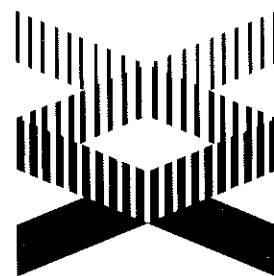


# Human Genome news



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## Researchers Find Myotonic Dystrophy Gene

Only 2 weeks after announcing that specific genetic alterations on chromosome 19 had been linked to myotonic dystrophy, research teams reported that they had almost simultaneously pinpointed the gene responsible for this complex heritable muscular disorder. Papers on the structural defect in the locus appeared in *Nature* on February 5. Subsequent reports on finding the gene were published in *Cell* on February 21 and in *Science* on March 6.

Investigators showed that the structural defect associated with myotonic dystrophy may grow larger with each generation and that the increase in size is associated with the severity of the disease. The enlarged gene area, consisting of a trinucleotide repeat (CTG) in the DNA sequence, is usually copied 5 to 30 times in people without myotonic dystrophy. Researchers found between 50 and several thousand copies of CTG in 95 to 98% of people with myotonic dystrophy symptoms, with the larger number of repeats appearing in the most severely affected patients. These findings build on those made last year for the gene that causes the fragile X syndrome (an inherited form of mental retardation).

Three sets of the investigators, who collaborated during the past 4 years to find the defect, described their results in separate papers in *Nature*. These groups were the following:

1. An eight-person Lawrence Livermore National Laboratory (LLNL) team, led by Pieter de Jong, that worked with groups headed by Robert G. Korneluk (Children's Hospital of Eastern Ontario, Canada) and Bé Wieringa (University of Nijmegen, Netherlands).
2. A group headed by Keith Johnson (Department of Anatomy of Charing Cross and Westminster Medical School, London).
3. A collaborative effort between a team led by Duncan J. Shaw, Peter S. Harper, and Helen Harley (Institute of Medical Genetics, University of Wales College of Medicine, Cardiff) and another headed by David Brook and David Housman (Massachusetts Institute of Technology Center for Cancer Research).

Subsequently, the researchers listed in the teams above and C. Thomas Caskey and Henry Epstein (Baylor College of Medicine) published the *Science* and *Cell* papers that pinpointed the gene's location. →

**International  
Teams  
Culminate  
4-Year Effort**

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## Genome News

### Myotonic dystrophy contact:

- **Jim Brown (MDA)**  
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U.S. Secretary of Energy James D. Watkins congratulated members of the DOE-funded LLNL Human Genome Center and noted, "This is one of the early fruits of the Human Genome Project, and we can expect to see these advances coming with increasing frequency in the years to come."

Discovery of the gene should lead to the development of tests for earlier detection of this normally late-onset autosomal dominant disease, including detection before symptoms appear. Knowledge of the gene's normal function will allow a better assessment of the defective gene's consequences and possibly lead to improved diagnostic procedures and treatment methods for the disorder, which is estimated to appear in at least 1 in 8000 people worldwide each year.

In addition to the DOE Human Genome Program, the NIH National Center for Human Genome Research, the Muscular Dystrophy Association (MDA) of United States and Canada, the Muscular Dystrophy Group of Great Britain, the Eurogene European Community Genome Program, the Wellcome Trust, and several other international organizations supported this work.

Most of the mapping was done using cosmid clones produced at LLNL, and a major portion of the mapping was performed by LLNL scientists who focused their study on the middle of chromosome 19. To link the work of Korneluk and Wieringa, who were mapping the chromosome from opposite ends, de Jong and Cara Aslanidas (LLNL) supplied both groups with key recombinant DNA clones containing the segment with the defect. LLNL investigators identified yeast artificial chromosome (YAC) clones containing the defect, using a collection produced by Maynard Olson's group at Washington

University in St. Louis. These unstable YACs were used to isolate the appropriate stable cosmid clones.

Anthony Carrano, Director of the LLNL Human Genome Center, noted that LLNL has a full suite of resources to assist in identifying, isolating, and mapping genes for chromosome 19. These include a foundation chromosome 19 cosmid contig map spanning an estimated 80% of the chromosome; high-density cosmid and YAC filters to assist collaborators in mapping genes; a chromosome 19 database accessible via Internet; and chromosome flow-sorting technology to create specialized libraries as part of the National Laboratory Gene Library Project.

Myotonic dystrophy, one of many heritable muscular diseases, causes spasms, weakness, and wasting in voluntary muscles and often produces difficulty in relaxing muscles (myotonia). A characteristic of this disease, which was first described in the early 1900s, is the highly variable severity of the symptoms, even among affected members of a single family.

Also known as dystrophia myotonica and Steinert's disease, myotonic dystrophy affects both men and women and usually appears in adolescence or early adulthood, although at least one often-fatal form causes symptoms that are noticeable at birth. The disease can cause heart problems, gastrointestinal complications, cataracts, premature balding, mental slowness, and sleep disorders; affected individuals may die of heart or respiratory failure in their 50s or 60s.

Another widespread muscular disorder is Duchenne muscular dystrophy, a childhood disease that is linked to the X chromosome and almost always affects males. Symptoms appear within the first 5 years, and the disease progresses very rapidly, with death occurring in the patient's late 20s. The gene responsible for Duchenne was found in 1986 in the laboratories of Louis Kunkel (Harvard Medical School), Kay Davies (John Radcliffe Hospital, Oxford, England), and Ronald Worton (Hospital for Sick Children, Toronto, Canada) [Monaco et al., *Nature* 323, 646-50 (Oct. 16, 1986)]. About 40 neuromuscular disorders are currently targeted by research efforts sponsored by the American MDA and other funding organizations. ♦

### Resource

#### NCHGR Provides Marker Catalog

The National Center for Human Genome Research (NCHGR) has prepared a catalog of index-quality markers and interim maps available as of January. Characterized by a heterozygosity of at least 70%, the markers include restriction fragment length polymorphisms and markers based on microsatellites or other DNA sequences. The catalog, an interim summary of the index marker/framework map project [see *HGN* 3(2), 1-2 (July 1991)], includes information on accessing the markers and using them to localize genetic markers to specific intervals. [Contact: NCHGR Office of Communications; Bldg. 38A, Room 617; 9000 Rockville Pike; Bethesda, MD 20892; 301/402-0911, Fax: 301/480-2770.] ♦

## Gene Mapping May Yield Insights into Breast Cancer Development

Researchers at the University of California, Berkeley (UCB), are using genetic mapping techniques to zero in on a gene that may be responsible for many cases of hereditary breast cancer and may also play a role in ovarian cancer.

Mary-Claire King, professor of genetics and epidemiology at UCB, recently told an audience at the NIH Human Genome Lecture Series that locating the gene could enrich understanding of breast cancer in general, leading to earlier detection and eventually to more-effective treatment.

The suspect gene, BRCA1, is known to lie on the long (q) arm of chromosome 17. By identifying DNA markers linked to the gene in certain families, King's group and others around the world are attempting to pinpoint the gene's exact location.

Scientists believe several different genes are implicated in breast cancer, with variation among individuals. According to this model, a tumor will develop only after a critical number of genes are damaged by mutations. These mutations may be inherited from a parent, or the genetic damage may occur de novo in a single breast cell.

Most breast cancer is not caused by an inherited predisposition. The disease is so widespread, however, that even the small familial proportion of cases constitutes a large number of affected individuals and is thus an important genetic condition, King said. Basing her estimate on the families her group has studied, King said that the BRCA1 gene may cause breast or ovarian cancer by age 50 in about 1 of 170 women.

### Modern Disease

Breast cancer is a disease characteristic of modern women's lives, King said, because its increased incidence in industrialized countries appears to be due in part to societal changes. Earlier menstruation resulting from better nutrition, coupled with delay or absence of childbearing as women pursue education and careers, make for much longer periods of time in which breast cells are "bathed in a hormonal milieu that is very supportive for division," she noted.

"Unlike . . . lung cancer, there's no single risk factor we can change or would want to change," she said. "We're not going back to

the ways our grandmothers lived, so it's up to modern women, with the help of modern men, to solve the problem."

### Genetic Markers

Genetic epidemiologists like King construct pedigrees of families that have multiple cases of breast cancer across generations, often locating the families with the help of physicians treating the women. DNA testing must be done on blood samples from large numbers of family members, both male and female, to determine whether a genetic marker is associated with breast cancer in a particular family. King said that these markers simply detect a site on chromosome 17 that can be tracked in the family by tracking the marker.

Progress in gene mapping comes through identifying new markers progressively more closely linked to the putative disease-gene site. The closer the linkage, the narrower the piece of chromosome on which researchers can focus their efforts.

To be useful, a marker must be highly polymorphic—many forms, or alleles, must exist in the population. In a case of perfect linkage within a family, a specific form of the marker shows up in the DNA of all women with breast cancer and in none who are unaffected. The reality is usually more complicated. Women showing the marker may be "susceptibles," carrying the breast cancer gene but not having the disease because they are still relatively young or because they are protected in some way. Conversely, sporadic occurrences of environmentally caused cancers may arise in women who lack both the marker and the gene.

### DNA Rearrangements

Another possibility is what geneticists call a recombination event, in which a parent's own chromosomal DNA is rearranged during meiosis (sperm or egg production). Offspring who carry the breast cancer gene will then have a different form of the marker from the parent and ancestors who carried it.

Although recombination adds uncertainty to the study of pedigrees in one sense, it serves as an important tool in nailing down

### Investigators Identify Linked Markers To Pinpoint Location of Gene

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## Genome News

### Search for Breast Cancer Gene Narrows

a gene's precise location. When further pedigree analysis shows that recombination has occurred between a marker and the gene, parts of the chromosome proximal or distal to the marker can be eliminated from consideration.

