Human Genome news

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Instrumentation Is Key to Mapping, Sequencing

Joe Gray, Director, Division of Molecular Cytometry, University of California, San Francisco

DOE Improving Current Systems, Exploring New Technologies

Two key Human Genome Project goals – creation of a physical map of the genome and determination of genomic DNA sequence – require significant advances in biophysical instrumentation. To meet this need, the DOE Human Genome Program has initiated several instrumentation development efforts, some to support ongoing mapping and sequencing systems and others to explore completely new technologies. Several approaches are summarized below to provide an overview of current initiatives in this rapidly advancing field.

PHYSICAL MAPPING

New instruments are beginning to contribute significantly to several important procedures used in physical map assembly:

- identification of overlapping cloned fragments by (1) nucleic acid hybridization and (2) fingerprinting by pattern analysis of electrophoretically separated DNA fragments produced by restriction enzyme digestion and
- determination of DNA fragment order and separation along the genome by fluorescence in situ hybridization (FISH) to interphase nuclei and metaphase chromosomes.

Overlap Identification by Hybridization

Identifying contiguous cloned DNA fragments by hybridization usually requires the fragments to be deposited on a membrane to support the hybridization process – typically a rate-limiting step. Other rate-limiting aspects include preparation and replication of ordered clone collections (usually in microtiter trays) and detection of the labeled probe hybridizing to the DNA samples on the membrane.

Several laboratories are working to automate this process. Scientists Joseph Jaklevic and colleagues at Lawrence Berkeley Laboratory (LBL) have developed a robotic system that orders individual colonies into arrays to identify yeast or bacterial colonies carrying cloned DNA sequences; the system then

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Instrumentation Development

New Methods Improve Contig Orientation, Localization

transfers DNA from each arrayed colony onto a hybridization membrane. The group also is developing a system to record and store autoradiographic images showing the hybridized probe locations. A key component of this system is a photostimulable phosphorimaging plate that allows image generation without a film intermediate.

Tony Beugelsdijk and coinvestigators at Los Alamos National Laboratory (LANL) have automated the production of high-density DNA grids on nylon membranes, starting with cloned sequences arrayed in microtiter dishes. The number of separately resolvable DNA samples per unit area is increased 16-fold during transfer of the clones to the membranes. The group has also developed a system for replication of libraries stored in microtiter trays.

Restriction Fingerprinting

This procedure identifies overlapping cloned sequences by analyzing the restriction pattern produced by digestion with one or more restriction endonucleases. Overlapping clones will have several fragments of the same size. This process is limited by the electrophoresis time required for DNA fragment separation.

High-Voltage Capillary Electrophoresis Increases Separation Speed

Anthony Carrano and coworkers at Lawrence Livermore National Laboratory (LLNL) use an Applied Biosystems, Inc. (ABI) electrophoresis system to automate and multiplex the process. In this approach fluorescent labels are ligated (attached) to restriction enzyme–digested cosmids. The fragments are separated electrophoretically and detected using a laser scanner. Multiplex operation is achieved by ligating fluorochromes (that fluoresce at different wavelengths) to separate cosmid digests, mixing these differentially labeled digests together with a standard, and running several in each gel lane.

Barry Karger and coinvestigators at Northeastern University are increasing separation speed by applying high-voltage capillary electrophoresis; they use linear polyacrylamide as the electrophoretic separation medium to achieve reproducible separation of DNA fragments ranging from 50 bp to several kb in 2 to 10 minutes. Norman Dovichi and colleagues at the University of Alberta, Edmonton, Canada, are developing a parallel capillary system that will support electrophoresis of 32 capillaries simultaneously.

Fluorescence In Situ Hybridization

The contig (contiguous set of clones) assembly methods described above are limited in that they do not always provide information on contig orientation and location on chromosomes. FISH allows localization of contig elements to metaphase chromosomes and establishment of their orientation.

Barbara Trask and coworkers at LLNL have developed dual-color FISH techniques applicable to metaphase chromosomes and interphase nuclei. Metaphase mapping localizes contig elements to within ~2 Mb along the genome, while interphase mapping allows contig element ordering in the 100-kb to 2-Mb range. Brigitte Brandriff and others at LLNL are developing hybridization to germ cell chromatin for ordering cosmids separated by < 100 kb.

