Human Genome news

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

ISSN: 1050-6101

Vol. 4, No. 5, January 1993

BNL Researchers Achieve Sequencing Advance

Hexamer Strings Facilitate Primer Walking for DNA Sequencing

Researchers at the Brookhaven National Laboratory (BNL) recently announced a major advance in the primer walking approach to DNA sequencing. They found that saturating a DNA template with a single-stranded binding (SSB) protein allows strings of hexamers (pieces of DNA that are six nucleotides long) to cooperate in priming DNA synthesis. The discovery, reported in the December 11, 1992, issue of *Science* by Jan Kieleczawa, John J. Dunn, and F. William Studier, promises to accelerate sequencing tenfold while dramatically decreasing costs.

David Galas, Associate Director of the DOE Office of Health and Environmental Research, says the process should enable scientists to fully automate sequencing and "may be the key to gaining the capability needed to fully sequence the human genome and the genomes of other organisms."

"Walking" Down a Template Chain

In enzymatic sequencing by primer walking, a short, known DNA sequence is used with the enzyme DNA polymerase to "prime" or trigger the synthesis of a new DNA strand complementary to a template of unknown sequence. The sequence of about 500 bases on the new chain can be determined with standard gel electrophoresis methods, and a short stretch at the end of the newly determined sequence is then used to design another primer to extend or "walk" down the next 500 bases. Successive primers selected in this way are used to determine an entire unknown DNA sequence.

The authors believe primer walking is the best strategy for sequencing cosmids (clones containing about 40,000 bp of DNA). The preparation of only one DNA sample is needed to sequence an entire cosmid, without the need for subcloning or multiple template preparation. Primer walking offers low redundancy and high accuracy, and sequence assembly is straightforward. Sequencing of problem areas is facilitated by the freedom to select almost any site for priming.

DOE, NIH Guidelines for Sharing Data, Resources Given on p. 4

In This Issue. . .

Genome News

Different Hexamer Combinations Should Allow Selective Priming

The independent discovery by Levy Ulanovsky's team (Weizman Institute, Israel) of conditions suitable for primer walking with short oligomers will be described in *Proceedings of the National Academy of Sciences*.

Conventional primer-walking strategies are slow and expensive; a single primer (usually 15 to 20 bases long) can take up to 2 days to prepare and costs about $50. BNL researchers set out to improve the strategy and reduce the cost. The idea was to use shorter, reusable ("generic") primers that could be stored in a library rather than having to synthesize a new primer for each use.

For sequencing, primers must be long enough to pair at only one place in the template DNA; if more than one site is primed, the reactions interfere with each other and no sequence can be read. A typical 18-base primer would pair only once in 69 billion bases of random sequence, so the researchers reasoned that much shorter primers could be useful in sequencing a template such as a cosmid. Different combinations of short primers might also be used to construct longer, more-specific ones.

Selective Priming

While exploring this approach, the investigators discovered that coating the template DNA with SSB protein from *Escherichia coli* allows highly selective priming by combinations of three or four hexamers. One hexamer would normally prime at many sites on a cosmid template, making sequence impossible to read. The researchers found that adding SSB prevents individual hexamers from priming but stimulates the combinations to prime if they can pair at adjacent sites on the template. Use of appropriate hexamer strings should allow selective priming at almost any unique stretch of 18 nucleotides in a cosmid DNA. Over 500 hexamers and more than 300 hexamer combinations have been tried, with 60 to 90% of the combinations giving readable sequence.

When the DNA is saturated with SSB (about 2.5 µg SSB/1 µg DNA), very strong priming by the 3′ hexamer is obtained. Temperature is critical, with 0°C being optimal; at higher temperatures priming becomes much less efficient. The process works on cosmid DNAs, denatured double-stranded DNA, and polymerase chain reaction products.

Primer Library

A complete library of all 4096 possible hexamers could supply the primers needed to sequence the human genome at less than $0.01 per sequencing reaction, the authors noted. Synthesized on a micromole scale, each hexamer preparation could prime thousands of reactions, and libraries of primers could be distributed at reasonable cost.

The BNL laboratory has purchased an entire hexamer library, which investigators are using to explore the limits of the method and to look for rules for selection of the hexamer strings most likely to prime well. The researchers are now using the material to sequence the genome of a virus containing about 40,000 bp and are planning to sequence the 1-Mb genome of the bacterium that causes Lyme disease.

Automating the Process

If primer walking with hexamer strings proves to be reliable and efficient, the entire sequencing process could be automated. From an array of hexamers, templates, and reagents, robots could assemble sequencing reactions and load the products onto gels. Sequence information could flow directly into a computer, perhaps through fluorescent detection.

A computer could assemble the emerging sequence of each template, select the string of hexamers needed for each step of primer walking, and even select primers for resolving ambiguous or difficult regions of the sequence. The goal is to obtain large amounts of accurate sequence data with little need for skilled human intervention.

To eliminate the electrophoresis bottleneck, the investigators envision an instrument using an array of 100 capillary gels to produce more than 100,000 bp of finished sequence per day.

The success of the method will depend on how efficiently and reliably hexamer strings can prime sequencing reactions on a wide variety of templates. If the method works as well as initial results suggest, it should provide a big boost to genome sequencing.◊

Reported by Denise Casey
HGMIS, Oak Ridge National Laboratory

Chromosome Maps Chosen Runner-Up *Science* Molecule of the Year

Chromosome maps were the first runner-up to nitric oxide in the *Science* competition for 1992 Molecule of the Year [see *Science* **256**, 1862–65 (December 18, 1992)]. To be eligible, a scientific advance must have earned a place in scientific history in a particular year. The article cited 1992 as a landmark year for the Human Genome Project because scientists completed high-resolution physical maps for two human chromosomes, as well as two separate genetic linkage maps of the whole genome. The article also reported that the goal of mapping the entire human genome by 1995 is now clearly within reach.◊

Genome News

DNA Chip Promises Faster Sequencing

International Cooperation Among Industry, Academia, National Laboratories Leads to New Sequencing Technology Development

The NIH National Center for Human Genome Research has awarded 3-year, $2-million grants to the Houston Advanced Research Center (HARC) in Houston, Texas, and the Affymax Research Institute in Palo Alto, California, to develop sequencing by hybridization (SBH) technologies. These technologies, which have the potential to increase DNA sequencing rates 100 or more times, are based on the identification of target sequences by their complementary binding to oligonucleotide probes on an immobilized matrix, called a chip.

HARC, an independent, nonprofit research organization fostering scientific and technological research and emphasizing technology transfer, will oversee the design, fabrication, and testing of chips ("genosensors"). Affymax will apply VLSIPS™ (very large scale immobilized polymer synthesis) chip technology to DNA sequencing. Kenneth Beattie heads the multidisciplinary HARC team that also includes Mitchell Eggers, chemists from the Baylor College of Medicine Center for Biotechnology led by Michael Hogan, and a microfabrication team led by Daniel Ehrlich at the Massachusetts Institute of Technology. The Affymax group, led by Stephen Fodor, includes Robert Lipshutz (Wagner Associates), Ronald Davis (Stanford University School of Medicine), and Pavel Pevzner (Pennsylvania State University).

