of documentary programs on the Discovery and Learning channels and includes video previews of all 35 episodes of *Assignment Discovery*, the commercial-free series designed for teachers to tape and use in grades 6–12 classrooms. Experienced educators known as Subject Area Managers provide peer support by suggesting related activities, insights, and Internet links. The DOE Human Genome Program Web site (*http://www.er.doe.gov/production/oher/hug_top.html/*) was listed as a link for *Next Step: Future Technologies* (Part 1), which will air again on May 20 from 9:00 to 9:30 a.m.◊

MUTATION Prototype Newsgroup

The MUTATION prototype newsgroup was established to enhance the rate of transfer of mutation technology and Human Genome Project findings to clinical and research problems. Mutation in any organism, environmental mutagenesis, and mutation mechanisms are discussed, including new mutation-detection technologies, databases, and problems. To subscribe, e-mail to *biosci-server@net.bio.net*; leave the subject line blank and enter *subscribe mutation* in the message body. For help: *biosci-help@net.bio.net*; to post and reply to messages: *mutation@net.bio.net*. ◊

Newsletter for Genetic Counselors

The National Society of Genetic Counselors (NSGC) has published *Perspectives in Genetic Counseling* for 17 years. The quarterly newsletter features articles on counseling issues, news from the NSGC board and committees, resource reviews, announcements, a bulletin board and student corner, letters to the editor, a calendar of professional meetings, and employment opportunities for genetic counselors and students. [Nonmembers, $25 annually. Send check payable to NSGC to Bea Leopold; 233 Canterbury Dr.; Wallingford, PA 19086 (610/872-7608, Fax: -1192, *beansgc@aol.com*)] ◊

Gene-Server Additions

The University of Houston Gene-Server recently added a series of servers for *Drosophila*, *Arabidopsis*, and nematode gene identification and analysis. They are, respectively:

- **dspl**, **aspl**, and **nspl** (splice-site prediction for genes);
- **fexd**, **fexa**, and **fexn** (exon finding in genes); and
- **fgened**, **fgenea**, and **fgenen** (gene modeling).

Help files: *service@bchs.uh.edu;* send *man servicename* in the subject line (e.g., Subject: *man fexn*). [Information on Gene-Server: *HGN* 7(1), 12 (May–June 1995) and *http://dot.imgen.bcm.tmc.edu:9331/gene-finder/gf.html*] ◊

WHO Guidelines on Ethical Issues

Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetics Services was published in 1995 by the Hereditary Diseases Programme of the World Health Organization (WHO). Written by Dorothy Wertz (Shriver Center), John Fletcher (University of Virginia), Kåre Berg (University of Oslo), and Victor Boulyjenkov (WHO, Geneva), the book suggests basic guidelines for providing medical services related to genetics. The authors consider ethical issues associated with modern medical genetics and seek to demonstrate how these issues could be addressed. Includes international bibliography on ethics and legislation. Free of charge. 117 pages, paper. [Contact: V. Boulyjenkov, Fax: +44-22/791-0746] ◊

RHMAP and SIMLINK

RHMAP and SIMLINK, two software programs for genetic analysis, are distributed via WWW (*http://www.sph.umich.edu/group/statgen/software*). RHMAP is used for statistical analysis of radiation hybrid mapping data, and SIMLINK is used to evaluate the statistical power of a proposed linkage study. Both are written in FORTRAN 77 and previously were distributed free on floppy diskettes only. [Contact for software and updates: Michael Boehnke, University of Michigan (313/936-1001, Fax: /763-2215, *boehnke@umich.edu*)] ◊

Mycobacterium Database Release

The latest release of the *Mycobacterium* database MycDB is accessible through the following addresses:

- *http://www.biochem.kth.se/MycDB.html*
- *http://probe.nalusda.gov:8300/other/index.html*
- *gopher://probe.nalusda.gov:7000/11/genome.databases/mycdb/*

[Contact: Staffan Bergh; Royal Institute of Technology; Stockholm, Sweden (+46-8/790-9230, Fax: /245-452, *staffan@biochem.kth.se*) or Stewart Cole; Institut Pasteur; Cedex, France (+33-1/4568-8446, Fax: -8593, *stcole@pasteur.fr*)] ◊

GDB Forum

Genome Database 6.0: An Experiment in Community Curation

Faced with the challenge of storing and distributing the burgeoning mapping data of the Human Genome Project, the Genome Database made a serious assessment of its role as manager and curator. Some shortcomings recognized by the genome community included the need to graphically display maps based on the data, create a more representational data model, and increase GDB's ability to accumulate and curate mapping data within a reasonable time. Clearly, GDB's curatorial staff could not grow sufficiently to accommodate the last requirement, so focus shifted to developing a new curatorial model that allowed more community interaction. In addition, a major redesign of GDB was accomplished with new technologies to replace the underlying schema. The result was GDB 6.0.

The development of GDB 6.0 called for a new schema based on the Object Protocol Model (OPM) tools of Victor Markowitz's group at Lawrence Berkeley National Laboratory. OPM defines more explicitly the relationships between GDB object classes and their attributes (such as genomic segments and genes) and between pairs of classes. Most important, the new schema is easier for GDB users to understand and query.