Even as the search narrows, however, several suspect genes are known to lurk in the 17q21 neighborhood of the markers. "We are now down to a region of about 6 cM (gene map units, based on recombination frequency), where a year ago [the distance] was about 50," King said. "There are probably about 250 genes in the region."

Among them are genes for HERZ, a truncated form of epidermal growth factor that acts as an oncogene in some cells; the retinoic acid receptor (RARA), a possible anticarcinogen; and 17HSD, an enzyme that converts the active form of estrogen to a relatively inactive form.

"Now we are trying to develop these genes as highly polymorphic markers and see if any of them are perfectly coinherited with breast cancer in early-onset families," King said.

Finding a gene for breast cancer might make possible earlier diagnosis via blood testing. "If we can back up diagnosis by . . . 10 cell divisions [earlier than is now possible with mammography], we gain a lot in terms of the likelihood that cells have broken off and are on their way to killing the host," King noted.

More speculative is the possibility of using the errant gene to design new therapies. For example, monoclonal antibodies might be created that would carry drugs to cancer cells that may have strayed throughout the body. An even more enticing (though currently remote) goal would be to target treatments directly to the malfunctioning gene or its product, reversing the disease process.

"Can we actually reverse the altered phenotype?" King asked. "It's not out of the question, but we won't know until we know what the altered phenotype is." ♦

*Reported by Tom Reynolds  
NIH National Cancer Institute*

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 and Safety Research Division at Oak Ridge National Laboratory, which is managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy, under Contract DE-AC05-84OR21400.

## UNESCO Awards Fellowships, Plans Conferences

In 1991 the United Nations Educational, Scientific, and Cultural Organization (UNESCO) Coordinating Committee for the Human Genome Project selected 21 scientists from 19 countries to receive UNESCO/Third World Academy of Sciences Human Genome Fellowships. The recipients, chosen from 75 applicants, are nationals from Algeria, Argentina, Cameroon, Chile, China, Costa Rica, Cyprus, Czechoslovakia, Egypt, Guinea, India, Indonesia, Myanmar, the Republic of Korea, Peru, Spain, Ukraine, Russia, and Yugoslavia.

Designed to promote international cooperation in the human genome community by stimulating and facilitating research and training, the 1- to 3-month fellowships enable scientists from developing countries to carry out research in well-established scientific centers and to learn new research techniques. The committee, which plans to meet twice in 1992, asks interested applicants to write to F. Zharov (UNESCO) at the address in the box below. Investigators are urged to inform colleagues and collaborators in Third-World countries about these fellowships.

### *UNESCO Plans Next North-South Conference for May 12-15 in Brazil*

The first annual UNESCO North-South Human Genome Conference will be held May 12-15 in Caxambu, Brazil. The purpose of the conference is to increase interaction between scientists from developed countries and those of the Third World. The second conference is planned for Thailand in 1993, and the third will probably take place in China in 1994. ♦

*Reported by Santiago Grisolia  
UNESCO*

#### UNESCO Fellowship contact:

• F. Zharov  
UNESCO  
1 rue Miollis  
75015 Paris

## NCHGR Initiates Eastern European Programs

To help achieve the goals of the Human Genome Project, the NIH National Center for Human Genome Research (NCHGR) is making research opportunities available to scientists of Central and Eastern Europe through the (1) International Genome Research Collaborative Program and (2) International Genome Research Fellowship Program. The project was developed in cooperation with the Eastern European program of the NIH Fogarty International Center. For the purposes of this program, Central and Eastern Europe are defined as Bulgaria, the Czech and Slovak Federal Republic, Hungary, Estonia, Latvia, Lithuania, Poland, Romania, all other republics of the former U.S.S.R., and Yugoslavia.

Applications are encouraged in the following areas:

- Construction of high-resolution genetic and physical maps.
- Development of (1) new or improved DNA sequencing methods; (2) computer tools, information systems, and strategies for collecting, storing, retrieving, analyzing, interpreting, and distributing large amounts of mapping and sequencing data; or (3) technology to support Human Genome Project objectives.

### International Genome Research Collaborative Program (R03)

To facilitate collaboration between U.S. and Central and Eastern European scientists, NCHGR will provide financial assistance for extended visits by foreign investigators in U.S. laboratories and for the purchase of equipment and supplies to enhance collaborative projects at foreign institutions. These fellowships are intended for senior investigators who are doing independent research in a country with an organized human genome program.

Projects will be supported through the non-renewable small grants mechanism for 1 to 3 years at U.S. institutions that have an NCHGR grant with at least 1 year remaining. These awards will provide the following:

- Up to \$20,000 a year in direct costs for materials, supplies, and equipment to support genomic research in the foreign laboratory or the foreign scientist's work at the U.S. sponsor's laboratory.

- A maximum of \$24,000 a year (\$2000 a month) in living expenses while the foreign scientist is in the United States. The visitor must spend at least 6 months in the United States; 12 months is desirable.
- Travel expenses for the foreign collaborator and for at least one reciprocal laboratory visit by the U.S. and foreign collaborators each year for the duration of the award.

The application must demonstrate that the proposed collaboration will enhance the scientific contributions of both U.S. and foreign scientists and further the goals of the Human Genome Project. Foreign collaborators must be associated with an organized human genome program in their home countries and hold a position in a nonprofit institution that will allow time and facilities for conducting the research.

### International Genome Research Fellowship Program (F05)

The purpose of these fellowships is to provide foreign junior scientists (not yet in an independent research position) with training opportunities in U.S. laboratories, to promote the exchange of ideas and information about the latest advances in mapping and sequencing technology, and to improve the potential of the fellow's home institution to pursue genomic research.

The minimum support period is 12 months with a maximum of 24 months. Support provides a U.S. living allowance of \$2000 a month, round-trip air fare, and an allowance of \$1200 a month to the U.S. host institution for health insurance and research supplies.

The applicant must be proficient in the English language and have a Ph.D., M.D., or equivalent degree. Also required is post-doctoral experience of up to 10 years in genetics, molecular biology, or other discipline that can be applied to genome research, such as computer science, chemistry, physics, mathematics, or engineering. The fellow must be assured of a position to which he or she can return when the fellowship is completed and must obtain an invitation to work with a U.S. scientist who is the principal investigator of an NCHGR grant and who will act as collaborator and host. ◊

### Collaborative Program for Senior Scientists

Application Receipt Dates Each Year:

- June 1
- October 1
- February 1

### Fellowship Program for Junior Scientists

Application Receipt Dates Each Year:

- May 10
- September 10
- January 10

### Contact for both programs:

- David A. Wolff  
International  
Research and  
Awards Branch  
NIH  
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## Genome News

**Mouse database contacts:****EMG**

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**Second NIH-DOE Joint Mouse Working Group**

The second meeting of the NIH-DOE Joint Mouse Working Group was held September 15–16, 1991, in Boston. Different topics were the focus of each of four sessions:

- Mouse Genome Center at the Massachusetts Institute of Technology (MIT);
- U.K. Mouse Genome Project;
- status of the mouse genetic map; and
- requirements for completing a 1-cM genetic map of the mouse.

For a list of working group members, see *HGN* 3(1), 10 (May 1991).

**MIT Mouse Genome Center**

Eric Lander (MIT Mouse Genome Center) discussed progress at the center, which is sponsored by the NIH National Center for Human Genome Research, in constructing

- a genetic map consisting of 2000 ordered polymorphic markers that are maximally useful (i.e., highly variable, typable by polymerase chain reaction, and easy to distribute) and
- a physical map of genetically ordered 1- to 2-Mb contigs. Closure is not one of the goals, so the map will have gaps.

Lander indicated good progress during the first 12 months, with about 400 markers having been isolated and 338 mapped. He plans to supply data periodically to the Encyclopedia of the Mouse Genome (EMG) after the information has been shown to be error free. EMG integrates data from a variety of mouse genome databases with software that generates graphical displays of cytogenetic or linkage maps.

**U.K. Mouse Genome Project**

Steve Brown (St. Mary's Hospital Medical School, London) indicated that the U.K. Mouse Genome Project is linked to the European mouse genome program through the European Collaborative Interspecific

Backcross (EUCIB) project, which includes the Pasteur Institute in Paris, the Medical Research Council Resource Center in London, and Freie Universität, Berlin. The goal of EUCIB is to provide a resource for genetic typing rather than to generate a complete map. The EUCIB database will be used to store mouse probe and mapping data; provide interlocus recombination data and LOD scores; derive gene order from haplotype data; and ultimately store yeast artificial chromosome (YAC) clone reference data. The resource—a 1000-animal backcross between C57BL/6 and *Mus spretus*, planned to provide a genetic resolution of 0.3 cM at a confidence level of 95%—is expected to be available later this year with about 5 to 10 mg of DNA available from each backcross mouse.

Another component of the U.K. Mouse Genome Program is the generation of cDNAs, primarily to find genes. The cDNAs will be isolated from mouse testes and 8.5-day-old embryos; highly abundant cDNA species will be eliminated through hybridization; random cDNAs will be sequenced from each end of the insert; and cDNAs will be mapped onto somatic cell hybrid panels and the EUCIB DNA panels.

**Status of the Mouse Genetic Map**

Neal Copeland (NCI-Frederick Cancer Resource and Development Center) summarized the progress of several laboratories using the genomic approach to mapping the mouse. Joe Nadeau (Jackson Laboratory) reported on the Genomic Database of the Mouse (GBASE), which consists of published mouse genetic map data. Nadeau stated that GBASE contains information on 3375 loci (3191 with genetic locations) and about 2100 probes and clones; not all are mapped. Many databases are available on diskette through the EMG Project, a key goal of which is to consolidate databases on the genetics and biology of the laboratory mouse and to present these data in a standardized, readily learned, easy-to-use format.