SBH Principles and Challenges

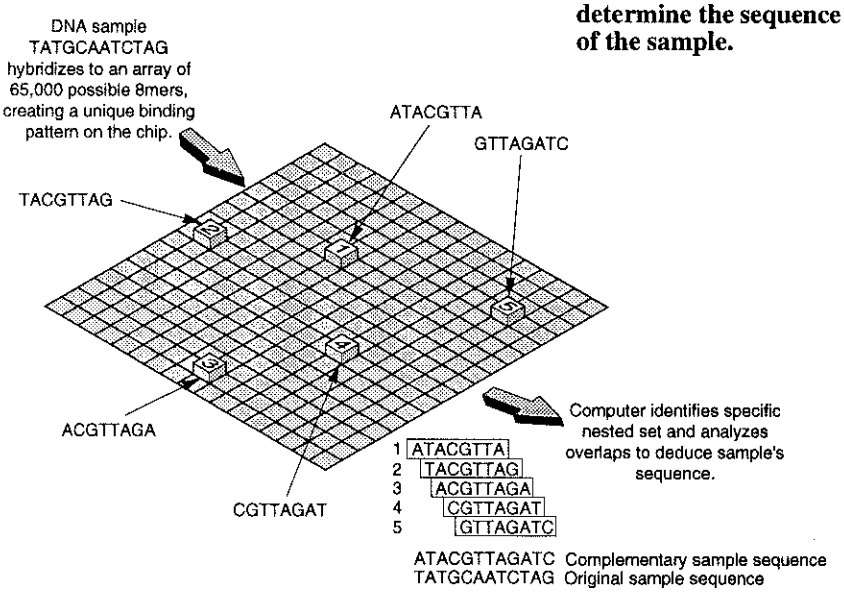
The SBH concept was independently conceived 4 to 5 years ago by several European scientists—Radomir Crkvenjakov and Radoje Drmanac in Belgrade, Yugoslavia (now at Argonne National Laboratory), Edwin Southern and William Baines in the United Kingdom, and the group headed by Andrei Mirzabekov at Englehardt Institute in Moscow. In principle, hybridization of a target sequence with a complete set of all probes of a given length [e.g., all 65,536 (4^8) octamers] can reveal the complete oligonucleotide content of the DNA sample; this information is input to computational algorithms that output extended DNA sequence. Each chip is expected to contain thousands to millions of individual synthetic DNA probes arranged in a grid-like pattern and miniaturized to the size of a dime.

Both DOE and NIH have invested in this emerging method, which is gaining widespread recognition for its potential use in genetic analysis, especially in sequence comparisons (diagnostics and polymorphic marker analysis). SBH technology involves many technical challenges, among them multiple occurrences of probe sequences within the target, promotion of highly accurate hybridization over a wide range of base compositions, preparation of miniaturized DNA arrays, sensitive detection of hybridization, computer processing of hybridization data, and automated manipulation of numerous DNA samples.

HARC Strategies

The developmental grant to HARC supports work in four project components:

- attachment of oligonucleotide probes to surfaces via a variety of linker arms;
- detection of hybridization by permittivity measurements within microfabricated sample wells containing microelectrodes and surface-bound probes (capture of long target strands by the short surface-bound probes elicits a change in the electrical properties within a sample well);
- development of initial SBH applications for genome mapping; and



Human Genome News 3(6), 12–13, 16 (March 1992) included a report on the international SBH workshop held in Moscow in November 1991. The next SBH international workshop is tentatively scheduled for October of this year. [Contact: Kenneth Beattie; HARC; The Woodlands, Tx 77381 (713/363-7947, Fax: -7914, Internet: *beattie@star.harc.edu*).]

The DNA sequencing "chip" is a solid substrate comprising an array of many short DNA pieces (in this example octamers) having known, overlapping sequences. A longer sample DNA of unknown sequence will bind (A to T, C to G) to chip octamers that have sequences complementary to particular 8-base segments on the sample. The specific binding pattern can be read by a computer, and the resulting nested octamer set is used to determine the sequence of the sample.

Genome News

Computational Tools To Be Developed

- establishment of a program to make SBH broadly available within the research community through a variety of methods, including an electronic information network.

The team will develop means for microrobotic placement of oligonucleotides to form a miniaturized chip and develop computational tools for analyzing hybridization data.

HARC has initiated collaborations with research groups led by Robert Foote and Bruce Jacobson (Oak Ridge National Laboratory) and Mirzabekov. HARC's collaboration with Mirzabekov's group is being supported by a grant from the International Genome Research Collaborative Program sponsored by NCHGR.

Affymax Strategies

Long-term research goals at Affymax are (1) construction of spatially defined arrays of oligonucleotide probes by applying newly developed techniques in light-directed polymer synthesis to oligonucleotides and (2) assessment of the feasibility of using these arrays in SBH. This effort requires the three developments described below.

An efficient, low-cost strategy for generating large arrays of oligonucleotides using photolithographic techniques and solid-phase chemical synthesis. Initially developed at Affymax to synthesize peptides on a glass surface for protein recognition, this approach substitutes a photoremovable protecting group for the standard acid-labile dimethoxytrityl groups at the 5'-hydroxyl coupling site in standard phosphoramidite synthesis. This allows integration of photolithography, miniaturization, and combinatorial synthesis methods into the solid-phase synthesis cycle.

A detection technology capable of assaying hybridization of target molecules to surface-bound oligonucleotides. Affymax researchers hope to achieve this goal by tagging target DNA with fluorescent reporter groups and then reading the array with epifluorescence microscopy. This approach will allow assessment of hybridization kinetics, identification of the hybrid on the array, and real-time analysis of target DNA–oligomer disassociation behavior.

Algorithms to interpret the results of hybridization experiments. Affymax will attempt to develop efficient applications for sequencing, sequence checking, physical mapping, functional mapping, homology search, and the detection of introns and exons.

Affymax is also funded as a Small Business Innovation Research project in the DOE Human Genome Program.◊

Reported by Denise Casey
HGMIS, Oak Ridge National Laboratory

NIH, DOE Guidelines Encourage Sharing of Data, Resources

At its December 7, 1992, meeting, the DOE-NIH Joint Subcommittee on the Human Genome approved the following sharing guidelines, developed from the DOE draft of September 1991.

The information and resources generated by the Human Genome Project have become substantial, and the interest in having access to them is widespread. It is therefore desirable to have a statement of philosophy concerning the sharing of these resources that can guide investigators who generate the resources as well as those who wish to use them.

A key issue for the Human Genome Project is how to promote and encourage the rapid sharing of materials and data that are produced, especially information that has not yet been published or may never be published in its entirety. Such sharing is essential for progress toward the goals of the program and to avoid unnecessary duplication. It is also desirable to make the fruits of genome research available to the scientific community as a whole as soon as possible to expedite research in other areas.

Although it is the policy of the Human Genome Project to maximize outreach to the scientific community, it is also necessary to give investigators time to verify the accuracy of their data and to gain some scientific advantage from the effort they have invested. Furthermore, in order to assure that novel ideas and inventions are rapidly developed to the benefit of the public, intellectual property protection may be needed for some of the data and materials.

After extensive discussion with the community of genome researchers, the advisors of the NIH and DOE genome programs have determined that consensus is developing around the concept that a 6-month period from the time the data or materials are generated to the time they are made available publicly is a reasonable maximum in almost all cases. More rapid sharing is encouraged.

Whenever possible, data should be deposited in public databases and materials in public repositories. Where appropriate repositories do not exist or are unable to accept the data or materials, investigators should accommodate requests to the extent possible.

The NIH and DOE genome programs have decided to require all applicants expecting to generate significant amounts of genome data or materials to describe in their application how and when they plan to make such data and materials available to the community. Grant solicitations will specify this requirement. These plans in each application will be reviewed in the course of peer review and by staff to assure they are reasonable and in conformity with program philosophy. If a grant is made, the applicant's sharing plans will become a condition of the award and compliance will be reviewed before continuation funding is provided. Progress reports will be asked to address the issue.◊

DOE, NIH ELSI Grantees Evaluate Progress

Meeting Fosters Collaboration, Provides Input for Future Direction

NIH and DOE grantees and contractors addressing the ethical, legal, and social implications (ELSI) of human genome research met on September 14–16, 1992, along with the NIH-DOE ELSI Working Group. The purposes of the meeting, held halfway through the Human Genome Project's first 5-year period, were to evaluate progress, foster collaboration, and provide input for the future direction of the ELSI program.

Human Genome Project managers Elke Jordan [National Center for Human Genome Research (NCHGR)] and John Wooley and David Smith (both at the DOE Office of Health and Environmental Research) welcomed attendees in an initial plenary session. Sylvia Spengler (Lawrence Berkeley Laboratory) gave a brief overview of genome research, its methodologies, and recent scientific accomplishments from which both medical advances and difficult ethical and social choices will arise.