Data in GDB 6.0 are now divided into a family of interrelated data sets consisting of the biological data (the mapping data component), the citation database (literature citations), and the registry (information on people and organizations). This separation of information can be viewed as a pilot effort toward federating genomic databases across the Internet. GDB 6.0's use of an extensible object broker furthers this effort by addressing the problem of incompatible architectures among genomic databases and by managing communication among frequently changing schemas, database technologies, and user interfaces.

With the priority to improve data representation of genetic and physical maps and to visualize and query graphical maps, GDB staff developed a model to represent regions of the genome in multiple resolutions; produce maps based on experimental data; and provide for more sophisticated querying on position, order, and distance. "Mapview" works across platforms with a Web external viewer that is integrated with Netscape and provides the capability to query further on objects contained in the map. Several enhancements were built into the user interface, such as the ability to browse all maps in the database and download preextracted versions in compressed formats for viewing later. GDB 6.0 included linkage and cytogenetic maps in its initial release, and other maps are being added as quickly as possible.

GDB Access Via WWW

The GDB Web server is available directly at the following URLs:

- **United States** *http://gdbwww.gdb.org/*
- **Australia** *http://morgan.angis.su.oz.au/gdb/docs/gdbhome.html*
- **France** *http://www.infobiogen.fr/gdbwww/*
- **Germany** *http://gdbwww.dkfz-heidelberg.de/*
- **Israel** *http://inherit1.weizmann.ac.il/gdb/docs/gdbhome.html*
- **Japan** *http://gdb.gdbnet.ad.jp/gdb/docs/gdbhome.html*
- **Netherlands** *http://www-gdb.caos.kun.nl/gdb/docs/gdbhome.html*
- **Sweden** *http://gdb.embnet.se:443/gdb/docs/gdbhome.html*
- **United Kingdom** *http://www.hgmp.mrc.ac.uk/gdb/docs/gdbhome.html*

GDB User Support Offices

UNITED STATES
Baltimore, Maryland
help@gdb.org

AUSTRALIA
Sydney
bucholtz@angis.su.oz.au

FRANCE
Villejuif
gdb@infobiogen.fr

GERMANY
Heidelberg
gdb@dkfz-heidelberg.de

ISRAEL
Rehovot
lsprilus@weizmann.weizmann.ac.il

JAPAN
Tokyo
mika@gdb.gdbnet.ad.jp

NETHERLANDS
Nijmegen
post@caos.caos.kun.nl

SWEDEN
Uppsala
help@gdb.embnet.se

UNITED KINGDOM
Cambridge
admin@hgmp.mrc.ac.uk

The GDB 5.6 browser was replaced by another Web interface based on an application called Genera, developed by Stan Letovsky at GDB. With a modified Genera, query and edit forms are generated automatically from the GDB 6.0 schema. This allows users to move easily among query, update, and insert operations. Although GDB 6.0 was released as read-only in January, editing capabilities are anticipated shortly. Editing capabilities were delayed to ensure complete and accurate migration of the data.◊

What Does GDB 6.0 Mean for the Genome Community?

GDB 6.0 represents a fundamental change in the way users navigate the data. Data representation has been improved by the graphical display of various mapping methodologies, the ability to make more complex queries, and timely data accessibility for the community as a whole. Genome Database views this undertaking as a step toward providing another tool for the genome community, one that will allow greater access not only to the data contained within GDB but to information stored throughout the world in related databases. GDB hopes Version 6.0 will promote increased community participation in support of the Human Genome Project.

Chipperfield Leaves GDB

Michael A. Chipperfield has resigned his post as acting director of data acquisition and curation at Genome Database, effective March 1. He has accepted a position as database consultant with Sybase Corporation.

Chipperfield was one of the original members of the GDB staff, having moved to Johns Hopkins from Yale University in 1990 when GDB was established in Baltimore. He was assistant director until assuming the position of acting director in September 1995. An asset to the GDB mission, Chipperfield is well known and respected among editors of the Human Genome Organisation chromosome committees and other members of the genome community.◊

☛ Coriell Cell Repositories Seeking, Distributing Material

The National Institute on Aging Cell Repository. Blood or biopsy material is requested from well-documented patients with diseases related to aging to establish cell cultures for distribution to the scientific community.

The National Institute of General Medical Sciences' Human Genetic Mutant Cell Repository. Cell cultures and DNA are being distributed for the following:

- Regional mapping panels, consisting of 5 to 10 human-rodent somatic cell hybrids with deletion or derivative human chromosomes, for chromosomes 3, 4, 5, 11, 15, 17, and 18.
- Standards for comparative genome hybridization containing from 1 to 5 X chromosomes: 45, X; 46, XX; 47, XXX; 48, XXXX; and 49, XXXXX. An additional one, 49, XYYYY, is also available.
- Patients with characterized *BRCA1* gene mutations (including missense, nonsense, and frameshift mutations) and other familial breast cancer patients.