Future mouse database needs include (1) physical mapping data structure to handle incoming data, (2) one central database that includes all information about the mouse, (3) tools for analyzing map data, (4) integration of information

**HGMIS Supplies Newsletters for Meetings, Other Activities**

The Human Genome Management Information System (HGMIS) supplies multiple copies of *Human Genome News* for educational purposes to people conducting seminars, lectures, meetings, or similar activities. Requests should be made at least 3 weeks prior to the date newsletters are needed. See HGMIS contact information on page 20. ◇

from various mouse crosses, (5) methods for integrating the genetic and physical maps, (6) maps of telomeres and centromeres, (7) more-precise ways of identifying candidate genes, and (8) methods for transferring information from map-rich species such as human and mouse to map-poor species such as cow and dog.

### Requirements for Completing the Mouse Genetic Map

The group agreed that the original goal to construct a 1-cM mouse genetic map is still appropriate and feasible and that the map should include genes and anonymous DNA sequences. The project is about one-third accomplished, with some 1000 markers (genes and anonymous DNA sequences surrounding CA repeats) established in well-ordered genetic maps; the markers are largely derived from the interspecific backcrosses. An additional 500 to 1000 loci have been linked to chromosomes and subchromosomal regions using recombinant inbred strain analyses and other mapping methods.

Acknowledging the contribution of anonymous DNA markers in the completion of a genetic map with evenly spaced markers, the working group made the following recommendations:

- Fill in existing gaps by mapping additional functional genes and anonymous loci;
- Continue development of both genome-wide and chromosome-specific genetic mapping efforts. The chromosome-by-chromosome approach will promote the production of more-dense genetic maps and allow for the elaboration of physical maps from genetic maps;
- Develop widely accessible mouse genetic mapping resources to accelerate the mapping of genes by making available responsive and timely YAC screening services;
- Encourage development of new technology to facilitate genetic and physical mapping efforts, more-efficient mapping strategies, and sequence-based methods of analysis;
- Develop a centralized public database and database tools that provide easy access to map data;
- Simplify access to DOE facilities and other large laboratories and genome

centers that routinely perform techniques such as chromosome sorting and library construction to accelerate the mapping efforts of individual laboratories.

### Other Considerations

The working group recognized the need for international cooperation to pursue the mapping project in a cohesive manner (see related article, p. 15) and felt that a future meeting of the working group could be devoted to a discussion on sharing resources and databases.

Members will prepare a paper on using the mouse map to facilitate construction of the human map and on the value of the mouse map to basic biology. They suggested that such a document should be widely disseminated and published in *Human Genome News*. ◇

*Reported by Bettie J. Graham  
NIH NCHGR*

**A complete meeting report is available from the Mouse Working Group.**

#### Contact:

- Bettie J. Graham, Chief Research Grants Branch  
NIH NCHGR  
Bldg. 38A, Room 617  
Bethesda, MD 20892  
301/496-7531  
Fax: 301/480-2770

### Resource

#### List of Databases

*Science* magazine has compiled a list of key genome-related databases that contain human genetic mapping data, DNA and RNA sequences, and protein sequences and structures. The listing also describes several model organism sequencing and mapping databases [*Science* 254, 201-4 (Oct. 11, 1991)]. ◇

### Michigan Center Provides Samples, Tours

**T**he Genome Education Program of the University of Michigan Human Genome Center will supply high school science teachers with the following materials for performing laboratory exercises on cytogenetics and sequencing:

1. Kit containing chromosomes from cultured rodent cell lines, ready to drop onto slides and stain, with complete directions for carrying out the exercise and a description of how the cells were prepared. \$5.00 to cover the cost of postage.
2. Packet entitled *Unraveling Life, Sequencing the Human Genome*, which gives background information on the theory behind sequencing, different sequencing techniques, and the application of this technology to modern genetics. Contains diagrams and real sequencing autoradiographs that allow students to read the sequence of a piece of DNA. Free except for return postage on autoradiographs.

The education program at the Human Genome Center conducts 1-hour onsite tours of center laboratories for classes and extra-curricular groups. The number of tours each month is limited to minimize disturbance to the research. Contact: Paula Gregory, Education Director; Human Genome Center; University of Michigan; Ann Arbor, MI 48109; 313/764-8050. ◇

## Genome News

### Researchers Expand Number of Known Markers by 36%

## Arabidopsis Project Reports Success

The science steering committee of the Multinational Coordinated *Arabidopsis thaliana* Genome Research Project reported "remarkable progress" in first-year accomplishments. Researchers expanded by 36% the number of known genetic markers for the plant, due in part to new techniques for singling out, identifying, mapping, and moving genes. More than 200 new mutations were identified and associated with genes controlling embryo development, metabolism, reproduction, photosynthetic capacity, and resistance to disease.

A small flowering plant belonging to the Brassica family (and related to cabbages, cauliflowers, and brussel sprouts), *Arabidopsis* undergoes the same processes of growth, development, flowering, and reproduction as other plants. With about 30 times less DNA than a corn or human genome and very little repetitive DNA, the plant's smaller genome, prolific seed production, tolerance for growing in high densities, and 5- to 6-week reproduction cycle make *Arabidopsis* a popular model in the study of plant biochemistry, genetics, and physiology.

Investigators hope to identify and characterize all the genes and sequence the entire *Arabidopsis* genome by the year 2000, an achievement that would lead to a much deeper understanding of all flowering plants and have the potential to modify economically important crops. ◇

Current and future reports of the science steering committee are available from

- Machi Dilworth  
NSF Division of Instrumentation and Resources  
1800 G Street, NW, Room 312  
Washington, DC 20550  
202/357-7652, Fax: 202/357-7568  
Internet: "mdilworth@nsf.gov"

*Mosaic* is the National Science Foundation (NSF) magazine of current work and thought in research areas with which NSF is concerned. An article by Ben Patrusky on the plant and *Arabidopsis* genome project appeared in the summer 1991 issue of *Mosaic*. Subscription information: United States, \$9.50 (yearly), \$3.00 (single copy); other countries, \$11.90 and \$3.75. [Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.] ◇

### NSF Funds Ohio State *Arabidopsis* Resource Center

NSF announced in September 1991 the award of up to \$1.9 million over 5 years to Ohio State University to establish a resource center for *Arabidopsis* genome studies. The center will collect, preserve, and distribute seeds, genetic probes, and other resources for the rapidly expanding community of investigators studying the plant *Arabidopsis thaliana*. Randy Scholl, Associate Professor of Molecular Genetics, directs the center (614/292-1982, Fax: 614/292-0603; Internet: "scholl.1@osu.edu").

Establishment of the center was one of the priorities of the Multinational Coordinated *Arabidopsis thaliana* Genome Research Project. The U.S. center at Ohio State coordinates its activities with the seed center at the University of Nottingham, England, and with the DNA clone center at the Max Planck Institute in Cologne, Germany.

An additional grant of about \$300,000 over 5 years was made to Michigan State University to develop a comprehensive computerized database management system for online access to information about resources at the Ohio State center. The Michigan State project, which is partly funded by the U.S. Department of Agriculture through the Office of Plant Genome Research, is headed by Sakti Pramanik (517/353-3177, Fax: 517/336-1061; Internet: "pramanik@cpswh.msu.edu"). ◇

### Resource

#### ATCC Index Available in Print and Online

*ATCC Microbes and Cells at Work*, 2nd edition, is an index of special applications for the microorganisms, cell lines, recombinant DNA materials, and viruses in the vast collection of cultures at the American Type Culture Collection (ATCC) in Rockville, Maryland. This edition, available in both printed and electronic form, contains 1200 new entries, 50 new pages of text, and a bibliography of over 6300 citations. New application categories include probes containing sequences for disease diagnosis, clones for plasmid-induced production, oncogenes, hosts (for transfection/transformation), special uses for cell lines, and ATCC quality-control strains. 1991. [ATCC Marketing NR 82; 12301 Parklawn Drive; Rockville, MD 20852; 301/881-2600; Fax: 301/231-5826; Telex: 908768.] ◇



## GDB™ and OMIM™ Solutions

This column will appear periodically in *Human Genome News* to feature answers to questions that Genome Data Base (GDB) and Online Mendelian Inheritance in Man (OMIM) users frequently ask GDB User Support. For help with other questions and problems or to offer suggestions, readers should contact their local User Support office (see box, p. 10).

- How do I find microsatellite polymorphisms?

**Answer:** Direct retrieval of polymorphism data is not possible, but this data can be found by retrieving loci that are polymorphic.

### Upcoming GDB Enhancements Near Completion

Two enhancements to GDB are near completion. (1) Beginning in April, each node will manage its own local user registration so new users can be added more quickly. (2) Users at Baltimore and the remote nodes will be able to use the messaging system to communicate with their local "help" station, GDB editors, and many probe contacts; messages should include the phone number or e-mail address to which the recipient can respond. This message feature, currently available only to Baltimore users, will be included in the next full release of GDB expected this fall. ◇

### New GDB Remote Node Opens in Australia

To increase GDB accessibility outside the United States, a series of official, self-supporting distribution nodes (remote user sites) is being established to offer database and user support services equivalent to those available from GDB in Baltimore. In addition to the remote nodes in the United Kingdom and Germany, Australia is now offering online service.