Francis Collins (University of Michigan Human Genome Center) discussed the clinical implications of the Human Genome Project, stressing the difficulty of systematically addressing ELSI issues while the science is itself a moving target. He noted that presymptomatic DNA diagnosis for genetic diseases will be widespread within several years and that development of options and systems for genetic services will require continued attention from both the biomedical and ELSI communities.

The wider importance of developing sound ethical policies related to genetics was underscored by Robert Gellman (U.S. House Committee on Government Operations staff), who spoke of the need to protect the privacy of genetic information. He cited credit reports and other personal information that are being used for direct marketing and other purposes beyond their original intent. The government operations committee, concerned that personal genetic data not be similarly abused, has called for a joint DOE-NIH advisory commission to develop policy for management of genetic information.

Nancy Wexler, chair of the working group, noted that because the accomplishments of the ELSI program cannot be measured with the same precision as genome science, ELSI grantees have a special responsibility for demonstrating that their funds are spent wisely.

Following the plenary session, investigators participated in one of four discussion panels organized according to the high-priority areas selected by the working group:

- design and delivery of genetic services,
- fairness in the use of genetic information,
- privacy of genetic information, and
- public and professional education.

In a fifth discussion session, the NIH Cystic Fibrosis (CF) Consortium discussed the full range of high-priority issues raised by the present-day example of CF. In all the panels, grantees were asked to describe their projects briefly and share preliminary conclusions or findings. Because the majority of ELSI grants were awarded within the last year, most presentations focused on research plans.

After reviewing the current portfolio, workshop participants identified several areas in which the need for additional high-quality projects would continue:

- **Client-Centered Assessments of New Genetic Services and Technologies.** Attendees emphasized the need for qualitative studies of cross-cultural and psychosocial factors in individual and family perception, experience, and reaction to new genetic services. They also recommended that the ELSI program obtain more input from people affected by genetic disorders, including parents of children with disabilities.
- **Education.** Participants suggested that the ELSI program direct educational initiatives to elementary schools, where the curriculum is usually flexible and classes are often characterized by high levels of teacher and student enthusiasm. Two public television series on the impact of genetics on medicine and health are forthcoming, and curriculum development at the high school level has received

➡

Contacts for ELSI program abstracts

- **NIH:**
  Elinor Langfelder
  Fax: 301/402-1950
- **DOE:**
  Daniel Drell
  Fax: 301/903-7363

Instructional Unit Sent to High School Biology Teachers

At the ELSI meeting, Joseph McInerney (Colorado College) announced that the DOE-funded instructional unit "Mapping and Sequencing the Human Genome: Science, Ethics, and Public Policy" was being sent to every U.S. high school biology teacher. [For more information on the module, see *HGN* 4(4), 9 (November 1992).] ◊

Genome News

Two Public Television Series To Focus on Genetics' Impact on Medicine, Health

much attention from the ELSI program. However, participants were concerned about the lack of large-scale educational initiatives for nonstudent populations, nonmedical professionals, and the millions who do not watch public television. Genetic services are available to people who may have little understanding of biology and genetics but who are exposed to symbols of genetic determinism in the media. Education is a significant component of any informed decision to use genetic services.

- **Interpreting Genetic Variation.** Participants reemphasized the importance of exploring the ethical and social implications of new genetic information about human traits not related to disease. As genetic explanations are elaborated for these traits, new and different kinds of public and professional policy issues will be raised.

Informed Consent for Testing

Members of the 3-year NCHGR-sponsored CF consortium discussed issues raised by increased access to CF-carrier testing. In the first year, consortium members collaborated to develop educational materials, informed consent documents, and psychological assessment measures, which were critiqued by workshop participants. At issue were the extent to which CF study results could be generalized to other types of disorders and the challenge of obtaining informed consent for carrier testing. Participants questioned the ability to keep research test results confidential and also asked how researchers should determine and communicate the risk of insurance loss to a person identified as a CF carrier.

Communication

ELSI programs have facilitated communication among grantees who are focusing on common themes. For example, DOE has organized a collaboration of grantees and contractors studying issues of genetic privacy. Topics being addressed include ownership of genetic information, management of research records, military use of genetic data, storage of DNA samples, and the disposition of records and materials in DNA banks after a research program ends. Grantees are also researching the scope of protection afforded by state laws regarding genetics and privacy. In addition, principal investigators working on insurance issues are members of the DOE-NIH subcommittee's ELSI Task Force on Genetics and Insurance [see *HGN* **4**(3), 5 (September 1992)].

This workshop helped to foster both formal and informal grantee collaborations by providing a forum for the exchange of materials and ideas. A postworkshop evaluation indicated that participants gained much insight from analyzing specific projects and issues in the work of their colleagues and in the larger arena of the Human Genome Project. Investigators said they would like to convene again in about 2 years, when the CF consortium will have concluded its studies, the insurance projects will have issued reports, and more empirical data will be available for analysis and contribution to the policymaking processes.◊

Reported by Elinor Langfelder
NIH NCHGR

Feingold Joins NCHGR Research Grants Branch

Elise Feingold has joined the National Center for Human Genome Research (NCHGR) as a program administrator in the Research Grants Branch, where she will oversee genetic-mapping research grants and individual fellowships. Her duties will also include coordination of single-chromosome mapping workshops. Feingold comes to NCHGR from the NIH Office of Extramural Programs, where she was a grants associate.

After obtaining her Ph.D. in human genetics from Yale University, Feingold was a postdoctoral fellow in the National Cancer Institute (NCI) Laboratory of Biochemistry, where she worked with Dean Hamer. She studied the regulation of metallothionein gene expression and received an individual National Research Service Award from NCI for her work.

As a staff fellow in the Clinical Hematology Branch at the NIH National Heart, Lung, and Blood Institute, she worked with Arthur Nienhuis on structure-function analysis of the monocyte-macrophage colony stimulating factor (CSF-1) receptor. The knowledge gained from this work aided in her study of hereditary persistence of fetal hemoglobin, a condition in which fetal hemoglobin expression is disregulated.◊

Publication Features LANL Genome Program

A special issue of *Los Alamos Science* (No. 20, 1992) focuses on the genome program at Los Alamos National Laboratory (LANL). The 338-page volume, containing numerous excellent graphics, includes an introduction to the Human Genome Project; principles of classical and molecular genetics; mapping goals and technologies, particularly for chromosome 16; informatics; rapid DNA sequencing; ethical, legal, and social issues; and descriptions of the basic ideas and challenges behind the research. [Limited number of copies available from the Center for Human Genome Studies; LANL, MS M885; Los Alamos, NM 87545 (505/667-3912)].◊

Genome News

NIH Workshop Considers Review Policies for Genetic Family Studies

On October 5–6, 1992, the NIH National Center for Human Genome Research (NCHGR) and Office of Protection from Research Risks (OPRR) convened a workshop to discuss issues faced by institutional review boards (IRBs) when reviewing applications for public funds to conduct human genetic studies involving families. The surge in efforts to identify disease-related genes has increased dramatically the number of genetic studies that IRBs are asked to review. The purpose of the conference was to determine the appropriateness of developing NIH guidance for IRBs and to identify areas needing clarification. Participants included representatives from voluntary health associations, genetic researchers and counselors, subject recruiters, IRB chairs, legal experts, and research policymakers.

Crucial differences exist between genetic family studies and other types of research involving human subjects. First, in pedigree studies, psychosocial rather than physical risks often require careful scrutiny by IRBs, who currently do not have guidelines for evaluating psychosocial risk. Second, because the "research subjects" are related, their individual decisions and rights may be in direct conflict with those of other relatives. Finally, the diagnostic potential of many family studies removes the boundary between research and therapy.

Discussions were organized around commissioned briefing papers and preliminary work by groups such as the American Association for the Advancement of Science, the Alliance of Genetic Support Groups, and the American Society of Human Genetics. Sessions emphasized five core areas of research policy: (1) recruitment strategies, (2) identification and communication of risks and benefits within the informed consent process, (3) disclosure of interim results, (4) policies on withdrawal and limited participation, and (5) publication practices.