Joe Gray (University of California, San Francisco; formerly at LLNL) and colleagues have developed a semiautomated computer-assisted microscope to facilitate mapping by FISH. This instrument allows simultaneous determination of the chromosomal locations of several differentially labeled clones. The number of simultaneously mapped probes is increased by identifying clones according to fluorescence intensity ratios.

DNA Fragment Analysis

Longer-range projects also are under way to facilitate DNA fragment analysis. Leonard Lerman's group at the Massachusetts Institute of Technology is evaluating the usefulness of thermal stability mapping, which is independent of restriction sites and does not require cloning. This approach, based on hybridization-pattern analysis to DNA fragments separated by two-dimensional denaturing gradient gel electrophoresis, is being tested using human genomic DNA and bacteriophage lambda DNA.

DNA SEQUENCING

Sequencing the human genome and genomes of important model organisms is likely to require sequence information for 10^{10} to 10^{12} bp of DNA. Although substantial sequencing advances have occurred in recent years, current approaches are still not sufficiently powerful for large-scale projects. Improvements are needed to facilitate DNA preparation for sequencing and to increase sequencing rate and accuracy.

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.

Sanger/Maxam-Gilbert Methods

Routine sequencing procedures entail separation and size measurement of DNA fragments resulting from the four sequencing reactions needed for each sequence analysis. Separation procedures require several hours and can reliably separate fragments with single-base resolution to only a few hundred base pairs.

Investigators at Leroy Hood's California Institute of Technology laboratory played an important early role in alleviating this bottleneck by automating the separation, replacing autoradiographic fragment-size analysis with fluorometric detection, and developing a procedure known as multiplexing for running a few differentially labeled DNA fragment collections in each gel lane; the ABI line of commercial sequencers uses this approach.

George Church and colleagues at Harvard University have extended the multiplex approach by increasing to over 40 the differentially detectable DNA fragment collections that can be run in each lane and to over 700 the bases that can be resolved in each lane. A multiplex sequencing effort using Sanger biochemistry also is proceeding under Raymond Gesteland and Robert Weiss at the University of Utah. Both the Hood and Church laboratories are also working to increase sequencing efficiency through the automation of other steps, such as DNA extraction, amplification, fragment generation, and labeling.

The multiplex approach is made increasingly powerful by adding to the number of samples that can be analyzed in each lane. Bruce Jacobson and colleagues at Oak Ridge National Laboratory (ORNL) are using resonance ionization mass spectrometry to resolve fragments labeled with stable tin and iron isotopes.

Several laboratories are working on other approaches to improve the DNA fragment separation rate and extend the fragment size that can be separated per run. Capillary electrophoresis is useful in mapping and sequencing because it allows rapid fragment separation (see Karger, p. 2). Future goals include developing fully automated instrumentation.

Investigators at Lloyd Smith's University of Wisconsin laboratory and Jacobson and his colleagues are using ultrathin 50- to 75-μm gels to increase the fragment separation rate (standard gel thickness is about 400 μm). In addition, these groups, as well as those of Peter Williams at Arizona State University and Winston Chen at ORNL, are applying mass spectrometry to high-speed fragment sizing. In this approach, individual DNA molecules are volatilized (e.g., by laser ablation), ionized, and sized by high-resolution mass spectrometry. Work is now concentrated on the volatilization and ionization steps of this process, which is attractive because of its speed and because of the potential for analysis of longer DNA fragments.

Laboratories Working To Increase Fragment Separation Rate and Size

Other Sequencing Approaches

Several new strategies are being explored that have the potential to improve sequencing rate and cost by several orders of magnitude.

Flow cytometry. An approach under development by Richard Keller and colleagues at LANL uses flow cytometry to sequence one DNA molecule at a time by

- labeling one strand of the DNA molecule with a base type–specific fluorescent molecule,
- cleaving the individual bases from one end of the molecule, and
- identifying the bases fluorometrically.