[Contact: Coriell Cell Repositories (800/752-3805 or 609/757-4848, Fax: -9737, *http://arginine.umdnj.edu/ccr/ccr.html*)] ◊

ELSI Working Group Responds to *The Bell Curve*

This statement was developed by the NIH-DOE Joint Working Group on the Ethical, Legal, and Social Implications of Human Genome Research (ELSI Working Group). Portions of this statement, which was endorsed by the National Society of Genetic Counselors, have appeared in Science *and other publications. [Questions or information about the statement: Dorothy Nelkin (212/998-8347); other correspondence: Jean McKay (301/402-0955, Fax: -0837)]*

In 1994, a highly publicized book, Richard Herrnstein and Charles Murray's *The Bell Curve*, claimed that IQ is largely genetically determined and that the differences in IQ between ethnic groups are substantially explained by genetic factors. We are especially concerned about the impact of *The Bell Curve* and books developing similar themes, because we believe that the legitimate successes of the Human Genome Project in identifying genes associated with human diseases should not be used to foster an environment in which mistaken claims for genetic determination of other human traits gain undeserved credibility.

Herrnstein and Murray suggest that IQ explains social problems such as crime, welfare dependence, and single parenting. They state that socio-cultural barriers to personal advancement have largely been removed and, consequently, social success and high IQ are highly correlated. They assert that, to the extent that IQ is genetically determined, programs to eliminate inequalities are thus doomed to failure. Herrnstein and Murray are especially concerned that high birth rates among the poor and the "dysgenic" behavior of women with high IQs, who are not bearing enough children, are threatening the population with genetic decline. According to them, these trends are "exerting downward pressure on the distribution of cognitive ability in the United States."

The authors follow this analysis with policy recommendations. They propose eliminating welfare, which they believe subsidizes births among poor women, thus lowering the average intelligence of the population. They suggest ending remedial education programs because the results are not worth the cost, given the claimed significant genetic determination of IQ differences. They urge the development of programs of social support that would encourage women from the higher socio-economic classes to have more children.

Neither Herrnstein nor Murray is a geneticist nor have they carried out studies themselves on the genetic basis of behavior. Their lack of training and experience in genetics does not disqualify them from evaluating genetic research nor from drawing their own conclusions. However, as geneticists and ethicists associated with the Human Genome Project, we deplore *The Bell Curve*'s misrepresentation of the state of genetic knowledge in this area and the misuse of genetics to inform social policy.

We urge consideration of the following three points:

First, Herrnstein and Murray invoke the authority of genetics to argue that "it is beyond significant technical dispute that cognitive ability is substantially heritable." Research in this field is still evolving, studies cited by Herrnstein and Murray face significant methodological difficulties, and the validity of results quoted is disputed. Many geneticists have pointed out the enormous scientific and methodological problems in attempting to separate genetic components from environmental contributors, particularly given the intricate interplay between genes and the environment that may affect such a complex human trait as intelligence.

Second, even if there was consensus on the heritability of cognitive ability, lessons from genetics are misrepresented. The authors argue that because cognitive ability is substantially heritable, it is not possible to change it and the remedial education is not worth the effort or cost. This is neither an accurate message from genetics nor a necessary lesson from efforts at remedial education. Heritability estimates are relevant only for the specific environment in which they are measured. Change the environment and the heritability of traits can change remarkably. Saying a trait has high heritability has never implied that the trait is fated to be. Height is both genetically determined and dependent on nutrition. Common conditions in which genetics play a role, such as diabetes or heart disease, can be corrected with insulin or cholesterol-lowering drugs and diet. The disabilities associated with single-gene conditions, such as phenylketonuria or Wilson disease, can also be prevented or significantly ameliorated by medical or nutritional therapy.

Third, the more scientists learn about human genes the more complexity is revealed. This complexity has become apparent as more genes correlated with human genetic diseases are discovered. We are only beginning to explore the intricate relationship between genes and environment and between individual genes and the rest of the human genome. If anything, the lack of predictability from genetic information has become the rule rather than the exception. Simplistic claims about the inheritance of such a complex trait as cognitive ability are unjustifiable; moreover, as the history of eugenics shows, they are dangerous.

Genetic arguments cannot and should not be used to determine or inform social policy in the areas cited by Herrnstein and Murray. Since the lessons of genetics are not deterministic, they do not provide useful information on deciding whether or not to pursue various programs to enhance the capabilities of different members of society. Those decisions are moral, social, and political ones.◊

URLs for Web

As a service to our readers, from time to time *HGN* will list pertinent uniform resource locators (URLs) for molecular biology and biology resources accessible through WWW.