Workshop Recommendations

Nonphysical risk: Risk to participants in genetic research may go beyond "just a blood draw." Workshop participants agreed that collecting empirical data about the nonphysical risks of genetic research should be a significant component of future studies. Investigators and IRBs should consider that diagnosis of a genetic disease may affect such aspects as the individual's ability to change jobs or obtain health insurance. Investigators must develop sensitivity to these issues, and IRBs should expect researchers to defend their approach in the research proposal.

Education: To provide an adequate review of pedigree study protocols, IRB members need to become familiar with the specifics of pedigree research, especially psychological and social risks and the uncertainty of a study's outcome. Education should be a continuous process because new advances in genetics are made almost daily and IRB membership rotates regularly. In addition, researchers need to be educated about IRB expectations. Consumer groups and voluntary health associations can play a significant role in recruitment, education, and support of research participants.

Languages: The language level used in the informed consent process should be understandable and appropriate. Interpreters must be provided for those who are hearing impaired or speak no English.

Counseling: Counseling for research participants should be stressed by IRBs, and differences between psychological and genetic counseling should be recognized by investigators. Researchers should not overlook voluntary health organizations as a source of emotional support for participants and as a bridge of trust between subjects and investigators.

Early Withdrawal: IRBs should recognize that people withdraw from projects for various reasons. They should ensure that researchers explain to participants what will happen and the potential uses or consequences of information or samples.

Publication: Some discussants were concerned about the lack of a formalized system to preserve confidentiality when disguised pedigrees are published. They felt that policies should be developed to balance various interests and minimize participants' risk and that the conventional practice of publishing pedigrees should be evaluated further by scientific journal editors,

(see Pedigree Studies, p. 9)

Groups Agree on Need To Provide Guidelines for Review Boards

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.◊

Genome News

Automated Technologies May Allow Simultaneous Mapping of Chromosomes

Whitehead-MIT Genome Center to Map Entire Genome

The NIH National Center for Human Genome Research (NCHGR) has awarded a grant totaling $8.3 million in the first year to the human genome center headed by Eric Lander at the Whitehead Institute for Biomedical Research and the Massachusetts Institute of Technology (MIT). The grant will renew and expand the work of Lander and his colleagues in (1) constructing physical maps of mouse and human genomes and (2) further refining mouse genetic linkage maps. These researchers developed and tested techniques for genome-wide mapping when they constructed a genetic linkage map covering the entire mouse genome.

"Progress in physical mapping has been greater than we expected in our planning for the Human Genome Project," says NCHGR Deputy Director Elke Jordan. "It is prudent for us at this time to take full advantage of newly developed mapping technologies to speed the project along so the tools can be delivered to the scientific community as quickly as possible."

Investigators have previously constructed physical maps one chromosome at a time, but improved and more-automated technologies, including mega–yeast artificial chromosome (YAC) clones, have led the Whitehead-MIT center group to attempt physical mapping of all mouse and human chromosomes at once.

Whitehead-MIT center activities will consist of three research projects and six core facilities. The research projects and their directors are the following:

- Mouse genomic mapping [Lander and David Page (Whitehead-MIT)];
- Human genomic mapping [Lander, Page, Nic Dracopoli (MIT), Daniel Cohen (Centre d'etude du Polymorphisme Humain {CEPH} and Genethon), and Jean Weissenbach (Institute Pasteur and Genethon)]; and
- A pilot study to introduce YACs into the mouse germline [Rudolph Jaenisch (Whitehead-MIT)].

The core facilities include:

- Informatics [Nathan Goodman (Whitehead Institute), James Orlin (MIT), and Joseph Nadeau (Jackson Laboratory)];
- DNA sequencing;
- Instrumentation [Lander, Paul Matsuidaira (Whitehead-MIT), and Cohen];
- Materials [Cohen, Shirley Tilghman (Princeton University)]; and
- Administration.

New Markers To Be Identified

Work on mouse and human genomes will allow scientists to compare information about gene structure and function in the two species. The mouse and human genomes are more than 90% homologous, and many mouse genes carry out functions identical to their human counterparts. Several disease-related genes identified in mice have been found to be similar in humans.

Lander and his coworkers will generate from the mouse genome 6000 markers of simple sequence length polymorphisms (SSLPs) spaced an average of 300,000 bp apart. This set of markers will allow scientists to locate individual genes quickly and separate the contributions that several genes may make to a single trait or disease.

The group will also identify 10,000 sequence tagged site (STS) markers covering the whole mouse genome at a low-resolution rate of about 1 STS every 300,000 bp of DNA. Further work will be needed to increase the resolution of the physical map to 1 STS every 100,000 bp as called for in the 5-year plan for the Human Genome Project. SSLPs, which can also serve as STSs, will be used to tie information from the genetic map to the physical map. Center researchers will develop a YAC library of cloned DNA from the mouse genome and order the clones using STSs.

Because the data generated will be critical to physical mapping efforts by the community of genome scientists, center researchers have developed a policy to ensure access to materials and information. (See margin text on sharing policy.) The CEPH mega-YACs, now at the Whitehead genome center, have been copied and distributed to three centers, which are now making additional copies for wide distribution to researchers.◊

Anne Adamson
HGMIS, Oak Ridge National Laboratory

Whitehead-MIT Genome Center Sharing Policy

All clone libraries, marker sequences, and maps will be distributed promptly and will not be patented. As soon as results are confirmed and before publication, data will be released in batches into the public domain. No access to materials or information will be granted to any commercial entity before public release.

In October 1992 Page and Cohen independently published the first physical maps of entire human chromosomes (Y and 21, respectively). [See *Science* 258, 52–86 (October 2, 1992); *Nature* 359, 380–86 (October 1, 1992); and *HGN* 4(4), 1–4 (November 1992).]

Significant New Data Now Accessible from GDB

Data and maps relevant to landmark genomic-research papers published recently in *Science* and *Nature* are now accessible on the Genome Data Base (GDB). These datasets include (1) a listing of over 800 polymorphic markers presented by Jean Weissenbach and colleagues (*Nature* **359**: 794–901), (2) genetic baseline maps constructed by the NIH and Centre du Polymorphisme Humain collaborative mapping group for all human chromosomes except Y (*Science* **258**: 67–86), and (3) a YAC contig–STS map of chromosome 21 provided by Ilya Chumakov's group (*Nature* **359**, 380–87). Authors are encouraged to submit maps and other data directly to GDB (see box at right for complete address).◊

Please note new address of U.S. GDB User Support.

Pedigree Studies *(from p. 7)*

NIH, and others. Informed consent should include notification about publication plans, and permissions should be obtained again before unexpected findings are published. IRBs should have the opportunity to evaluate the dissemination plan in each protocol.

Coercion: Appropriate and inappropriate recruitment practices should be identified and conveyed to IRBs, although they should recognize that each situation is unique. IRBs should ensure that the investigator has developed an adequate recruitment strategy with resources to execute it. IRB policy guidelines also need to be developed regarding the involvement of children in pedigree studies.

Workshop participants evaluated a draft chapter on genetic family studies for an OPRR guidebook for IRBs. They also recommended adding a session on genetics to the OPRR-Food and Drug Administration regional workshops for IRB members. Finally, members recommended that the NCHGR program on ethical, legal, and social issues publicize its interest in cofunding research on the psychosocial impact of participation in a genetic family study.◊

Elinor Langfelder
NIH NCHGR

GDB User Support, Registration

To become a registered user of GDB and OMIM, contact one of the User Support offices listed at right (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. 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.

GDB and OMIM Training Course Schedule

Comprehensive hands-on training courses on the use of GDB and OMIM will have at least one computer workstation for two participants. Registrants will receive at least 3 weeks notice if insufficient registration causes class cancellation.

- The general course for scientific users provides a basic understanding of the databases and relationships among 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 below). Courses are free, but attendees must pay their own travel and lodging expenses. Hotel information and directions will be mailed with registration materials.

As interest in GDB continues to grow, organizations around the world will offer training that requires access to GDB in Baltimore. Notifying GDB User Support about planned training activities will enable the staff to ensure database availability by scheduling maintenance and repairs at other times.