This approach has the theoretical advantages of (1) requiring only a single molecule, (2) generating sequence information at a high rate, and (3) allowing application to long DNA fragments. Single-molecule detection has been demonstrated, and work is now under way to develop single-molecule manipulation techniques and base labeling and cleaving procedures. LANL and Life Technologies, Inc. (GIBCO BRL) have entered into a cooperative agreement to collaborate on the development of this technology [see *HGN* 3(1), 5–7 (May 1991)].

Novel Approaches Show High Potential

Scanning Tunneling and Atomic Force Microscopies. Several laboratories are exploring scanning tunneling (STM) and atomic force microscopies for DNA sequence analysis. These approaches, based on the direct visualization of individual bases in DNA molecules attached to atomically flat substrates, have the theoretical advantages of requiring only a few molecules and generating sequence data at a high rate. Near-atomic-resolution images of DNA molecules have been produced by several laboratories, but sample and substrate preparation and base recognition must be substantially improved before this approach is reliable.

Wigbert Siekhaus and colleagues at LLNL are developing improved methods for deposition and bonding onto substrates, such as pyrolytic graphite for STM DNA analysis. So

Multiplex Techniques Are Increasing Sequencing Efficiency

Instrumentation Development

Established Techniques Now Applied to Sequencing:

- Flow Cytometry
- STM
- X-Ray Diffraction
- Hybridization

far their system can resolve individual adenine and thymine molecules deposited on these substrates. Troy Wilson and others at Miguel Salmeron's LBL laboratory are developing STM with a decreased scanning force to reduce scanning damage and to explore new procedures for attaching DNA molecules to the scanning substrate. Raoul Kopelman and coinvestigators at the University of Michigan are developing molecular exciton microscopy, based on the interaction of mercury-labeled bases with a laser-illuminated crystalline scanning tip, to distinguish specific bases during scanning without application of any mechanical force. Bruce Warmack, Tom Ferrell, and ORNL colleagues have demonstrated that STM can routinely image DNA prepared by electrospray and have also shown that covalent attachment of DNA to a substrate surface offers advantages for STM imaging.

X-Ray Diffraction. Gray, Jim Trebes, and LLNL colleagues have described an approach to DNA sequence analysis based on X-ray diffraction from arrays of DNA molecules. Four samples, one for each base labeled with an efficient X-ray scatterer such as mercury, are prepared for each sample. The distances between labels (and hence the sequence) are determined by analysis of the X-ray diffraction pattern from an ordered array of labeled molecules. Theoretical studies indicate that illumination with a bright X-ray source, such as a synchrotron, might generate an interpretable diffraction pattern from a DNA sample in a few seconds. The feasibility of this approach has been demonstrated theoretically, and recent experiments suggest that the preparation of properly ordered arrays of molecules from nanogram amounts of DNA might be the most challenging aspect of this approach.

Sequencing by Hybridization (SBH). Another novel approach to sequencing comes from Radoje Drmanac, Radomir Crkvenjakov, and colleagues at Argonne National Laboratory, who are pursuing SBH of multiple, short oligonucleotide probes to DNA samples. Sequence information is determined by mathematical analysis of the probe hybridization pattern. The advantage of this technique is that it does not require preparation of labeled DNA samples or fragment sizing; however, it does require a large number of hybridization reactions (e.g., 500 to 3000 hybridizations of 6 to 8 mers for sequencing 1- to 10-kb DNA fragments). Miniaturization of SBH by forming arrays of either DNA or oligonucleotides attached to microbeads is being developed to facilitate this process.

Robert Foote and coworkers at ORNL are developing the synthesis of microscale arrays of defined oligonucleotide sequences on planar supports to simplify SBH. The synthesis of 65,536 8-mer oligonucleotides in only 32 chemical reactions can occur by methods under development. A practical way to implement this approach would be to hybridize fluorescently labeled DNA samples against the array and read the pattern instrumentally. ◊

NCHGR Sets Human Genome Lecture Series

The NIH National Center for Human Genome Research (NCHGR) is sponsoring The Human Genome Lecture Series to be held in Building 10 on the NIH campus in Bethesda, Maryland. The September lecture will be in the Masur Auditorium; the other lectures will take place in the Lipsett Auditorium.