Bioinformatics and Computational Biology

BioSCAN for rapid search and analysis of biological sequences: *http://genome.cs.unc.edu/project.html*

Sequence alignment and modeling system: *http://www.cse.ucsc.edu/research/compbio/sam.html*

Heterogeneous Database Management Systems: *http://gizmo.lbl.gov/HDBMS/HDBMS.html*

NIH Molecular Modeling (3-D structure and physiochemical properties): *http://molbio.info.nih.gov/modeling/*

Biotechnology and Molecular Biology

Bio-wURLd collection of links: *http://www.ebi.ac.uk/htbin/bwurld.pl/*

BME*net* biomedical engineering: *http://bme.www.ecn.purdue.edu/bme* or *gopher://fairway.ecn.purdue.edu/*

Biotechnology Section, WWW Virtual Library: *http://www.webpress.net/interweb/cato/biotech/*

Biotechnology Information Center, USDA National Agricultural Library: *http://www.inform.umd.edu:8080/EdRes/Topic/AgrEnv/Biotech/*

Molecular biologists' Internet introduction, links: *http://www.ifrn.bbsrc.ac.uk/gm/lab/docs/iftmb.html*

***Journal of Molecular Biology*:** *http://www.hbuk.co.uk/jmb/*

***Nature* magazine:** *http://www.nature.com/*

***Science* magazine:** *http://www.aaas.org/science/*

Ethics and Education

Biotechnology law, pharmaceutical and biotechnology clientele: *http://biotechlaw.ari.net/*

Ethics and Genetics, A Global Conversation: *http://www.med.upenn.edu/~bioethic/genetics.html*

Eubios Ethics Institute: *http://www.biol.tsukuba.ac.jp/~macer/index.html*

Genetics educational sourcebook: *http://www.netspace.org/MendelWeb/*

Genscope software project for biology teachers: *http://copernicus.bbn.com/genscope/home.html*

Rural Advancement Foundation International (RAFI): *http://www.charm.net/~rafi/rafihome.html*

International

Biotechnology research projects in Europe: *http://www.library.knaw.nl/cgi-bin/biorep_search.pl/*

Chromosome editors (HUGO): *http://gdbwww.gdb.org/gdb5.6/docs/editors.html*

European Molecular Biology Laboratory: *http://www.embl-heidelberg.de/*

European Molecular Biology Network newsletter (*embnet.news*): *http://www.be.embnet.org/embnet.news/*

Japanese Human Genome Project: *http://www.genome.ad.jp/*

Model Organisms

***Arabidopsis* cDNA Sequencing Analysis Project:** *http://lenti.med.umn.edu/*

Dog Genome Project: *http://mendel.berkeley.edu/dog.html*

Non-Redundant *Bacillus subtilis* (NRSub) database: *http://acnuc.univ-lyon1.fr/nrsub/nrsub.html* or *http://ddbjs4h.genes.nig.ac.jp/*

Rat strain information, lab code names: *http://www.anex.med.tokushima-u.ac.jp/index.html*

Nucleotide Sequences

IMGT nucleotide sequence information for immune system genes: *http://www.ebi.ac.uk/contrib/imgt*

Molecular Probe Data Base of synthetic oligonucleotides: *http://www.ist.unige.it/interlab/mpdb.html*

Proteins

Cambridge Crystallographic Data Center: *http://csdvx2.ccdc.cam.ac.uk/*

Coiled-coil region prediction in amino acid sequences: *http://theory.lcs.mit.edu/~bab/paircoil.html*

Department of Crystallography, Birkbeck College, London: *http://www.cryst.bbk.ac.uk/*

Kabat protein sequence database: *http://immuno.bme.nwu.edu/*

NAOMI 3-D protein-structure program: *http://www.ocms.ox.ac.uk/~smb/Software/N_details/naomi.html*

Protein Data Bank: *http://www.pdb.bnl.gov/*

***Protein Science* magazine:** *http://www.prosci.uci.edu/*

Secondary structure assignment database (DSSP), program: *http://www.sander.embl-heidelberg.de/dssp/*

Protein structural classification: *http://www.prosci.uci.edu/scop/*

Protein scientists' WWW resources: *http://www.prosci.uci.edu/ProSciDocs/WWWResources.html*

MGD Release 3.1 Enhancements

Release 3.1 of the Mouse Genome Database (MGD) (*http://www.informatics.jax.org*) offers the following enhancements:

- Access to the new Gene Expression Database (GXD) Index, a collection of references indexed by gene-expression-data content.
- Chromosome Committee 1995 reports in hypertext format for enhanced readability and in original format for downloading via ftp.
- Mammalian Homology information in "Oxford Grid" format, which provides an overview of homology between two selected species.
- Linkage map tool for generating mouse chromosome map displays with options to view homologies, specify a chromosomal region, or add markers to a map. Retrieved maps can be displayed using the *Encyclopedia of the Mouse Genome* application or formatted as PostScript files for printing.

[User Support: 207/288-6445, *mgi-help@informatics.jax.org*] ◊

This newsletter is prepared at the request of the DOE Office of Health and Environmental Research and the NIH National Center for Human Genome Research by the Biomedical and Environmental Information Analysis Section of the Health Sciences Research Division at Oak Ridge National Laboratory, which is managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy, under Contract DE-AC05-96OR22464.◊

Calendar of Genome Events*

April 1996

17–19. 4th Intl. Nature Genetics Conf.: Genetic Susceptibility and Complex Traits; Vancouver, Canada [D. Berger, 212/726-9281, Fax: /696-9594, *conference@natureny.com*]

18. Richard A. Mathies: Developing New Tools for the Genetic Revolution; Bethesda, MD [NCHGR Lect. Series, E. Feingold, 301/496-7531, Fax: /480-2770, *fey@cu.nih.gov*]