The Australian node is run by the Australian National Genomic Information Service (ANGIS), an arm of the Australian Genomic Information Center at the University of Sydney (see gray box, p. 10). The service, intended primarily for users in Australia, is also accessible internationally via the Australian Academic and Research Network (AARNet) and Internet. Modest registration fees help support this node. ◇

On the RETRIEVE LOCI screen, enter "sat" (for satellite) in the *Variation Type* field. Data in other relevant fields can also be entered. For example, to retrieve microsatellite loci on chromosome 5, enter "5" in the *Location* field. To see related allele data for a specific locus after the polymorphic loci have been retrieved, use the **Call** menu option to enter the Polymorphism Manager and then the Alleles and Allele Population/Frequency Managers.

- How do I find all the CA repeat polymorphisms on chromosome 21?

**Answer:** As stated in the previous example, polymorphism data cannot be retrieved directly; loci that are polymorphic must be retrieved first. The appropriate code for (CA)<sub>n</sub> is "dinuc" (for dinucleotide repeat). To see all the code choices for the *Variation Type* field, move the cursor to that field and select *Field Values*. On the RETRIEVE LOCI screen, enter "dinuc" in the *Variation Type* field and "21" in the *Location* field. Boolean operators can be used in the *Variation Type* field; enter "tri or tet" for polymorphisms with tri- or tetranucleotide repeats.

(see *Solutions*, p. 10)

### GDB Answers Questions from Users

## GDB and OMIM Training Course Schedule

Two comprehensive hands-on training courses on the use of GDB and OMIM are being scheduled in Baltimore and other locations:

- The general course for scientific users provides a basic understanding of the databases and the relationships among the different types of data.
- The course for users with editing privileges includes instructions on adding, modifying, and deleting GDB data.

Class frequency and location will be determined by demand (schedule at right). Courses are free, but attendees must pay their own travel and lodging expenses. Hotel information and directions will be mailed with registration materials.

Contact: GDB User Support; 410/955-7058, press 4 after greeting; Fax: 410/955-0054; Internet: "help@welch.jhu.edu".

### Planned Exhibitions

- FASEB, Anaheim, Calif., April 5-10
- AAP/AFCR/ASCI, Baltimore, Md., May 1-4

COURSE	DATES
<b>BALTIMORE</b>	
Editing	May 3-5
General User	May 16
(Two 1-day courses for MLA attendees)	May 17
General User	June 15-16
General User	July 12-13
Editing	Sept. 13-15
General User	Sept. 21-22
General User	Nov. 23-24
<b>LONDON (HARROW)</b>	
Editing	Aug. 17-18
Editing	Aug. 19-20
General User	Aug. 21
<b>SAN FRANCISCO</b>	
Editing	Nov. 6-7
General User	Nov. 8
(1-day course for ASHG attendees)	

## GDB Forum

### GDB User Support, Registration

To become a registered user of GDB and OMIM, contact one of the User Support offices listed below (a user may register to access both Baltimore and a remote node). Questions, problems, or user-registration requests may be sent by telephone, fax, or e-mail. (Note change in GDB telephone numbers in Baltimore.) User-registration requests should include name, institutional affiliation, and title (if applicable), street address (no P.O. box numbers), telephone and fax numbers, and e-mail address.

#### USER SUPPORT OFFICES

##### United States

GDB User Support  
Welch Medical Library  
1830 E. Monument Street,  
Third Floor  
Baltimore, MD 21205  
410/955-7058  
Fax: 410/955-0054  
Internet:  
"help@welch.jhu.edu"

The Help Line is staffed from 9 a.m. to 5 p.m. EST for information on accounts, technical support, data questions, and training courses. Calls received after hours will be forwarded to the appropriate voice mail and returned as soon as possible. To obtain a user's local SprintNet (Telenet) number for locations within the United States: 800/736-1130.

##### United Kingdom

Christine Bates  
Human Gene Mapping  
Program Resource Center  
CRC, Watford Road  
Harrow, Middx HA1 3UJ, U.K.  
(Int.) 44/81-869-3446  
Fax: (Int.) 44/81-869-3807  
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"reisner@ee.su.oz.au"

### Solutions (from p. 9)

Once the polymorphic loci with dinucleotide repeats have been retrieved, call the Polymorphism Manager for each locus. Since a locus may have several types of associated polymorphisms, check the *table* view in Polymorphism Manager for those with dinucleotide listed in the *Polym Type* column. The *Annotation* field (detail view) includes

information about the specific repeat pattern [e.g., (CA)<sub>n</sub>].

- How can I get past the 9th allele of 15 alleles for the Mfd139CA/Mfd139GT probe?

**Answer:** Viewing allele band-size data involves moving around a matrix. Use the **Go To** menu option to display other alleles and band sizes not shown on the screen. (The ">" and "<" symbols indicate that more band sizes occur.)

The **Go To** submenu includes **Next, Previous, First, Last, Left, and Right**. Select the direction in the matrix you want to go. **Left** and **Right** will move horizontally to display different band sizes. **Next, Previous, First, and Last** will move vertically to display different alleles. ◇

### Informatics Resources\*

#### Free Genome-Related Software Available

##### CHROMINFO Computer Program

CHROMINFO, developed by Prakash Nadkarni and Stephen Reeders (Yale University), is a free computer program intended to serve as a liaison tool for researchers working on the same chromosome in different laboratories. This simple-to-use program, which is designed to record order, distance, and other information for loci on any chromosome, is menu driven and makes maximum use of the mouse. Users can edit information and add fields and text. The program was written for the Apple Macintosh (requires at least 3 Mb RAM) and works with the commercial database 4th Dimension (ACIUS). Yale University; Section of Nephrology; Department of Internal Medicine; School of Medicine; 2073 LMP; P.O. Box 3333; New Haven, CT 06510-8056; 203/785-7403; Internet: "nadkarni@cs.yale.edu".

##### GeneID and NetGene Online Systems for Prediction of Gene Structure

GeneID, an artificial intelligence system for analyzing vertebrate genomic DNA, predicts exons and gene structure. NetGene predicts human mRNA splice sites and associated coding regions and gives the confidence level for each prediction. A prototype (version 1.0) now provides access to both programs in a fast, automatic, e-mail response system, which is free to the research community. For information on accessing the system, send the message "geneid info" to "geneid@darwin.bu.edu" over Internet.

GeneID and NetGene have been tested thoroughly on sets of genes from GenBank®; evaluations of these tests are available in NetGene (S. Brunak et al.) and in a computer file for Macintosh ("Geneid.sit.hqx") that can be obtained by including the line "Preprint Request" in the e-mail to "geneid@darwin.bu.edu".

Users of MBCRR and BMERC national computer resources have online access from their accounts. For subscription information, contact Tom Graf at "tom@mbcrr.harvard.edu". The following references contain more details on the systems: S. Brunak et al., *J. Mol. Biol.* **220**, 49-65 (1991) and R. Guigo et al., *J. Mol. Biol.*, in press (1992). Questions may be addressed to Steen Knudsen; University of West Florida; Bioinformatics Resource; University of West Florida; Gulf Breeze, FL 32561-3999; 904/934-2448, Fax: 904/934-9201; Internet: "steen@darwin.bu.edu".

##### Software Database

GenBank invites developers to add their products to the GenBank Software Clearinghouse database of molecular biology software available from vendors. To add sequence analysis programs or to obtain a copy of the clearinghouse, which is stored in relational database format, contact: Kate Yudin; GenBank c/o IntelliGenetics, Inc.; 700 E. El Camino Real; Mountain View, CA 94040; 415/962-7364; "abe@genbank.bio.net". ◇

\*More informatics resources on p. 17.

## First Workshop on Chromosome 2

The First International Workshop on Chromosome 2 was held October 12–13, 1991, in Washington, D.C., to consider the genetic and physical map of human chromosome 2. Twenty-nine participants from six countries attended the conference, which was sponsored by the NIH National Center for Human Genome Research, the European Community, the U.K. Medical Research Council, and the Centre d'Etude du Polymorphisme Humain (CEPH).

Presentation of the CEPH consortium map opened the meeting. Four groups had used genotyping data to produce maps with markers having a ratio of at least 1000:1 in favor of linkage. About 35 markers were ordered along the chromosome, with an average map length of 450 cM in females and 270 cM in males. Attendees largely agreed on marker order and identified markers for haplotyping (determining the particular combination of genetic markers present in a genomic area in an individual). Each group submitting maps for the consortium will meet to decide which markers should be used for the genetic framework map.

Separate sessions were held on genetic and physical maps, specific disease loci, and resources for studying chromosome 2.

### Genetic Maps

A discussion of the CEPH consortium map and the mapping data in non-CEPH families by Andrew Pakstis (Yale University) revealed large gaps between markers on the genetic map and only a limited number of highly informative markers. Sean Todd (University of Texas, San Antonio) presented data on a number of new (CA)<sub>n</sub> repeats at or near genes already mapped to chromosome 2.

### Physical Maps

Physical mapping to produce overlapping yeast artificial chromosome (YAC) or cosmid contigs is still at a preliminary stage for chromosome 2. Pieter de Jong [Lawrence Livermore National Laboratory (LLNL)] described chromosome flow sorting and the preparation of phage and cosmid libraries, expected to be completed this spring. The phage library will be distributed through the American Type Culture Collection. Cosmid clones can be obtained by hybridizing high-density filters of the arrayed cosmid library; filters

and clones will be available from the Human Genome Center at LLNL. Harvey Mohrenweiser (LLNL) described the success of this approach in screening for gene- and marker-positive cosmids for human chromosome 19.

Fa-Ten Kao (Eleanor Roosevelt Institute) discussed the microdissection of parts of chromosome 2 and the production of three libraries of microclones in the regions 2p23–p25, 2p21–p23, and 2q35–p37. Tom Strachan (St. Mary's Hospital, Manchester, England) described the isolation of YAC contigs from the region 2q35–q37.