For further information or to schedule an appointment with the speaker, contact

- Carol Dahl, NCHGR, at 301/402-0838. ◊

Date and Time	Speaker and Affiliation	Lecture Title
September 19 11:30 a.m.	David Botstein Stanford University School of Medicine	Why We're Sequencing the Yeast Genome
October 17 11:30 a.m.	Nancy Wexler Hereditary Disease Foundation and Columbia Presbyterian Medical Center	The Human Genome Project and Its Social Impact
November 20 2:00 p.m.	Thomas Marr Cold Spring Harbor Laboratory	New Computational Methods for Genome Analysis
December 19 11:30 a.m.	Mary Claire King University of California, Berkeley	Genetic Mapping of Human Breast Cancer
January 16, 1992 11:30 a.m.	Robert Waterston Washington University School of Medicine	Mapping and Sequencing the **Caenorhabditis elegans** Genome
February 20, 1992 11:30 a.m.	Lloyd Smith University of Wisconsin, Madison	High-Speed DNA Sequencing in Ultrathin Gels
March 19, 1992 11:30 a.m.	Dorothy Nelkin New York University	Social Implications: Genetics and Popular Culture
April 16, 1992 11:30 a.m.	Jeanne Lawrence University of Massachusetts Medical School	Genome Mapping and Functional Organization of the Interphase Nucleus
May 21, 1992 11:30 a.m.	Francis Collins University of Michigan School of Medicine	The Human Genome Project and the Future of Medicine

Rine Named Acting LBL Center Director

Jasper D. Rine was named on May 13 the Acting Director of the Human Genome Center at Lawrence Berkeley Laboratory (LBL) and to a position in the LBL Cell and Molecular Biology Division, of which the center is a major component. Rine will maintain his current professorship of genetics at the University of California, Berkeley (UCB), which he joined in 1982.

"The Human Genome Center at LBL is an opportunity to establish for the biology community the same synergistic relationship between LBL and the UCB campus that exists in physics and chemistry," Rine said. "The Berkeley environment is one of the few places where a major research university and a major DOE facility are physically adjacent, and I believe this proximity can foster interaction to catalyze new scientific discoveries." Rine expects to add an emphasis on genetics and genetic analysis to the current strengths in instrumentation, informatics, and physical mapping.

As a member of the LBL Human Genome Center Advisory Committee, Rine will meet with Cochairs Leroy Hood (California Institute of Technology) and Gerald Rubin (UCB), David Cox (University of California, San Francisco), and David Botstein (Stanford University) to identify priorities in human genome research and to ensure that the work at the center complements the efforts at other laboratories.

Rine holds a Ph.D. in molecular genetics from the University of Oregon and was a postdoctoral fellow at the Stanford University School of Medicine. For a number of years his laboratory research has focused on the use of genetically tractable organisms to study human disease. His more recent research has turned toward developing the methodology for exploiting natural genetic polymorphisms to study the inheritance of natural variation. ◇

Reported by Anne Adamson
HGMIS, ORNL

Jasper D. Rine
Acting Director
Human Genome Center
Lawrence Berkeley
Laboratory

DOE Awards Postdoctoral Fellowships

The DOE Office of Health and Environmental Research (OHER) has announced awards of five Human Genome Distinguished Postdoctoral Fellowships. The winners, listed below with their graduate departments and host institutions, were selected from 42 applicants.

The program, now in its first cycle, was created to offer challenging training opportunities for recent doctoral degree recipients to conduct research in support of the DOE Human Genome Program. Fellowship periods of up to 2 years are served at university and DOE laboratories having substantial DOE-sponsored research supportive of its Human Genome Program. Stipends are $35,000 for the first year and $37,000 for the second. Applicants must hold or expect to complete their doctoral degrees within 3 years of starting their fellowships. The next application deadline is February 1, 1992. (See p. 21 for contact information.)