21–27. DNA Forensics: Science, Practice, and Future; Santa Fe, NM [Cambridge Symposia, 617/630-1399, Fax: -1395, *symposia@cambridge.org, http://www.cambridge.org/symposia/*]

27–May 1. 37th Annual *Drosophila* Res. Conf.; San Diego [S. Bernstein, 619/594-5629, Fax: -5676, *sbernst@sunstroke.sdsu.edu, http://morgan.harvard.edu/dros-conf.html*]

29–30. Advances in Nucleic Acid-Based Technologies: Emerging Technologies, Enabling Techniques, and Clinical Utility; Amsterdam [CHI, 617/630-1300, Fax: -1325, *chi@healthtech.com, http://www.healthtech.com/conferences*]

29–30. Task Force on Genetic Testing; Baltimore [J. Brown, 410/955-7894, Fax: -0241, *jbrown@welchlink.welch.jhu.edu*]

May 1996

2–3. ELSI Working Group; Washington, DC [W. Seawright, 301/402-0955, Fax: -0837]

2–3. Diagnostic Gene Detection Technology for Infectious Agents and Human Genetic Diseases; Coronado, CA [IBC, 508/481-6400, Fax: -7911, *inq@ibcusa.com*]

3–6. Biomedicine '96; MMS/AAP/AFCR/ASCI, Washington, DC [M. Stallings, 609/848-1000 ext. 264, Fax: -5274, *mstallings@slackinc.com*]

6–7. Gene Vector Development; IBC, Coronado, CA [see contact: May 2–3]

6–8. Chromosome 21 Workshop; Cold Spring Harbor, NY [J. Korenberg, 310/855-7627, Fax: /652-8010, *jkorenberg@mailgate.csmc.edu*]

8–12. 1996 Genome Mapping and Sequencing Meeting; CSHL, Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845, *meetings@cshl.org, http://www.cshl.org*]

9–12. Conference on Gene Therapy; TIGR, Hilton Head, SC [C. Sadler, 301/838-3509, Fax: -0229, *therapy@tigr.org*]

11. 1996 Eastern Great Lakes Molecular Evolution Conference; Ithaca, NY [C. Aquadro, 607/254-4838, or -4840, Fax: /255-6249, *cfa1@cornell.edu*]

12–16. Chromosome 11 Workshop; Buffalo [T. Shows, 716/845-3108, Fax: -8449, *tbs@shows.med.buffalo.edu*]

16. David Burke: Microfabricated Structures for Integrated DNA Analysis; NCHGR, Bethesda, MD [see contact: April 18]

16–19. **Women and Genetics in Contemporary Society; Zanesville, OH [H. Holmes, 413/549-1925, Fax: -1226, *fholmes@pltpath.umass.edu*]

20–21. NIH Natl. Advisory Council for Human Genome Res.; Washington, DC [J. Ades, 301/402-2205, Fax: -2218, *ja51b@nih.gov*]

23. Melvin Simon; TIGR/NIST, Rockville, MD [TIGR/NIST Distinguished Speakers Series, D. Hawkins, 301/838-3501, Fax: -0209, *dhawkins@tigr.org, http://www.tigr.org*]

June 1996

1–4. 4th Canadian Plant Tissue Culture and Genetic Engineering Conf.; Saskatoon, Canada [R. Gallays, 306/975-5571, Fax: -4839, *rgallays@pbi.nrc.ca*]

2–6. ASBMB/AAI/ASIP; New Orleans [FASEB, 301/530-7010, Fax: -7014]

2–6. **First Intl. Congress on Extremophiles; Estoril, Portugal [G. Antranikian, +49-40/7718-3117, Fax: -2909, *Antranikian@tu-harburg.d400.de*]

2–7. 10th Intl. Workshop on Molecular Genetics of the Mouse; Spa, Belgium [A. Goffinet, +32-81/724-277, Fax: -280, *agoffinet@cc.fundp.ac.be*]

6–7. Intellectual Property Issues: Critical Challenges for Biomedicine and Genomics; CHI, Philadelphia [see contact: April 29–30]

9–12. Genomic Information: Ethical Implications; Seattle [M. Barnard, 206/616-1864, Fax: /685-7515, *mbarnard@u.washington.edu*]

9–13. BIO '96 Intl. Biotechnol. Meeting and Exhibition; Philadelphia [BIO, 202/857-0244, Fax: -0237]

9–14. Frontiers of Sci.: Nucleic Acids; New Hampton, NH [GRC, 401/783-4011, Fax: -7644, *grc@grcmail.grc.uri.edu*]

10–11. Fifth Intl. Bioinformatics and Genome Res. Conf.; CHI, Baltimore [see contact: April 29–30]

12–14. Chromosome 17 Workshop; Israel [D. Lancet, +972/834-3683, Fax: -4112, *bmlancet@weizmann.weizmann.ac.il*]

12–15. 4th Intl. Conf. on Computational Biol.: Intelligent Systems for Molecular Biol. '96; St. Louis [D. States, 314/362-2135, Fax: -0234, *states@ibc.wustl.edu, http://ibc.wustl.edu/ismb96*]