### Disease Loci

In the past 2 years, at least five major disease genes have been mapped to chromosome 2, including those for induced Waardenberg syndrome (WSI, described below), holoprosencephaly, alveolar rhabdomyosarcoma involving t(2:13) translocation, protein C (PROC) deficiency causing a defect in the coagulation pathway, and the association of the alpha transfusing growth factor (TGFA) with cleft lip and palate.

**WSI.** Lindsay Farrer (Boston University Medical School) presented data from the WSI consortium group on the latest findings in mapping this locus. WSI, a syndrome characterized by deafness and dystopia conformis, is inherited in an autosomal dominant manner with a high penetrance (95%); a considerable degree of variability exists in phenotypic expression, along with evidence of genetic heterogeneity. The highest LOD score (6.31) has been detected with a marker for placental alkaline phosphatase (ALPP) at a recombination distance of 0.7, which places the WSI gene in the region 2q35–q37. However, no evidence was shown for linkage with other markers in the same region. The gene for fibronectin (FNI) maps about 11.6 cM distal of ALPP and shows no linkage in WSI families.

The biggest challenge in mapping the WSI locus is genetic heterogeneity and the lack of highly informative marker loci in the region. In an estimated 45% of the families studied, WSI was linked to the ALPP locus, and plans are under way to saturate this region with new polymorphic markers.

(see *Chromosome 2*, p. 12)

A more detailed report of the First International Workshop on Chromosome 2 will be published in the April issue of *Cytogenetics and Cell Genetics*.

### Attendees Identify Markers for Haplotyping

## Meeting Reports

**Human  
Genome**  
news



National Center  
for Human  
Genome Research

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

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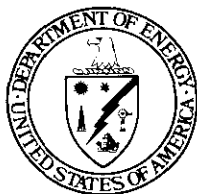
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## Moscow Workshop on Sequencing by Hybridization

A workshop on Sequencing by Hybridization (SBH) was held on November 19–20, 1991, at the Englehardt Institute of Molecular Biology in Moscow. Organized by the Human Genome Organization, the workshop was sponsored by DOE, the Wellcome Trust, and the Human Genome Project of the former U.S.S.R. The 44 participants, who came from the U.S.S.R., the United States, the United Kingdom, and Sweden, represented government and university research laboratories and several large and small companies.

The meeting was planned by Charles Cantor (Lawrence Berkeley Laboratory), Edwin Southern (Oxford University), and Andre Mirzabekov (Englehardt Institute of Molecular Biology).

SBH, developed independently by several research teams, is a set of related technologies that potentially could determine DNA sequence 100 or more times faster than now possible. Two formats are being developed for SBH:

1. A single oligonucleotide probe is used to examine an array of sample DNAs immobilized on a surface.

2. A single sample is hybridized to an immobilized matrix of oligonucleotides of overlapping sequence (a "chip"). If a chip for sequencing hundreds of thousands of nucleotides can be made inexpensively and if the sequencing procedure can be automated, the sequencing rate using SBH could approach millions of bases per day.

Meeting participants generally agreed that one or both SBH formats could develop into a useful sequencing tool in the near future, that appropriate combinations of conventional gel sequencing and SBH can be more efficient for genome sequencing than any one method, and that Format 1 can probably be implemented immediately.

The major obstacle to using SBH for sequencing is the lack of a full description of any sequence-dependent anomalies in short oligonucleotide interactions. Overcoming this obstacle will require parallel studies to generate large volumes of data. Such studies might simultaneously determine optimums for factors such as the surface to which samples are attached, the

(see SBH, p. 13)

## Chromosome 2 (from p. 11)

**Other Disease Loci.** Pieter Reitsma (University Hospital, Leiden, Netherlands) described the role of PROC in the coagulation pathway. Persons deficient in PROC (homozygotes) are prone to thrombus at birth while heterozygotes are at increased risk in their 30s and 40s. Alterations seen in the PROC gene include missense substitutions, splicing defects, and deletions up to 18 bp in length.

Max Muenke (Children's Hospital of Philadelphia) presented data on mapping the autosomal dominant disease holoprosencephaly, characterized by facial abnormalities and brain defects. Abnormalities have been seen on many chromosomes, including chromosome 2 deletions that overlap on the short arm at 2p21. Marker studies are under way to define the minimal specific-deletion region.

Fred Barr (Children's Hospital of Philadelphia) discussed the incidence of alveolar

rhabdomyosarcoma, which involves a (2:13) translocation with a breakpoint in 2q35. Studies will produce a pulsed-field map in this region using material from patients with deletions and translocations.

## Resources

A number of groups reported progress in preparing panels of hybrids carrying portions of chromosome 2, including irradiation, translocation, and deletion hybrids. By the next meeting, lists of hybrids should be available as a resource to anyone interested in chromosome 2 mapping.

A second workshop, to be held in San Francisco prior to the meeting of the American Society of Human Genetics in November, will be organized by Nigel Spurr [Imperial Cancer Research Fund (ICRF), England] and Susan Naylor (University of Texas Health Science Center, San Antonio). ♦

Reported by Nigel Spurr  
ICRF

## Meeting Reports

**SBH** (from p. 12)

way the sample is immobilized, kinds of samples, hybridization conditions, and the manner in which hybridization is detected.

Potential ambiguities in SBH require that data-analysis algorithms produce statistical estimates of the likelihood that particular sequences are consistent with available data. Work with SBH technologies may actually put such data-analysis tools in place before they are required for more conventional DNA sequencing.

Due to the expense of synthesizing numerous oligomers, the initial cost of full-scale SBH implementation will be a high percentage of expected overall costs. Participants felt that international collaboration would greatly benefit the field and recommended long-term cooperation in sharing raw data and software, facilitating scientific exchange visits, and establishing an annual workshop to assess progress and advance technology. As work proceeds, sharing of oligonucleotide samples and arrays should help to reduce cost and effort and facilitate comparisons of the efficacy of various SBH implementations. Careful integration and continual assessment of SBH development during this expensive early stage are important.

All potential uses of SBH may not be fully envisioned yet, but its value in sequence comparisons and clinical diagnostics seems clear. Funding parallel efforts in the many aspects of SBH now, and coalescing successful developments into a more unified approach later, would avoid costly premature specialization.

**Meeting Highlights**

Hans Lehrach (Imperial Cancer Research Fund, London) presented a mapping strategy for linkup of cosmids through oligonucleotide fingerprint matching. He announced that ordering of the *Schizosaccharomyces pombe* genome in cosmids is imminent; the major role of oligonucleotide hybridization in this inquiry was emphasized.

In a pilot test with several related but unknown sequences, Radomir Crkvenjakov and Radoje Drmanac (Argonne National Laboratory) demonstrated that SBH can produce correct DNA sequence de novo. No wrong bases were called in 343 bp of hybridization-determined sequence.

Drmanac and Crkvenjakov (using Format 1) and Mirzabekov (using Format 2 in a gel)

demonstrated the ability to distinguish between the hybridization of very short oligonucleotides to the complementary sequences and the hybridization of mismatched sequences or nonspecific binding to physical supports.

Drmanac presented results on the development of a hybridization data production line based on M13 clone libraries; 13,824 dots were made on an 8- by 12-cm filter by off-set printing of samples from 144 microtiter plates. Parallel clone growth and robotic spotting on filters in dense arrays will allow collection of up to 10 million clone-probe scores per day.

Southern described his laboratory's production of DNA probe arrays by an on-chip strategy that yields a complete array of 4<sup>s</sup> s-mers in s cycles (e.g., 65,536 octamers in 8 cycles). The Oxford group has made arrays of 4096 oligonucleotides on plates 20 by 20 cm.

Stephen Fodor described the approach being pursued by Affymax Research Corp., which uses addressable laser-activated photodeprotection in the chemical synthesis of oligonucleotides (or peptides) directly on a glass surface. Affymax scientists have recently developed new phosphoramidite derivatives capable of highly efficient light-activated detritylation and will now be evaluating these reagents for producing miniaturized DNA chips, including an octamer chip within a 1-square-in. area.

The Moscow group led by Mirzabekov is developing novel technologies for commercial production of sequencing chips that contain tens of immobilized oligonucleotides. They expect to produce chips with hundreds of oligonucleotides soon. Modified micro-electronic technologies should make possible the production of thousands of chips containing hundreds of thousands of immobilized oligonucleotides costing \$1.50 each.

Participants agreed on the need to explore the relative merits of hybridization detection by radioisotope decay, fluorescence, dielectric properties, and mass spectrometry.

For SBH Format 2, a major difficulty to be overcome is the need for more-complex chips, normalized matrices to compensate for the different stabilities of A-T and G-C base pairs in DNA duplexes, and methods for producing DNA fragments of narrow size

(see SBH, p. 16)

Workshop organizers collaborated to report on the meeting:

- Charles Cantor  
Lawrence Berkeley  
Laboratory  
Principal Scientist  
of the DOE  
Human Genome  
Program
- Edwin Southern  
Oxford University
- Andre Mirzabekov  
Engelhardt Institute of Molecular  
Biology

The full report of this meeting will be published in *Genomics* later this year.

## Meeting Reports

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**Attendees  
Represent  
Diverse  
Disciplines**


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A volume containing the talks from this conference is being planned under the title *Justice and the Human Genome Initiative*. The manuscript is under review.

## Justice and the Human Genome

The University of Illinois College of Medicine at Chicago (UICM) and DOE sponsored the conference, Justice and the Human Genome, in Chicago on November 8 and 9, 1991. Gerald Moss (UICM) opened the meeting, which was held to discuss the just and equitable use of data generated by the Human Genome Project. Some 135 attendees came from a broad range of fields such as law, philosophy, medicine, medical history, hospital administration, nursing, biotechnology, and public television. Marc Lappé and Timothy Murphy (both of UICM) organized the conference.