COURSE REGISTRATION INFORMATION: contact U.S. GDB User Support Office (at right).

PLANNED EXHIBITIONS (acronym list, p. 16)

- Experimental Biology, New Orleans, Mar. 28–Apr. 1.
- APP/AFCR/ASCI, Washington, D.C., Apr. 30–May 3

Course	Dates
BALTIMORE	
General User	March 22–23
General User	April 26–27
General User	June 21–22
Editing	March 4
Editing	May 10–11

USER SUPPORT OFFICES

United States

GDB User Support
Applied Research Laboratory
William H. Welch Med. Library
Johns Hopkins University
2024 E. Monument Street
Baltimore, MD 21205-2100
410/955-7058
Fax: 410/614-0434
Internet:
help@welch.jhu.edu

The Help Line is staffed from 9 a.m. to 5 p.m. EST for information on accounts and training courses, technical support, and data questions. 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
Internet: *cbates@uk.ac.crc*

Germany

Otto Ritter
Molecular Biophysics Dept.
German Cancer Research Center
Im Neuenheimer Feld 280
D-6900 Heidelberg, FRG
(Int.) 49/6221-42-2372
Fax: (Int.) 49/6221-42-2333
Internet:
dok261@cvx12.dkfz-heidelberg.de

Australia

Alex Reisner
ANGIS
Electrical Engineering Building, J03
University of Sydney
Sydney, N.S.W. 2006
Australia
(Int.) 61/2-692-2948
Fax: (Int.) 61/2-692-3847
Internet:
reisner@angis.su.oz.au

CORRECTION. HGMIS regrets errors on p. 10 of GDB Forum published in the last issue. The figure caption should read: "Relationships among GDB data managers and the Online *Mendelian Inheritance in Man*. Data are linked to citations in all managers except *Contact*." The last sentence of the box about GDB 5.0 Data Conversion should read: "Developers interested in obtaining the 5.0 schema and accompanying data dictionary should contact GDB User Support in Baltimore."◊

Meeting Reports

CSHL Workshop Teaches Human Genetics and Genome Analysis to Nonscientists

Workshop Designed for Nonscientists

The final workshop of the series was scheduled for February 4–7.

Contact:
- **Jan Witkowski 516/549-0507 Fax: -0672**

Human Genetics and Genome Analysis, a workshop planned and carried out by Jan Witkowski (Director, Banbury Center) and David Micklos and Mark Bloom (Director and Assistant Director, DNA Learning Center) was held December 6–9, 1992, at Cold Spring Harbor Laboratory (CSHL) on Long Island, New York. The learning center is the world's first science center devoted entirely to public genetics education, and Banbury is the 45-acre site of conferences and courses on molecular biology and on aspects of the biological sciences that bear significant social implications. The workshop, the third in a series sponsored by the DOE Human Genome Program, combined the expertise of the two CSHL units.

This intimate, 24-person workshop was designed for nonscientists who interface with human genetics research and society. Participants from all over the United States included teachers and other educators, editors, writers, congressional and science museum staff, lawyers, physicians, medical ethicists, and representatives of state governments and genetic support groups. Their varied backgrounds and perspectives enriched the learning experience, and attendees agreed that the course would enable them to better understand and represent scientific data.

The three workshop components were as follows :

Concept Seminars. Lectures presented by Banbury and DNA Learning Center staff introduced key concepts fundamental to human genome analysis. Micklos and Witkowski spoke on the Mendelian and modern views of the gene, respectively. Bloom explained how genes are cloned, and Witkowski discussed DNA diagnosis of human genetic diseases.

Feature Seminars. Seminars by working scientists provided insight into the research process. Nancy Press (University of California, Los Angeles Medical Center) spoke on population screening for genetic diseases; Patricia Ward (Baylor College of Medicine) discussed human genetic disease counseling; Kenneth Culver (NIH) described the first human gene therapy trials; and Ronald Davis (Beckman Neuroscience Center, CSHL) spoke of searching for the genetic basis of learning and memory.

Laboratory Work. Hands-on experiments provided direct experience with key techniques of gene analysis:

- Participants used restriction enzymes to cut DNA from the bacteriophage *lambda* and analyzed the resulting DNA fragments by agarose gel electrophoresis.
- A second experiment on bacterial transformation illustrated the direct link between an organism's genetic complement (genotype) and its observable characteristics (phenotype). A gene for antibiotic resistance was introduced into the bacterium *Escherichia coli* and, following overnight incubation, transformed bacteria were compared with untreated bacteria for their ability to grow in the presence of ampicillin.
- A third experiment examined DNA polymorphisms that are the basis of forensic DNA fingerprinting and genetic analysis. Participants prepared a sample of their own DNA from cells obtained by saline mouthwash and used the polymerase chain reaction to amplify polymorphic DNA fragments, which were then separated by electrophoresis.◊

Jennie Forehand (Virginia House of Delegates member), is instructed by Mark Bloom in a DNA fingerprinting experiment at the Cold Spring Harbor Laboratory Workshop.

Reported by Anne Adamson and Judy Wyrick HGMIS, Oak Ridge National Laboratory

Bioinformatics, Supercomputing, and Complex Genome Analysis

The Second International Conference on Bioinformatics, Supercomputing, and Complex Genome Analysis, hosted by the Supercomputer Computations Research Institute of Florida State University (FSU), was held June 4–7, 1992, at St. Petersburg Beach, Florida. The meeting, sponsored by DOE, the National Science Foundation, and industrial vendors, was attended by leading computational experts, experimentalists, and technologists from 13 countries. The conference goal was to provide a forum for experts from industry and academia to share ideas about the development of sophisticated methods for storing, retrieving, and interpreting the enormous amount of raw data being generated worldwide through the Human Genome Project. Keynote addresses were made by Robert J. Robbins (Director, Welch Laboratory, Johns Hopkins University) and Charles Cantor (Boston University).

Computers Essential to Genome Research

Robbins stated that the genome project—an attempt to create a database containing instructions for human development—is the most audacious information-management program ever undertaken. Computers are already playing an essential role in genome research: laboratory databases manage research materials; computer-controlled robots perform experimental manipulations; automated data-acquisition systems log experimental results; analytic software assists in interpreting data; software packages visualize data; and public databases allow scientists to share their findings with the world. Advanced computer tools will soon be required for manipulating, analyzing, and comparing entire genomes easily and quickly.

Analysis Strategies

Cantor reviewed the different levels of genome analysis and presented a strategy for going beyond current methods. He suggested that when the appropriate technology becomes available, the simultaneous study and analysis of complex genomes might be possible by using pools of samples, probes, or both.

More than 50 talks focused on problems and solutions involving complex genome analysis. Participants' key concerns fell into six major topic areas:

- Linguistic approaches to deciphering the genetic code by determining the grammar of genetic texts as sentences or paragraphs.
- Applications of neural networks to discern (1) splice junctions between fragments of DNA and (2) DNA or protein structure and function.
- Databases to store, handle, and disseminate data.
- Construction and integration of genetic maps of organisms and humans.
- Development of the best and fastest algorithms for genome sequence data analysis and interpretation.
- Testing of mapping and sequencing theories and models through interaction between theorists and experimentalists.

Although no special session was held on computer technology and mathematical models, the conference was interspersed with talks by vendors and mathematicians. Attendees agreed that computer power and speed are basic requirements for information handling and that new mathematical algorithms and computational methods can potentially transform information storage, visualization, interpretation, and transmission.