13–14. Molecular Genetic Profiling; CHI, Washington, DC [see contact: April 29–30]

14–15. Chromosome 19 Workshop; Glasgow, Scotland [H. Mohrenweiser, Fax: 510/422-2282, *harvey@cea.llnl.gov*]

14–17. 5th Nordic Genome Workshop; Laugavatn, Iceland [S. Ingvarsson, +354/5601-906, Fax: -943, *siguring@rsp.is*]

22–27. 1996 World Congress on In Vitro Biology. Biotechnology: From Fundamental Concepts to Reality; San Francisco [T. McMillan, 410/992-0946, Fax:-0949]

July 1996

8–12. Scientific, Legal, and Ethical Aspects of the Human Genome Project; Medford, MA (for high school biology teachers) [R. Yashon, 617/625-6165, Fax: /627-3995, *ryashon@pearl.tufts.edu*]

14–19. 8th Intl. Congress on Molecular Plant-Microbe Interactions; Knoxville, TN [UT Conferences, 423/974-0280, Fax:-0264]

14–20. **Crete 10th Anniversary Meeting: Molecular and Developmental Biology of *Drosophila*; Crete, Greece [S. Artavanis-Tsakonas, 203/737-4462, Fax: -2629, *http://morgan.harvard.edu/crete10.html*]

28–Aug. 2. Molecular Genetics; GRC, Newport, RI [see contact: June 9–14]

August 1996

4–6. Mathematical Analysis of Biological Sequences; Trondheim, Norway [K. Flornes, +47-73/593-520, Fax: -524, *flornes@imf.unit.no, http://www.imf.unit.no/conferences/mabs/*]

6–11. Yeast Genetics and Molecular Biology Meeting; Madison, WI [F. Winston, 617/432-7618, Fax: -7663, *winston@rascal.med.harvard.edu*]

14–18. Cancer Genetics and Tumor Supressor Genes; CSHL, Cold Spring Harbor, NY [see contact: May 8–12]

16–18. 9th Intl. Congress of Human Genetics; Rio de Janeiro [H. Krieger, +55-11/818-7328, Fax: -7417, *9ichg@biomed.icb2.usp.br*]

17–18. 5th Annu. Meeting of Intl. Genetic Epidemiology Society; Rio de Janeiro [R. Ottman, 212/305-9188, Fax: -2426, *ottmanr@sergievsky.cpmc.columbia.edu*]

18–23. Intl. Conf. on Luminescence and Optical Spectroscopy of Condensed Matter; Prague [J. Hala, +42-2/21911-421, Fax:-249, *halaicl@karlov.mff.cuni.cz, http://kchf-45.karlov.mff.cuni.cz/html/icl.htm*]

19–22. Intl. Symp. On Drug Discovery Technology; IBC, Boston [see contact: May 2–3]

28–Sept. 1. Mouse Molecular Genetics; CSHL, Cold Spring Harbor, NY [see contact: May 8–12]

September 1996

6–8. 1st Intl. Conf. on DNA Sampling: Human Genetic Research: Ethical, Legal, and Policy Aspects; Montreal [S. Elibyari, 514/343-2142, Fax: -7508, *genet@crdp.droit.umontreal.ca*]

6–8. Chromosome 9 Workshop; Oxford, U.K. [M. Povey, +44-171/387-7050, ext. 5043, Fax: -3496, *sue@galton.ucl.ac.uk*]

8–12. 4th *E. coli* and Small Genomes Meeting; Lake Arrowhead, CA [J.H. Miller, 310/825-8460, Fax: /206-3088, *jhmiller@ewald.mbi.ucla.edu*]

October 1996

3–5. 6th Intl. Workshop on Identification of Transcribed Sequences; Edinburgh [A. Brooks, *tony@alpha.medgen.uu.se* or K. Gardiner, *gardiner@eri.uchsc.edu*]

5–8. 8th Intl. Genome Sequencing and Analysis Conf.; TIGR, Hilton Head, SC [C. Sadler, 301/838-3509, Fax: -0229, *seqconf@tigr.org*]

6–8. Chromosome 18 Workshop; Boston [G. Silverman, 617/355-6416, Fax: -7677, *silverman_g@a1.tch.harvard.edu*]

18–20. Structural Function of Telomeres and Centromeres; Oxford, U.K. [N. Spurr, Fax: +44-171/269-3802, *spurr@icrf.icnet.uk*]

26–28. Chromosome 8 Workshop; San Antonio, TX [R. Leach, 210/567-6947, Fax: -6781, *leach@uthscsa.edu*]

26–29. NSGC 15th Annu. Educ. Conf.; San Francisco [B. Leopold, 610/872-7608, Fax: -1192, *beansgc@aol.com*]

29–Nov. 2. ASHG; San Francisco [M. Ryan, 301/571-1825, Fax: /530-7079]

November 1996

7–8. Natl. Conf. on Preparing Schools for the Genetic Revolution; Lincoln, NE [G. Wright, 402/472-8881, Fax: -8412, *gwright@unl.edu, http://nncf.unl.edu/conf/call.html*]◊

*Dates and meeting status may change; courses may also be offered at other times and places; check with contact person.
**Attendance is either limited or restricted.