### Meeting Highlights

Leroy Hood (California Institute of Technology) presented the scientific and historical overview of the Human Genome Project. He cited many advances expected from the project in basic science, biotechnology, and medical therapy, as well as challenges to social and institutional equity.

Daniel Kevles (California Institute of Technology), author of a noted history of eugenics, explained why he thought past abuses would not be paralleled in the use of forthcoming genomic characterizations. The democratic nature of social institutions and a better understanding of the limitations and abuses of genetic interventions should provide adequate safeguards, Kevles said.

Norman Daniels (Tufts University) offered an account and critique of actuarial practices underlying insurance availability and controlling access to U.S. health care. He addressed the important ethical question of how differences in human health should be treated, arguing that health interests must be protected in ways that are independent of genetic need.

Robert F. Murray, Jr. (Howard University) cautioned that genomic characterization of disease will not necessarily bring cures and that genetic "problems" often have moral and social foundations. That is, genetics may be expected to solve problems that result from social inequity rather than from individual genetic incapacity.

George Annas (Boston University) reviewed possible legal regulation of the uses of genomic data to protect the privacy that plays such an important role in American social and political history.

Arthur Caplan (University of Minnesota) discussed ways in which eugenic interests have worked against humanity and how the study of particular groups has sometimes led to disadvantages for them. Even if clear abuses can be avoided, he said, important problems will remain to be considered.

Lori Andrews (American Bar Foundation) discussed genomic information in relation to reproductive rights and ways in which problems arising from the use of such data will challenge the traditional distinction between public and private issues.

Robert Pokorski (North American Reassurance Company) identified challenges that availability of personal genetic data will pose for insurability and access to genomic information in the United States. He noted especially the tensions existing among for-profit ventures, as well as humanitarian concerns about providing adequate health care.

Kenneth Vaux (UICM) offered a theological perspective on the emergence of genomic study and was especially concerned about the way scientific studies could change current visions of human relationships and personal identity.

Leonard M. Fleck (Michigan State University) argued that certain considerations of justice warrant giving moral priority to the development of technologies that could be used to eliminate deleterious genes over the encouragement of other kinds of emerging lifesaving technologies.

Murphy (UICM) addressed ways in which the genome project might work against scientific novelty and moral pluralism. He cautioned against the use of genomic characterizations to reinforce or create new classes of human inferiority.

Closing the conference, Lappé spoke of the need to pay special attention to genetic susceptibility in formulating all public policy. He also raised for discussion the central question of how persons identified with genetic abnormalities will be accommodated through social policies directed at creating adaptive environments. ♦

*Reported by Timothy Murphy  
UICM*

## Fifth Mouse Genome Mapping Workshop

The growing focus on use of the mouse as an important tool for characterizing and mapping human disease genes was emphasized strongly at the Fifth Mouse Genome Mapping Workshop at Lunteren, Netherlands, in October 1991. Decades of genetic mapping in the mouse, allied with more-recent advances in molecular mapping, have provided a dense genetic map of the mouse genome, and concomitant expansion of the human genetic map has made possible the characterization of most linkage groups conserved between mouse and human genomes.

Human geneticists have unparalleled opportunities for identifying mouse mutants and candidate genes that may be homologous to human disease genes and for relating the mapping of candidate human gene sequences to mutant loci in the mouse. Identifying such homologies in the mouse provides an excellent vehicle for further studies of the genetics, pathophysiology, and potential therapy of human diseases with genetic components.

New mutations at mouse loci can be generated by several techniques—radiation, chemical mutagenesis, or gene targeting. Identification of deletion mutations is an aid to understanding the structure-function relationships at a particular locus and also to mapping in the region.

### The Genetic Map: New Tools, Cooperation Speed Mapping Efforts

#### Interspecific Backcrosses

The development of interspecific backcrosses as a genetic mapping tool was an important turning point in mapping the mouse genome. Interspecific backcrosses use two different mouse species as the parents: laboratory strains are crossed to the wild mouse species *Mus spretus*, and the F1 progeny are usually backcrossed to the laboratory strains. The divergence between parental strains in interspecific backcrosses allows every DNA marker to be mapped; gene order is determined by a simple haplotype analysis because the crosses are multipoint. (Multipoint means that individual progeny from the backcross are each analyzed with many DNA markers; the genetic analysis thus involves many points along the chromosome.) A number of genome-wide genetic maps developed using largely classical probe technology were presented at the meeting, demonstrating that

the density of mapped probes is rapidly approaching the target of 1 marker/cM. (See related article, p. 6.)

#### New Markers

Mouse and human geneticists are now using new tools for rapid production of genetic maps. In mouse, the most common dinucleotide repeat (CA)<sub>n</sub> is spaced on average every 18 kb. Markers such as microsatellites are highly variant (90%) in interspecific crosses and even in intraspecific crosses, where about half the markers vary between two different parental inbred strains.

Random amplified polymorphic DNA (RAPD), a new class of markers generated by polymerase chain reaction with short random ten-nucleotide oligomers, has been shown to be highly variable between species and laboratory strains and represents an additional large source of markers for genome mapping.

#### Cross Referencing the Maps

The full value of the detailed probe and microsatellite maps under construction will be realized only if the maps are cross referenced. For each chromosome, committees have already determined a number of reference loci (spaced at 10- to 20-cM intervals) to act as common anchor points for the various backcross mapping programs. Cross referencing will enable the better use of raw data in newly developed database software for compilation of mouse genetic maps.

#### Genome-Wide Mapping Efforts

The power of dense genetic maps of the mouse genome has been demonstrated recently by the localization of a number of new loci involved with disease, developments that have been accelerated by use of genome-wide maps of rapidly usable

⇒

### Use of Mouse as Tool for Mapping Human Genes Seen as Unparalleled Opportunity

#### International Mammalian Genome Society

Lunteren was the site of the inauguration of the International Mammalian Genome Society (IMGS) and the first meeting of its elected secretariat. IMGS will organize annual mapping workshops through a central office presently located in Buffalo, New York (Contact: Verne Chapman, Roswell Park Memorial Institute, 716/845-5840, Fax: 716/845-8169); help coordinate the activities of chromosome committees; advise on database developments; and foster relationships with the Human Genome Organization (HUGO) through the HUGO Mouse Genome Committee. ◇

## Meeting Reports

A full report from each mouse chromosome committee was recently published in a special issue of *Mammalian Genome* [Volume 1: S1-534 (1991)]. The report included a chromosome map, locus list, and reference loci assigned for each chromosome.

### Encyclopedia of the Mouse Genome

Version 1.0 of the database has been released and is available on disk from Jackson Laboratory. Contact:

- Janice Ormsby  
207/288-3371  
Fax: 207/288-5079

microsatellite loci. Analyzing backcross progeny from a cross using the nonobese diabetic (NOD) strain of mouse with microsatellite loci covering most of the mouse genome has identified new susceptibility loci on mouse chromosomes 1, 3, and 11 and defined the likely location of homologous loci in the human genome. This NOD strain has a disease that is similar to Type I diabetes in humans. Interestingly, the susceptibility gene on mouse chromosome 1 is linked to the Lsh locus, which is involved with susceptibility to bacterial and parasitic infections and, like Type I diabetes, could have a macrophage involvement. Similar genetic analyses in a rat cross segregating for hypertension have identified a major blood pressure gene on chromosome 10 close to the angiotensin-converting enzyme (ACE) gene.

### The Physical Map

#### High Regional Marker Density

Interspecific backcrosses have been used in several major studies to provide very detailed genetic maps in a number of defined regions of the mouse genome, in particular those harboring interesting mutations. In many cases, the backcross has included the mutation of interest to identify closely linked startpoints for physically mapping and characterizing the mutant gene.

These detailed regional maps often have a marker spacing of 1 cM or less (corresponding to 2 Mb or less) and allow linkup of adjacent markers through pulsed-field gel electrophoresis to provide physical maps of substantial megabase regions of the mouse genome. Each physical map provides a framework for establishing overlapping maps of yeast artificial chromosome (YAC) contigs that will supply access to all the underlying sequences. Whereas genome-wide approaches to YAC contig mapping probably have room for further development, the first major efforts are likely to be in regions already saturated with markers and where rudimentary physical maps are in place.

#### Mouse YAC Libraries

Access to mouse YAC libraries is a key issue for the development of the mouse and human genome programs. Isolating mouse YAC clones homologous to human disease genes is an important step in beginning the genetic and possible transgenic analysis in the mouse. Princeton University, Imperial Cancer Research Fund, and St. Mary's Hospital (London) have constructed partial *EcoR* I YAC libraries with the pYAC4 vector.

Embryonic YAC contigs have been constructed in several regions of the mouse genome, a process that will be greatly improved by techniques for rapidly identifying overlapping clones.

### Informatics

The mouse genome informatics program at Jackson Laboratory is developing a fundamental mouse genome database [Encyclopedia of the Mouse Genome (see side column)] and software tools for the analysis and display of mouse map information. At present the Mouse Genome Database includes the Genomic Database of the Mouse (GBASE), Homology Database (HMDP), and the Mouse Cytogenetic Database (MCD); GENEVIEW, a software package for a wide variety of map presentations, has been developed at the U.K. Medical Research Council Radiobiology Unit at Harwell. A proposed mouse gene mapping consortium including all the major centers working on genome-wide mapping would have a pivotal role in maintaining the Mouse Genome Database and integrating genome-wide map information. ◊

*Submitted by Steve Brown  
St. Mary's Hospital Medical School, London*

### SBH (from p. 13)

distribution to avoid formation of secondary structures that interfere with hybridization.