Summary

The conference helped make the community aware of the current status and future challenges of bioinformatics and complex genome analysis. It also led to new ideas and collaborations between industry and academia and introduced new investigators to the field.◊

Reported by Richard Skoonberg and Hwa Lim
Florida State University

Contact:

Florida State University
Supercomputer Computations Research Institute
904/644-1010
Fax: -0098
Richard Skoonberg
Internet: ***skoonberg@scri.fsu.edu***
Hwa Lim
Internet: ***hlim@scri.fsu.edu***

Conference proceedings (ISBN: 981-02-1157-0), edited by Lim, James Fickett (Los Alamos National Laboratory), Cantor, and Robbins, will be published this spring by World Scientific Publishing Company; 1060 Main St., Suite 1B; River Edge, NJ 07661 (800/227-7562, Fax: 201/487-9656, Internet: ***wspc@scri.fsu.edu*****).**

Comprehensive Linkage Map Reprints Available

Reprints of the NIH/Centre d'Etude du Polymophisme Humain (CEPH) comprehensive linkage map (published in the October 2, 1992, issue of *Science*) are now available free of charge. The reprints contain expanded information on mapped genes and expressed sequences in addition to sex-specific chromosome maps. Contact: National Center for Human Genome Research; Bldg. 38A, Room 617; Bethesda, MD 20892 (Fax: 301/402-1950) or CEPH; 27 rue Juliette Dodu; 75010 Paris, France.◊

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.

Human Genome Management Information System:

Managing Editor
Betty K. Mansfield

Editors/Writers
Anne E. Adamson
Denise K. Casey
Kathleen H. Mavournin

Production Manager/Editor
Judy M. Wyrick

Production Assistants
K. Alicia Davidson
Larry W. Davis
Sheryl A. Martin
Laura N. Yust

Correspondence Address:
Betty K. Mansfield
ORNL
P.O. Box 2008
Oak Ridge,TN 37831-6050
Phone: 615/576-6669
Fax: 615/574-9888
BITNET: *bkq@ornlstc*
Internet: *bkq@ornl.gov*

Sponsor Contacts:

Daniel W. Drell
DOE Program Office
Germantown, MD 20545
301/903-4742
Fax: 301/903-5051
Internet:
drell@mailgw.er.doe.gov

Leslie Fink
NIH National Center for Human Genome Research
Bethesda, MD 20892
301/402-0911
Fax: 301/480-1950
Internet: *lsf@cu.nih.gov*

Human Chromosome 12 Mapping Workshop

The First International Human Chromosome 12 Workshop was held September 18–20, 1992, at St. Catherine's College, Oxford University. The meeting was supported by the European Commission through the Human Genome Organization, the U.K. Medical Research Council (MRC), DOE, and NIH. Organized by Ian Craig (University of Oxford), Robert Gemmill (Eleanor Roosevelt Institute), and Raju Kucherlapati (Albert Einstein College of Medicine), the conference was attended by 50 participants from Europe and the United States.

Because this was the first workshop on human chromosome 12, participants exchanged information about mapping research strategies. Five working groups evaluated data and prepared a group report. At the final plenary session, several consensus maps were developed.

Significant progress was reported since Human Genome Mapping 11 (held August 1991) in extending markers and incorporating them into the genetic and physical maps. Increases were noted in the number of mapped chromosome 12 genes (from 132 to 147), DNA segments (from 63 to 175), and yeast artificial chromosomes (YACs) (from 1 to more than 45). The genetic map has been improved significantly, and a list of 14 reference loci has been developed for physical and genetic mapping.

Resources. Several resources useful for chromosome 12 mapping were assembled at the meeting. These include (1) 2 somatic cell hybrids with chromosome 12 as their sole human constituent and (2) a panel of 14 somatic cell hybrids that contain chromosome 12 parts and divide the chromosome into 7 distinct regions (I–VII). [Additional information about the hybrid cell panel can be obtained from Martha Liao (Albert Einstein College of Medicine)]. A panel of uncharacterized radiation-reduced hybrids was reported by Kucherlapati. Lawrence Livermore National Laboratory (LLNL) has constructed phage and cosmid libraries from flow-sorted chromosomes, some of which are available through the American *Type Culture* Collection and others from LLNL [Contact: Pieter de Jong (LLNL), Fax: 510/423-3608].

CEPH Linkage Map. A chromosome 12 linkage map based on Centre d'Etude du Polymorphisme Humain (CEPH) families was recently published [Holt et al., *Science* **258**, 67–86 (1992)]. This map, reported by Tobias Gedde-Dahl (University of Oslo) and Helen Donis-Keller (Washington University) and updated at the workshop, spans 289 cM in females and 144 cM in males. The sex-averaged map has a resolution of 7 cM. E. Dawson (Institute of Psychiatry, London) presented an independent genetic map constructed from 22 microsatellite loci on a set of families termed Institute of Psychiatry Schizophrenia (IOPS). The overall frequency of recombination in these families seems to be somewhat lower than in the CEPH families.

YACs, Cosmids Mapped. A number of investigators have isolated YACs corresponding to chromosome 12 markers. One of these appears to map to 12 pter (Donis-Keller) and includes presumed telomeric sequences. A YAC contig located at 12p13 was reported by Kate Montgomery (Albert Einstein College of Medicine), and a second contig at 12q13.3 by Gemmill. A pulsed-field map for the 12q13.3 region was also presented. More than 100 cosmids were reported mapped to chromosome 12 by fluorescence in situ hybridization (Montgomery).

Genes Mapped. Since HGM 11, several disease genes and genes involved in translocations found in neoplasms have been mapped on chromosome 12. These include (1) spinal cerebellar ataxia type 2 (SCA2) mapped to a region flanked by D12S58 and PLA2 [Georg Auberger (University Hospital, Dusseldorf) and Rebecca Twells (St. Mary's Hospital, London)] and (2) heritable skin disorders involving cytokeratin loci KRT1 and KRT5. In addition, a consistent rearrangement involving a gene called CHOP or GADD153 was detected by Pierre Aman (University Hospital, Lund) in liposarcomas associated with translocations between chromosomes 12 and 16.

Mouse Homologs. The comparative mapping working group reported that homologues of 43 human chromosome 12 loci have been located in the mouse [Jo Peters (MRC, Harwell) and John Edwards (University of Oxford)]. Of these loci, 17 are on mouse chromosome 6 and others on 10 and 15.

(see Chromosome 12, p. 13)

International *E. coli* Genome Meeting Held

About 150 people attended the First International *Escherichia coli* Genome Meeting on September 10–14, 1992, in Madison, Wisconsin. Organized as a follow-up to the 1991 Banbury *E. coli* conference, the meeting consisted of invited talks, poster sessions, and hands-on workshops for researchers analyzing the *E. coli* genome at the genetic, sequence, and structural levels. Organizers included Bill Reznikoff (University of Wisconsin-Madison), Ross Overbeek (Argonne National Laboratory), Monica Riley (Marine Biological Laboratory), Kenn Rudd (National Library of Medicine), and John Roth (University of Utah). Topics and speakers are highlighted below.

Strategies. Investigators from several laboratories outlined the strategies used for large-scale sequencing (random-complete coverage, gap filling, and ordered) and the resulting data.

Sequence Analysis. Comparative sequence analyses were presented to help derive evolutionary trees, with evidence indicating that horizontal recombination occurs within the overall framework of vertical inheritance. The existence and location of repetitive sequences and insertion sequences were discussed.

Databases. Various databases available to the *E. coli* research community were described, as well as approaches to developing an integrated database. During the meeting, many participants experimented with various software packages.

Tools. Topics included molecular mechanisms for chromosome structure changes, genetic tools for analyzing genome structure, and computerized methods for identifying interesting sequences.

Networks. Many *E. coli* genes respond to multiple regulatory signals, and some are connected into overlapping networks. Speakers described several of these networks and the underlying physiological responses, including those involved in anaerobiosis, phosphate limitation, heat shock, and galactose utilization.

Structure. Analyses were presented on chromosome structure and proteins that generate and maintain interesting chromosome structures. Speakers also discussed how changing chromosome structure can affect gene expression.

Participants agreed on the need for a database coordination workshop, which will be organized by Manfred Kroeger (EMBL-Heidelberg), and for annual genome meetings. The 1993 conference is tentatively scheduled for September 9–13 in Madison.◊

Reported by Bill Reznikoff
University of Wisconsin-Madison

Chromosome 12 *(from p. 12)*

Informatics. Participants examined several databases and mapping tools presented by Martin Bishop (Cambridge University), Edwards, Bonnie Maidak (then at Genome Data Base), and others.