For Your Information

Training Calendar*

May 1996

3–5. 1996 Review Course in Med. Genetics and Genet. Counseling; NSGC, Pittsburgh [A. Lombard, 610/872-7608, #8, Fax: -1192]

3–5. Supercomputing Techniques for Biomedical Researchers; Pittsburgh [N. Blankenstein, 412/268-4960, Fax: -8200, *biomed@psc.edu, http://www.psc.edu/biomed/workshops.html*]

June 1996

6–18. Summer Inst. in Statistical Genetics; NCSU, Raleigh, NC [B. Weir, 919/515-3574, Fax: -7315, *weir@stat.ncsu.edu, http://ww2.ncsu.edu/ncsu/CIL/stat_genetics*]

10–14, 24–28. **Basic Linkage Course; New York [K. Montague, 212/960-2507, Fax: /568-2750, *km165@columbia.edu, http://linkage.cpmc.columbia.edu*]

11–18. Genetic-Epidemiologic Studies of Complex Diseases; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845, *meetings@cshl.org, http://www.cshl.org*]

July 1996

7–Aug. 2. Scientific, Ethical, and Social Challenges of Contemporary Genetic Technology; NEH/NSF, Tacoma, WA (appl. deadline: March 1; invited from faculty of U.S. colleges and univ.) [D. Magnus, 206/756-3508, Fax: -3500, *dmagnus@ups.edu*]

11–19. 16th Wellcome Summer School. Human Genome Analysis: From YAC to Gene; UMDS, London (appl. deadline: March 29) [P. Faik, +44-171/403-6998, Fax: /407-5281, *wss@umds.ac.uk*]

August 1996

4–9. Molecular Genetic Basis of Cell and Tissue Structure and Function; Copper Mountain, CO [FASEB, 301/530-7010, Fax: /571-0650, *src@faseb.org*]

4–16. Workshop on Molecular Evolution; Woods Hole, MA [C. Hamel, 508/289-7401, Fax: /457-1924, *admissions@mbl.edu, http://www.mbl.edu*]

21–26. 17th Wellcome Summer School. Human Genome Analysis: Genetic Analysis of Complex Traits; UMDS, London (appl. deadline: March 29) [see contact July 11–19]

October 1996

10–23. YACs in Structural and Biological Genome Analysis; Cold Spring Harbor, NY [see contact: June 11–18]

November 1996

6–19. Molecular and Cell Biology of *S. Pombe* and Other Yeasts; CSHL, Cold Spring Harbor, NY [see contact: June 11–18] ◊

Extended calendars and a list of organizations offering training are available at *http://www.ornl.gov/hgmis* or from HGMIS (see p. 12 for contact information).

U.S. Genome Research Funding

Investigators wishing to apply for funding are urged to discuss projects with agency staff before submitting proposals.

NIH National Center for Human Genome Research (NCHGR)

Program announcements listed in *NIH Guide for Grants and Contracts* (*gopher.nih.gov* and *http://www.nih.gov*).

NCHGR Program Contact: 301/496-7531, Fax: /480-2770

- ELSI: *Elizabeth_Thomson@nih.gov* or 301/402-4997.
- Genetic linkage mapping, annotation, and single-chromosome workshops: *Elise_Feingold@nih.gov*
- Informatics: *David_Benton@nih.gov*
- Large-scale mapping, sequencing of human and mouse genomes: *Jeff_Schloss@nih.gov or Jane_Peterson@nih.gov*
- Physical mapping technology, training, and special programs: *Bettie_Graham@nih.gov*
- Sequencing technology development, technology transfer, nonmammalian model organisms: *Carol_Dahl@nih.gov* or *Robert_Strausberg@nih.gov*

DOE Office of Health and Environmental Research (OHER) Human Genome Program

- Contact for funding information or general inquiries: *genome@er.doe.gov* or 301/903-6488.
- Relevant documents: *http://www.er.doe.gov/production/oher/hug_top.html*

Alexander Hollaender Distinguished Postdoctoral Fellowships

Research opportunities in energy-related life, biomedical, and environmental sciences, including human genome, global change, and supporting disciplines.

Next deadline: January 1997

- Contact: Barbara Dorsey, Oak Ridge Institute for Science and Education (423/576-9975, Fax: /241-5219)

Small Business Innovation Research (SBIR) Grants

DOE and NIH invite small business firms (less than 500 employees) to submit grant applications addressing the human genome topic of SBIR programs. The two agencies also support the Small Business Technology Transfer (STTR) program to foster transfers between research institutions and small businesses. Contacts:

- Kay Etzler; c/o SBIR Program Manager, ER-16; DOE; Washington, DC 20585 (301/903-5867, Fax: -5488).
- Bettie Graham (see contact, NCHGR). NIH SBIR due April 15, August 15, and December 15. STTR, December 1.