Highlights of the informatics section of the conference were new ideas for modeling hybridization, fragment reconstruction, and sequencing chip design. Development of efficient software to unify mathematical and heuristic solutions and optimize parameters in comprehensive simulation experiments in the megabase range is visualized as the next step in SBH informatics.

John Eider (Oxford University) presented a linear model for going from sequence to detected SBH signal using data from Southern's chip. This general model and the associated parameter-estimation techniques provide a solid basis for further development of the hybridization models.

In summary, meeting participants felt that the Moscow SBH workshop was unusually stimulating, and investigators left the meeting firmly committed to this technology. ◊



## For Your Information

**Informatics Resources****Distribution Information on Genomic Map Design**

Genomic Map Design (GMD) software programs for designing contig mapping experiments are now available. The three FORTRAN programs for generating the tables described in Fu et al.\* will be e-mailed on request; each is accompanied by a documentation file explaining the program's use. Requests may be made via the Internet address below.

- "arnold%gandal.dnet@server.uga.edu"

These programs also have been incorporated into a DNA sequence analysis package and can be accessed directly on the Biological Sequence/Structure Computational Facility (BS/SCF). Use the following address to request a BS/SCF guest account:

- "weise@gandal.dnet@server.uga.edu"

Questions about the programs may be directed to the author, Yun-Xin Fu:

- "fu%gsbs18.gs.uth.tmc.edu"

\*The theory on which GMD is based is described in Y.-X. Fu, W. E. Timberlake, and J. Arnold, "On the Design of Genome Mapping Experiments Using Short Synthetic Oligonucleotides," *Biometrics* (in press). The article may not appear until 1993. For a preprint, contact Jonathan Arnold; Genetics Department; University of Georgia; Athens, GA 30602; Internet: "arnold%gandal.dnet@server.uga.edu". Any published use of these programs should cite the above reference.

**EST Database**

A complete database report containing all available information on some 2500 human expressed sequence tags (ESTs) has been developed at the NIH National Institute of Neurological Disorders and Stroke. It is now accessible by anonymous file transfer protocol (ftp) from "briggs.ninds.nih.gov". Contained in the report are EST sequences, putative identifications, database search results, and available map positions, clone insert lengths, and GenBank® and Genome Data Base accession numbers. The report also lists American *Type Culture* Collection catalog numbers for the ESTs reported in Adams et al., *Science* 252, 1651 (1991) and Adams et al., *Nature* 355, 632 (1992). [Contact: Anthony Kerlavage, 301/496-8800, Internet: "arkerlav@briggs.ninds.nih.gov".] ◇

**ADDRESS CORRECTION****Genetics-Related Support Groups**

Alliance of Genetic Support Groups  
1001 22nd Street, NW, #800  
Washington, DC 20013-1133  
800/336-4794

**U.S. Genome Research Funding Guidelines**

Note: Investigators wishing to apply for NIH funding are urged to discuss their projects with agency staff before submitting formal proposals. DOE requires no prior discussion on preproposals.

**NIH National Center for Human Genome Research (NCHGR)**

Application receipt dates:

- R01, P01, R21, R29, P30, P50, K01,\* and R13 grants – February 1, June 1, and October 1.
- Individual postdoctoral fellowships and institutional training grants – January 10, May 10, and September 10.
- Small Business Innovation Research Grants (SBIR: firms with 500 or fewer employees) – April 15, August 15, and December 15.
- Research supplements for underrepresented minorities – applications are accepted on a continuing basis.
- Requests for Applications (RFAs) – receipt dates are independent of the above dates. Notices will appear in HGN and other publications.

\*Expedited review possible. Check with NCHGR staff during application development phases.

Program announcements are listed in the weekly **NIH Guide for Grants and Contracts**,\* which is available by

- Hard-copy subscription – call 301/496-7441.
- Remote login via modem to NIH Grant Line – call John James, 301/496-7554.
- Listserver computer network subscription – call Dottie Baker, 919/966-5625; BITNET: "pjones@uncvxl.bitnet" or Internet: "jones@samba.acs.unc.edu".

\*Expanded statements of RFAs listed in the NIH grants guide may be obtained from either of the two electronic sources or from NIH NCHGR in Bethesda, Maryland (301/496-0844).

**DOE Human Genome Program**

Solicitations for proposals will be announced in early spring issues of the **Federal Register** and **Science** and in other publications. Formal proposals will be due in August.

For further information, contact the program office via

- 301/903-5037 or FTS 233-5037; Fax: 301/903-5051 or FTS Fax: 233-5051; or Internet: "drell@mailgw.er.doe.gov".

**SBIR Grants.** DOE also invites small business firms to submit grant applications addressing the human genome topic of SBIR programs, which are designed to strengthen innovative firms in areas of research and development and to contribute to the growth and strength of the nation's economy. The human genome topic emphasizes instrumentation development for automated clone processing, improvements in DNA sequencing technologies, and enhanced sequence data storage and processing capabilities. Next submission date: fall 1992. For more information, contact

- Samuel Barish; SBIR Program Manager, ER-16; DOE; Washington, DC 20585; 301/903-5707.

**Human Genome Distinguished Postdoctoral Fellowships**

Next deadline: February 1, 1993. For further information, see HGN 3(3), 5 (September 1991) or contact

- Oak Ridge Associated Universities: 615/576-4805. ◇

**Funding for Technology Development****■ PA-92-50**

NCHGR invites applications to support research that will significantly advance Human Genome Project progress in technology development, mapping, DNA sequencing, and informatics. Eligible are universities, medical colleges, hospitals, and other public, private, and for-profit research institutions, including state and local government units. Foreign organizations also are eligible for the research project grants (R01). Besides R01, support for this program will be through pilot projects and feasibility studies (R21), program project grants (P01), and FIRST Awards (R29). Application Receipt Dates: February 1, June 1, and October 1.

- **Contacts:** Mapping Applications, Bettie Graham; Sequencing and Technology Development, Robert Strausberg; Informatics, David Benton; Grants Policy, Alice Thomas. [NCHGR; Building 38A, Sixth Floor; Bethesda, MD 20892; 301/496-7531.] ◇

## Calendar of Genome Events\*

### March .....

30–31. **Human Health Care in the New Genetic Age—Great Promise, Serious Dilemmas**; Columbia, SC [A. Smith, 803/779-4928, Fax: 1765-7756]

### April .....

3–10. **Keystone Symposia Meeting: Molecular Biology of Human Genetic Disease**; Copper Mountain, CO [Keystone Symposia, 303/262-1230, Fax: -1525]

4–5. **Chromosome X Workshop**; Amalfi, Italy [D. Toniolo, (Int.) 39/382-527967, Fax: -422286]

13–15. **Second European HUGO Conference: Human Genome Diversity**; Alghero, Sardinia [HUGO, Tel. & Fax: (Int.) 39/6-324-4340]

16. **NCHGR Lecture Series: Genome Mapping and Functional Organization of the Interphase Nucleus**; Bethesda, MD [C. Dahl, 301/402-0838]

20–21. **Third International Workshop on Chromosome 21**; Baltimore, MD [S. Antonarakis, 301/955-7872, Fax: -0484]

21. **Joint NIH-DOE ELSI Working Group Meeting** [E. Langfelder, 301/402-0911, Fax: 1480-2770]

27–28. **Tenth Annual Biotechnology Patent Conference**; Washington, DC [ATCC, 301/881-2600, Fax: 1231-5826]

27–29. **Third European Workshop on Cytogenetics and Molecular Genetics of Human Solid Tumors**; Porto, Portugal [S. Castedo, (Int.) 351/2-497-833, Fax: -410-3940]

### May .....

6–10. **\*Genome Mapping and Sequencing Workshop**; Cold Spring Harbor, NY

12–13. **Second International Workshop on Chromosome 5**; Chicago, IL [W. Neuman, 312/702-6201, Fax: -3163]

12–15. **UNESCO North-South Human Genome Conference**; Caxambu, Brazil [S. Pena, (Int.) 55/31-227-3496, Fax: -3792]

14–16. **Second Nordic Genome Workshop**; Oslo, Norway [H. Prydz, (Int.) 47/2-958-754, Fax: -694-130]

18. **\*National Advisory Council for Human Genome Research**; Bethesda, MD [J. Ades, 301/402-2205, Fax: -2218]

21. **NCHGR Lecture Series: Consequence of the Human Genome Project for the Future of Medicine**; Bethesda, MD [see contact: April 16]

27–31. **24th Annual Meeting of European Society of Human Genetics (ESHG)**; Elsinore, Denmark [ESHG, (Int.) 45/42-45-22-28, Fax: 45/43-43-11-30]

### June .....

4–7. **Second International Conference on Bioinformatics, Supercomputing, and Complex Genome Analysis**; St. Petersburg Beach, FL [H. Lim, 904/644-7046, Internet: "genome@scri.fsu.edu"]

7–9. **First International Workshop on Chromosome 6**; Ann Arbor, MI [J. Trent, 313/764-4509, Fax: -4534, A. Ziegler, (Int.) 49/30-30-35-2617, Fax: -3778]

12–14. **Second Chromosome 4 Workshop**; Leiden, The Netherlands [G. van Ommen, (Int.) 31/71-276293, Fax: -276075]

18–19. **Chromosome 15 Workshop**; Tucson, AZ [T. Donlon, 415/723-4923, Fax: -3147]

20–25. **1992 World Congress on Cell and Tissue Culture**; Tissue Culture Assoc., Washington, DC [P. Reinsfelder, 301/992-0948, Fax: -0949]

22–24. **Annual Meeting of the Electrophoresis Society**; Barr Enterprises, Research Triangle Park, NC [J. Cunningham, 301/898-3772, Fax: -5596]