The second chromosome 12 workshop, planned for this fall in the United States, is being organized by Kucherlapati, Peter Marynen (Center for Human Genetics, Leuven), and Craig.◊

Reported by Raju Kucherlapati
Albert Einstein College of Medicine
and
Ian Craig
University of Oxford

Los Alamos Develops and Distributes Map Assembly Software

SIGMA (System for Integrated Genome Map Assembly), a new software tool for building integrated genome maps, is being distributed by the Human Genome Information Resource of the Theoretical Biology Group at Los Alamos National Laboratory (LANL). SIGMA is an object-oriented, graphical map editor based on X windows and an object-oriented database management system (ObjectStore from Object Design, Inc.) with the OpenLook interface standard.

Some major features of SIGMA, designed by Michael Cinkosky and Jim Fickett (both at LANL):

- *Graphical map editing* through mouse-based, point-and-click operations.
- *Integrated genome maps* incorporating data on any type of map object, with measurements specified in any units. This allows data from many different types of maps to be combined into a single map.
- *User-configurable views* on a single map, each of which might emphasize a different aspect of the data.
- *Automatic map evaluation* providing constant feedback to the user on how well the drawing and data agree and identifying problems.
- *Support for collaborative map building* allowing researchers at different locations to work on the same map.
- *GDB Interface* importing maps from GDB for viewing. This feature will soon be able to produce GDB submissions in electronic form.

SIGMA is available from LANL without charge, although an ObjectStore license is required to maintain a local database. For more information on SIGMA, contact Cinkosky (505/665-0840, Internet: *sigma@t10.lanl.gov*).◊

Calendar of Genome Events (acronyms, p. 16)

February

15–19. *15th Annual Conference on the Organization & Expression of the Genome; Lorne, Victoria, Australia [S. Easteal, (Int.) 61/6-249-4719, Fax: -4712]

18. NCHGR Lecture Series. Richard Durbin: ACEDB Genome Database and Data Analysis from the Nematode Sequencing Project; Bethesda, MD [C. Dahl, 301/402-0838]

26–27. Charting the Genome: Implications of Genetic Technology for Healthcare Practitioners in the 1990s; Los Angeles [Pacific Ctr. for Health Policy and Ethics, 213/740-2541, Fax: -0149]

March

6–8. Chromosome 20 Workshop; Paris [C. Smith, 510/643-6376, Fax: -1188]

9. WSS. Eric Juengst, Ruth Hubbard, and LeRoy Walters: Is This The Brave New World?; Washington, DC [D. McIlwain, 301/565-8861, evenings until 9:00 p.m. EST]

11–12. First International Workshop on Human Chromosome 1; Cambridge, MA (abstract deadline: Dec. 15) [N. Dracopoli, 617/253-8575, Fax: /258-8728]

13–14. Legal Issues in Genetics Conference; Arlington, VA [MARHGN, 215/456-7910, Fax: -7911]

14–19. Scanning Tunneling Microscopy; GRC, Ventura, CA [A. Cruickshank, 401/783-4011, Fax: -7644]

18. NCHGR Lecture Series. Steve Warren: Triplet Repeat Expansion Mutations—Example of the Fragile X; Bethesda, MD [see contact: Feb. 18]

25. NCHGR Lecture Series. Francis Collins: Identification of Human Disease Genes by Positional Cloning; Bethesda, MD [see contact: Feb. 18]

April

12–18. Gene Therapy; Keystone, CO [1993 Keystone Symposia Meeting, 303/262-1230, Fax: -1525]

12–18. Genetically Targeted Research & Therapeutics–Antisense & Gene Therapy; Keystone, CO (abstract deadline: Dec. 2) [see contact: April 12–18, above]

15. NCHGR Lecture Series. Troy Duster: Socio-Historical Context of Genetic Explanations of Behavior; Bethesda, MD [see contact: Feb. 18]

18–20. Second International Chromosome 9 Workshop; Cape Cod, MA [D. Kwiatkowski, 617/278-0384, Fax: /734-2248]

18–21. *Third International Workshop on Human Chromosome 5; Laguna Beach, CA [J. Wasmuth, 714/856-7067, Fax: /725-2688]

23–24. Fourth International Human Chromosome 21 Workshop; Paris [J. Delabar, (Int.) 33/1-42-730-960, Fax: -659]

26–27. Eleventh Annual Am. *Type Culture* Collection (ATCC) Biotechnology Patent Conference; Washington, DC [ATCC Workshop Manager, 301/231-5566, Fax: /770-1805]

May

2–4. First International Workshop on Chromosome 8; Vancouver, Canada [S. Wood, 604/822-6830, Fax: -5348]

9–12. Am. Medical Informatics Assoc. (AMIA) 1993 Spring Congress; St. Louis [AMIA, 301/657-1291, Fax: -1296]

9–12. *Fourth Annual X Chromosome Workshop; St. Louis [M. Thomas, 314/362-7259, Fax: -1232]

12–16. Genome Mapping & Sequencing; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845]

14–15. Fourth International Workshop on Chromosome 3; Groningen, Netherlands [C. Buys, (Int.) 31/50-632-925, Fax: -947]

16. Chromosome 3 & Cancer; Groningen, Netherlands [see contact: May 14–15, above]

16–17. *National Advisory Council for Human Genome Research; Bethesda, MD [J. Ades, 301/402-2205, Fax: -2218]

19–22. 84th Annual Meeting of AACR; Orlando, FL [AACR, 215/440-9300, Fax: -9313]

20. NCHGR Lecture Series. Nancy Wexler: Long Day's Journey into Night—Search for the Huntington's Disease Gene; Bethesda, MD [see contact: Feb. 18]

20–22. First International Workshop on Chromosome 7; Marburg, Germany [K.-H. Grzeschik (Int.) 49/6421-28-4080, Fax: -5630]

June

2–4. ICES-ELPHO '93; Sandefjord, Norway (Preliminary Congress Workshops: June 1) [N. Solum, (Int.) 47/2-868-226, Fax: -303]

2–9. Symposium: DNA & Chromosomes; CSHL [see contact: May 12–16]

10–12. First International Chromosome 14 Workshop; Toronto [D. Cox, 416/813-6384, Fax: -4931]

17. NCHGR Lecture Series. Jasper Rine: Dog Genome Initiative—Towards the Genetics of Morphology and Breed Traits; Bethesda, MD [see contact: Feb. 18]

21–22. DOE/NIH Joint Subcommittee on the Human Genome; Bethesda, MD [see contact: May 16–17]

21–23. Second International Workshop on Chromosome 6; Berlin [A. Ziegler, (Int.) 49/30-3035-2617, Fax: -3778]

26–29. Human Gene Therapy; Washington, DC (abstract deadline: Mar. 15) [NY Acad. of Sci., 212/838-0230, Fax: -5640]

July

7–9. First International Conference on Intelligent Systems for Molecular Biology; Bethesda, MD (paper deadline: Feb. 15) [J. Shavlik, 608/262-7784, Fax: -9997, Internet: *ismb@nlm.nih.gov*]

10–11. Chromosome 4 Workshop; Stanford, CA [R. Myers, 415/476-8138, Fax: -8217]

31–Aug. 4. DNA Damage: Effects on DNA Structure and Protein Recognition; NY Acad. of Sci., Burlington, VT (poster abstracts by May 1) [see contact: June 26–29]

November

14–17. HGM '93 Workshop; Kobe, Japan [HGM Secretariat, (Int.) 81/6-454-4811, Fax: -4711]

Training Calendar**†

February

22–25. PCR Methodology; Columbia, MD (also offered at later dates) [Exon-Intron, Inc., 410/730-3984, Fax: -3983]

22–26. Recombinant DNA: Techniques & Applications; ATCC, Rockville, MD [C. Mills, 301/231-5530 or /881-2600, Fax: /770-2587]

March

1–2. Tissue In Situ Hybridization; Gaithersburg, MD (also offered at later dates) [Oncor, Inc., 800/776-6267 or 301/963-3500, Fax: /926-6129]

1–5. Recombinant DNA Methodology; Exon-Intron, Inc., Columbia, MD (also offered at later dates) [see contact: Feb. 22–25]

2–5. PCR Reaction/Cycle DNA Sequencing; ATCC, Rockville, MD [see contact: Feb. 22–26]

6–10. Kennedy Institute of Ethics Advanced Bioethics Course IV; Washington, DC [D. Michutka, 202/687-6771]

8–12. Recombinant DNA Methodology; Washington, DC [CATCMB/CUA, 202/319-6161, Fax: -5721]

12. Biotech Patents; San Francisco [BioConferences International, Inc., 301/652-3072, Fax: -4951]

16–19. Recombinant DNA Techniques; New Brunswick, NJ (early registration by Mar. 1) [Office of Continuing Professional Education, 908/932-9271, Fax: -8726]

➠

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

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

†NCHGR-funded event.