National SBIR/STTR conferences: Dallas, TX (April 29–May 1, 1996). Conference hotline: 407/791-0720; electronic registration: 203/379-9427.◊

DOE Office of Energy Research Invites Grant Applications

Notice 96-08: Promote substantive improvements in high-throughput, integrated approaches to large-scale human genome sequencing and its analysis. Solicited topics: (1) supportive instrumentation and automation systems; (2) assembly of multimegabase-scale, ordered, sequence-ready DNA clones; (3) informatics for the rapid assembly, analysis, and annotation of data from high-throughput sequencing; and (4) informatics for facile submission, retrieval, and visualization of data for single or multiple related databases. These databases specifically include the Genome Database and Genome Sequence Data Base.

Notice 96-09. Address ethical, legal, and social issues that may arise from the use of information and knowledge resulting from the Human Genome Project. These may include issues of privacy, confidentiality, ownership, control, and commercialization of genetic information.

Due Dates: Preapplications: March 28, 1996; applications: July 11, 1996.

Information contacts: 301/903-6488, Fax: -8521, *joanne.corcoran@oer.doe.gov* **Notice 96-08**, Topic 1: Gerald Goldstein, Topic 2: Marvin Stodolsky, Topics 3 and 4, Jay Snoddy. **Notice 96-09**: Dan Drell.◊

Computational Structure-Function Funding Available

Notice 96-03. Enhance understanding of structure-function relationships in biological macromolecules, particularly for diverse biotechnology applications. These include development of drugs, new and improved biomaterials, enzymes for removing environmental contaminants, and biomass for fuels. Applications that integrate existing software in novel ways or develop new computational strategies to exploit databases are particularly interesting.

Due Dates: Preapplications: January 23, 1996; applications: April 25, 1996.

Information contact: Matesh Varma (301/903-3209, Fax: - 0567, *matesh.varma@mailgw.er.doe.gov*).◊

Human Genome Management Information System Subscription/Document Request* (Vol. 7, No. 5)

Name _____
(First) (MI) (Last)

Affiliation _____

Department/Division _____

Street/P.O. Box/Building _____

City/State/Zip Code _____

Country _____ **Area of Interest** _____

Phone _____ **Fax** _____

E-Mail Address (important to list if you have one) _____

1. ___ *Human Genome News* ___New Subscriber ___Change of Name/Affiliation/Address (circle all that apply) ___Drop Subscription
2. ___ DOE *Human Genome 1993 Program Report* ___DOE *Primer on Molecular Genetics* (see *http://www.ornl.gov/hgmis/publicat/publications.html*)
3. ___ Reprint of "A New Five-Year Plan for the U.S. Human Genome Project" (*Science*, October 1, 1993) by Francis Collins and David Galas

*Please type, print carefully, or enclose a business card to ensure efficient shipping. To change name/address/affiliation or drop your subscription to *Human Genome News*, enclose your current *HGN* address label. Send to HGMIS address shown below and on p. 12.

SELECTED ACRONYMS

AAI Am. Assoc. of Immunologists
AAP Assoc. of Am. Physicians
AFCR Am. Federation for Clinical Research
AMIA Am. Med. Informatics Assoc.
ASBMB Am. Soc. for Biochem. and Mol. Biol.
ASCI Am. Soc. for Clinical Investigation
ASHG Am. Soc. for Hum. Genet.
ASIP Am. Soc. for Investigative Pathologists
BAC bacterial artificial chromosome
BIO Biotechnology Industry Organization
bp base pair
CHI Cambridge Healthtech Inst.
cM centimorgan
CSHL Cold Spring Harbor Lab.
DHHS Dept. of Health and Human Services
DOE Dept. of Energy
ELSI ethical, legal, and social issues
EST expressed sequence tag
FASEB Fed. of Am. Soc. for Exp. Biol.
FISH fluoresence in situ hybridization
GDB Genome Database
GRC Gordon Res. Conf.
GSDB Genome Sequence Data Base
HGM Human Genome Meeting
HGMIS Human Genome Management Information System
HUGO Hum. Genome Org.
IBC Intl. Bus. Communications
MGD Mouse Genome Database
MMS Molecular Medicine Society
NCHGR Natl. Ctr. for Human Genome Research
NCSU North Carolina State University
NEH/NSF Natl. Endowment for the Humanities/Natl. Sci. Foundation
NIH Natl. Institutes of Health
NSGC Natl. Soc. Of Genetic Counselors
PAC P1 artificial chromosome
PG Plant Genome
RH radiation hybrid
SSLP single-sequence length polymorphism
STRP short tandem repeat polymorphism
STS sequence tagged site
TIGR/NIST The Inst. for Genome Res./Natl. Inst. of Standards and Technol.
UMDS United Med. & Dental Schools
WWW World Wide Web
YAC yeast artificial chromosome

OAK RIDGE NATIONAL LABORATORY • MANAGED BY LOCKHEED MARTIN ENERGY RESEARCH CORP. • FOR THE U.S. DEPARTMENT OF ENERGY

Betty K. Mansfield
HGMIS
Oak Ridge National Laboratory
1060 Commerce Park, MS 6480
Oak Ridge, TN 37830, U.S.A.

Postmaster: Do Not Forward.
Address Correction Requested.
Return Postage Guaranteed.

BULK RATE
U.S. POSTAGE
PAID
OAK RIDGE, TN
PERMIT NO. 3

Printed on Recycled paper