### July .....

19–Aug. 2. **\*Second International Workshop: Open Problems in Computational Molecular Biology**; Telluride, CO [A. Konopka, 301/846-5396, E-mail: "konopka@jcrfv1.ncifcrf.gov"]

20–21. **First International Workshop on Chromosome 18**; Chicago, IL [M. LeBeau, 312/702-0795, Fax: -3163]

21–25. **Science Innovation '92: New Techniques and Instruments in Biomedical Research**; San Francisco, CA [Am. Assoc. for the Advancement of Sci. (AAAS), 202/326-6450, Fax: 1289-4021]

### August .....

16–21. **Ninth International Biotechnology Symposium & Exhibit**; Crystal City, VA (poster deadline: Mar. 31) [Am. Chem. Soc. (ACS), 202/872-6286, Fax: -6128]

18–23. **Molecular Genetics of Bacteria & Phages**; Cold Spring Harbor, NY [Cold Spring Harbor Laboratory (CSHL), 516/367-8346, Fax: -8845]

26–30. **Mouse Molecular Genetics**; CSHL, Cold Spring Harbor, NY [see contact: Aug. 18–23]

### September .....

2–6. **Cancer Cells: Genetics & Molecular Biology of Breast Cancer**; CSHL, Cold Spring Harbor, NY [see contact: Aug. 18–23]

13–15. **Third International Workshop on Human Chromosome 11**; San Diego, CA [G. Evans, 619/453-4100, ext. 279, Fax: 1558-9513]

17–20. **Third International Chromosome 22 Workshop**; Philadelphia, PA [B. Emanuel, 215/590-3856, Fax: -3764]

18. **\*National Advisory Council for Human Genome Research**; Bethesda, MD [see contact: May 18]

18–20. **Chromosome 12 Gene Mapping Workshop**; Oxford, England [I. Craig, (Int.) 44/865-275-327, Fax: -318]

20–23. **Chromosome 13 Workshop**; New York, NY [A. Bowcock, 214/688-3896, Fax: -8617]

22–26. **Gene Therapy**; CSHL, Cold Spring Harbor, NY [see contact: Aug. 18–23]

26–29. **Genome Sequencing and Analysis IV**; Hilton Head, SC [S. Wallace, 301/480-0634, Fax: -8588]

### October .....

7–9. **"The Impact of Molecular Medicine on Clinical Practice"** at the Anglo-American Conference; London [W. O'Reilly, 212/371-1150, Fax: -1151]

11–15. **Sixth International Mouse Genome Conference**; Buffalo, NY [V. Chapman, 716/845-5840, Fax: -8169]

15–18. **Human Genome '92**; Nice, France [AAAS, 202/326-6450, Fax: 1289-4021]

17–21. **First International Conference on Mathematical and Computational Analysis of the Human Genome and Its Mutation Load**; Szeged, Hungary [Human Genome Research, Ltd., (Int.) 36/62-23855, Fax: -23844]

### November .....

6–8. **NSGC 11th Annual Education Conference—Human Genome Project: Impact, Implications, and Issues**; San Francisco, CA (submission of papers deadline: May 29) [B. Leopold, 215/872-7608, Fax: -1192]

\*Attendance at meetings listed with asterisk is either limited or restricted. Dates may change; check with contact person.

## Training Calendar: Workshops and Coursework\*

### April.....

2-16. †Cloning & Analysis of Large DNA Molecules; Cold Spring Harbor, NY [CSHL, 516/367-8343, Fax: -8845]

6-9. PCR Methodology; Exon-Intron, Inc., Columbia, MD (also offered Sept. 14-17) [Workshop Coordinator, 410/730-3984, Fax: -3983]

6-11. cDNA Library Techniques; Life Technologies, Inc. (LTI), Germantown, MD (also offered at later dates) [L. Kerwin, 301/921-2250, Fax: 1258-8212]

23-24. Molecular Cytogenetics: Chromosome In Situ; Gaithersburg, MD (also offered at later dates) [Oncor, Inc. 301/963-3500, Fax: 1926-6129]

27-May 1. Recombinant DNA Techniques I; LTI, Germantown, MD (also offered at later dates) [see contact: April 6-9]

### May.....

3-5. GDB/OMIM Training Course; see schedule, p. 9.

4-9. Recombinant DNA Techniques II; LTI, Germantown, MD (also offered at later dates) [see contact: April 6-11]

11-13. PCR Techniques; Center for Advanced Training in Cell and Molecular Biology/Catholic Univ. of Am. (CATCMB/CUA), Washington, DC (also offered Oct. 12-14 in Lake Tahoe, NV) [Office Manager, 202/319-6161, Fax: -5721]

13. Introduction to PCR; Biotechnol. Training Programs (BTP), Durham, NC (also offered at other dates/locations) [S. Chance, 515/232-8306]

13-16. DNA Sequencing; CATCMB/CUA, Washington, DC [see contact: May 11-13]

15-16. DNA Databanks and Repositories; Bethesda, MD [K. Weedn, 202/576-2482, Fax: -0373]

18-20. Cloning and Hybridization Analysis of PCR Products; BTP, Durham, NC (also offered at other dates/locations) [see contact: May 13]

18-22. Recombinant DNA Methodology; CATCMB/CUA, Washington, DC (also offered May 26-30) [see contact: May 11-13]

19-22. †Introductory Linkage Course; New York, NY [K. Montague, 212/960-2507, Fax: 1568-2750]

20-21. Advanced IG Suite; Intelli-Genetics (IG), Mountain View, CA [N. Robinson, 415/962-7300, Fax: -7302]

27. In Situ Hybridization and Advanced Microscopy Workshop at the ESHG 24th Annual Meeting; Elsinore, Denmark [ESHG, (Int.) 45/42-45-22-28, Fax: 45/43-43-11-30]

### June.....

1-5. YACs and Phage Vectors in Large DNA Analysis; CATCMB/CUA, Washington, DC [see contact: May 11-13]

5-25. Advanced Bacterial Genetics; CSHL, Cold Spring Harbor, NY (application deadline: Mar. 15) [see contact: April 2-16]

15-19. Current Techniques for Plant Biotechnology; CATCMB/CUA, Washington, DC [see contact: May 11-13]

15-19. †Ethics and the Human Genome Project; Seattle, WA (application deadline: Mar. 15) [B. Brownfield, 206/543-5447]

15-19. Recombinant DNA and Cytogenetic Approaches for the Study of Genetic Disease and Gene Mapping; CATCMB/CUA, Washington, DC [see contact: May 11-13]

15-19. Recombinant DNA Methodology; Exon-Intron, Inc. (also offered at later dates) Columbia, MD [see contact: April 6-9]

15-25. Principles of Flow Cytometry; BTP, Colorado Springs, CO [see contact: May 13]

15-29. Advanced *Drosophila* Genetics; CSHL, Cold Spring Harbor, NY (application deadline: Mar. 15) [see contact: April 2-16]

22-26. Advanced Topics in Recombinant DNA; Exon-Intron, Inc., Columbia, MD (also offered July 20-24) [see contact: April 6-9]

22-26. Expression of Recombinant DNA in Mammalian Cells; CATCMB/CUA, Washington, DC [see contact: May 11-13]

29-July 19. Molecular Cloning of Neural Genes; CSHL, Cold Spring Harbor, NY (application deadline: Mar. 15) [see contact: April 2-16]

### July.....

9-18. Gene Targeting & Homologous Recombination; London [P. Faik, (Int.) 44/71-403-6998, Fax: -407-5281]

13-Aug. 1. Genome Technology; Salt Lake City, UT [R. Gesteland, 801/581-5190, Fax: 1585-3910]

20-31. Short Course in Medical & Experimental Mammalian Genetics; Bar Harbor, ME [Jackson Laboratory, 207/288-3371, ext. 1253]

21-Aug. 10. Advanced Molecular Cloning & Expression of Eukaryotic Genes; CSHL, Cold Spring Harbor, NY (application deadline: Mar. 15) [see contact: April 2-16]

21-Aug. 10. Yeast Genetics; CSHL, Cold Spring Harbor, NY (application deadline: Mar. 15) [see contact: April 2-16]

26-Aug. 14. †Societal Institute of the Mathematical Sciences Tutorial: Mathematical Sciences in Genomic Analysis; New Brunswick, NJ [D. Thomsen, 203/966-1008, Fax: 1972-6069]

31-Aug. 8. DNA Related Methods in Human Genetics: YAC Cloning in Genome Analysis; London [see contact: July 9-18]

### August.....

2-14. Molecular Evolution; Marine Biological Laboratory, Woods Hole, MA [F. Dwane, 508/548-3705, ext. 216]

10-14. RNA Isolation and Characterization; Exon-Intron, Inc., Columbia, MD [see contact: April 6-9]

17-18. PC/GENE; IG, Mountain View, CA [see contact: May 20-21]

19-20. GeneWorks; IG, Mountain View, CA [see contact: May 20-21]

24-27. †Partnerships in Teaching Biotechnology: Human Genome Technology Workshop; Ann Arbor, MI (also offered Aug. 28-29) [P. Gregory, 313/764-8050, Fax: -4133]

24-28. Advanced Recombinant DNA Methodology; ATCC, Rockville, MD [ATCC Workshop Manager, 301/231-5566, Fax: 1770-1805]

### October.....

8-21. Analysis & Genetic Manipulation of YACs; CSHL, Cold Spring Harbor, NY [see contact: April 2-16]

12-14. PCR Techniques; CATCMB/CUA, Lake Tahoe, NV [see contact: May 11-13]

26-Nov. 4. †Essential Computational Genomics for Biologists; CSHL, Cold Spring Harbor, NY [T. Marr, 516/367-8393, Fax: -8389]

\*Dates and course status may change, and courses may be offered at other times and places; check with contact person.

†NCHGR-funded event.