22–23. GDB/OMIM Training Courses [see schedule, p. 9]

22–26. In Situ Hybridization & Recombinant DNA Technology; Exon-Intron, Inc., Columbia, MD (also offered Nov. 29–Dec. 3) [see contact: Feb. 22–25]

24. Introduction to PCR; Los Angeles (also offered at later dates and various locations) [BTP, 800/821-4861, Fax: 515/232-8306]

25–26. DNA Sequencing without Radioactivity; BTP, Los Angeles (also offered at later dates and various locations) [see contact: Mar. 24]

25–26. Introduction to Molecular Cytogenetics; Oncor, Inc., Gaithersburg, MD (also offered at later dates) [see contact: Mar. 1–2]

29–30. Advanced Molecular Cytogenetics; Oncor, Inc., Gaithersburg, MD (also offered at later dates) [see contact: Mar. 1–2]

April

5. Medicine at the Crossroads; 9–11 p.m. on Monday nights in April [check local PBS listings]

5–9. Advanced Recombinant DNA Methodology; ATCC, Rockville, MD [see contact: Feb. 22–26]

13–26. †Cloning & Analysis of Large DNA Molecules; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845]

15–16. Quantitative RNA-PCR; BTP, Houston (also offered at later dates and various locations) [see contact: Mar. 24]

19–20. Basic Cloning & Hybridization Techniques; BTP, Houston (also offered at later dates and various locations) [see contact: Mar. 24]

May

17–18. Clinical Applications of PCR; BTP, Durham, NC (also offered at later dates and various locations) [see contact: Mar. 24]

17–20. *Introductory Linkage Course; New York [K. Montague, 212/960-2507, Fax: /568-2750]

17–21. Advanced Topics in Recombinant DNA; Exon-Intron, Inc., Columbia, MD (also offered July 19–23) [see contact: Feb. 22–25]

June

2–8. Medical Informatics; MBL, Woods Hole, MA (application deadline: Mar. 26) [D. Chrysler, 508/548-3705, ext. 401]

6–12. Kennedy Institute of Ethics 19th Annual Intensive Bioethics Course; Washington, DC [see contact: Mar. 6–10]

13–26. Sequencing Workshop; Salt Lake City, UT (early registration by Mar. 1) [Genome Tech. Workshop, 801/585-5606, Fax: /581-7796]

14–25. Workshops for Secondary School Biology Teachers: Project Genethics; Winter Park, FL (offered at later dates and various locations) [J. Hendrix, 800-537-9604]

21–26. Workshop for Secondary Science Teachers; Kansas City [D. Collins, 913/588-6043, Fax: -3995]

July

5–25. *Arabidopsis* Molecular Genetics; CSHL [see contact: April 13–26] ◊

For Your Information

U.S. Genome Research Funding Guidelines

Note: Investigators wishing to apply for NIH and DOE funding are urged to discuss their projects with agency staff before submitting proposals.

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 during application development phases.

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

- Hard-copy subscription: call 301/496-7441.
- Electronic version (E-Guide): Access through one of the following methods.
  1. Institutional Hubs. A designee receives automatic updates and distributes them locally to researchers. To use this NIH-preferred method, send a message naming the responsible person to Rebecca Duvall (BITNET: *q2c@nihcu*, Internet: *q2c@cu.nih.gov*).
  2. NIH Grant Line (also known as DRGLINE). User reads electronic bulletin board for weekly updates. Connection is through a modem, and a new feature allows files to be transmitted rapidly via BITNET or Internet. For more information, contact John James (301/496-7554 or BITNET: *zns@nihcu*).

*Full text 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. Preposals are due this spring and formal proposals this summer.

For further information, contact the program office via

- 301/903-5037, Fax: -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 research and development and to contribute to the growth and strength of the nation's economy. Applications are invited in only the following three subtopics: (1) Development of Improved DNA Sequencing Technologies; (2) Improvements in Genetic Data Storage, Processing, and Analysis; and (3) Development of Innovative Materials or Dissemination Techniques to inform students and the lay public about benefits, opportunities, and challenges arising from the Human Genome Project. Next submission date: March 8. For more information and a copy of the solicitation, contact

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

Human Genome Distinguished Postdoctoral Fellowships

Most recent deadline: February 1. To see if applications are still being accepted or for further information, contact

- Linda Holmes, Oak Ridge Institute for Science and Education: 615/576-4805.◊

Japanese Rice Genome Program Publishes Newsletter

The Rice Genome Research Program (RGP) of Japan produces *Rice Genome*, a newsletter devoted to plant genome mapping and analysis. The publication aims to enhance international cooperative research efforts for rice genome analysis and for the isolation and utilization of useful rice genes in plant breeding and biotechnology. Objectives of the program's first stage, which is expected to last 7 years, are to provide a physical map with DNA clones and a linkage map with markers in at least 2000 positions. In addition, cDNA catalogs will be made from different rice tissues (roots, leaves, etc.) for isolation of agronomically important genes.

Newsletter available free of charge: Editorial Office of *Rice Genome*; National Institute of Agrobiological Resources; 2-1-2, Kannondai; Tsukuba; Ibaraki 305, Japan [(Int.) 81/298-38-7469, Fax: (Int.) 81/298/38-7468].◊

Human Genome Management Information System

Subscription/Document Request (Vol. 4, No. 5)

Please type or print legibly. Enclose a business card, if possible. To change your name/address/affiliation or to be dropped from the mailing list, you must enclose your current newsletter address label to ensure that the proper entry is modified.

Name _____
(First) (MI) (Last)

Affiliation _____

Department/Division _____

Street and/or P.O. Box _____

City/State/Zip Code/Country _____

Phone _____ **Fax** _____

E-Mail Address _____ **Area of Interest** _____

1. ___ *Human Genome News*
   ___New Subscriber ___Change of Name/Affiliation/Address (circle all that apply) ___Drop Name from Mailing List
2. ___ *Understanding Our Genetic Inheritance, The U.S. Human Genome Project: The First Five Years, FY 1991–1995* (Joint DOE-NIH 5-Year Plan)
3. ___ DOE *Human Genome 1991–92 Program Report.*
4. ___ *Primer on Molecular Genetics.* (Included in program report above. Extracted as separate document for educational use.)

CALENDAR ACRONYMS

AAAS Am. Assoc. for the Advancement of Science

AACR Am. Assoc. for Cancer Research

AAP Association of American Physicians

ACEDB *Caenorhabditis elegans* Database

AFCR American Federation of Clinical Research

AMIA American Medical Informatics Association

ASCI American Society for Clinical Investigation

ATCC Am. *Type Culture* Collection

BTP Biotechnology Training Programs

CATCMB/CUA Center for Advanced Training in Cell and Molecular Biology/ Catholic Univ. of America

ELPHO Electrophoresis

GRC Gordon Research Conferences

HGM Human Genome Mapping

ICES International Council of Electrophoresis Societies

MBL Marine Biological Laboratory

NCHGR National Center for Human Genome Research

WSS Washington Seminar Series

Reader Comments:

HGMIS MAILING ADDRESS
Betty K. Mansfield
Oak Ridge National Laboratory
P.O. Box 2008
Oak Ridge, TN 37831-6050
U.S.A.