Oak Ridge Associated Universities (ORAU), which manages the program and the fellowship selection process, is a private, nonprofit association of 59 colleges and universities, as well as a DOE management and operating contractor. ORAU also manages two other OHER fellowship programs that complement the human genome fellowships—the Alexander Hollaender Distinguished Postdoctoral Fellowships and the Global Change Distinguished Postdoctoral Fellowships. ◇

Reported by Linda Holmes
ORAU

Next Application Deadline:

February 1, 1992

DOE Human Genome Distinguished Postdoctoral Fellows

Xiaohua Huang (Stanford University, Biophysical Chemistry)
Host: *University of California, Berkeley*

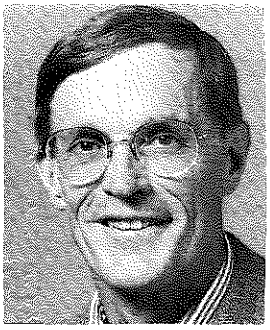
Ben Koop (Wayne State University, Molecular Biology and Genetics)
Host: *California Institute of Technology*

Markley Leavitt (University of Arizona, Molecular Biology)
Host: *The Salk Institute for Biological Studies*

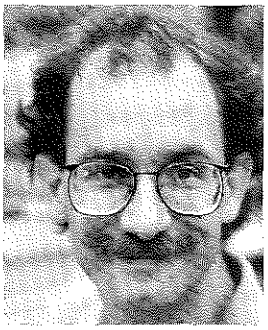
Carol Soderlund (New Mexico State University, Computer Science)
Host: *Los Alamos National Laboratory*

Harold Swerdlow (University of Utah, Bioengineering)
Host: *University of Utah*

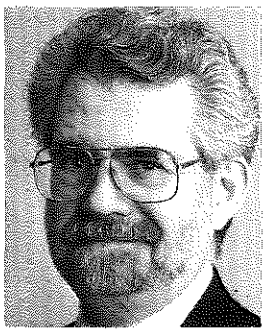
Genome News



Raymond F. Gesteland
University of Utah



Lloyd M. Smith
University of Wisconsin



Robert J. Robbins
Genome Data Base
Johns Hopkins University

DOE Names Gesteland, Smith to HGCC

Raymond F. Gesteland and Lloyd M. Smith were recently named by DOE to its Human Genome Coordinating Committee.

Gesteland is professor and Cochairman of the Department of Human Genetics at the University of Utah, where he moved in 1978 after having served as Assistant Director for Research and Senior Staff Investigator at Cold Spring Harbor Laboratory. At the University of Utah Eccles Institute, he is an investigator for the Howard Hughes Medical Institute Laboratory for Genetic Studies and a codirector of its human genome program. With coinvestigator Robert Weiss, Gesteland has been developing a total strategy for genome sequencing based on a core multiplex sequencing methodology. Gesteland received a B.S. in chemistry and an M.S. in biochemistry from the University of Wisconsin and a Ph.D. in biochemistry from Harvard University. He completed a predoctoral fellowship at Harvard University and a postdoctoral fellowship at the University of Geneva.

Smith has been an assistant professor of chemistry at the University of Wisconsin, Madison, since 1988. He received an A.B. in biochemistry from the University of California, Berkeley, in 1977 and a Ph.D. in biophysics from Stanford University in 1981. In 1982 he joined the California Institute of Technology, where he was the primary developer of the first fluorescence-based automated DNA sequencing instrument. In 1985 he was chosen as one of the top 100 innovators by *Science Digest*, and in 1989 he received both the Presidential Young Investigator Award and the Eli Lilly Analytical Chemistry Award. ◇

Robbins Joins Library, Genome Data Base

On August 1, Robert J. Robbins assumed the post of Director of the Laboratory for Applied Research in Academic Information, William H. Welch Medical Library, at Johns Hopkins University. He will also perform the duties of principal investigator for the informatics core of the Genome Data Base, located at Hopkins, where he will oversee the work of the computational staff. Robbins will serve as informatics liaison to other databases such as GenBank® and to national and international scientists performing genome-related research in laboratories and centers.

Robbins came to Hopkins from the National Science Foundation (NSF), where he was Program Director for Database Activities in the Biological, Behavioral, and Social Sciences; he was also detailed part time as an informatics advisor to the DOE Human Genome Program. Before joining NSF in 1987, Robbins was an associate professor in the departments of biological science and zoology at Michigan State University. ◇

NIH To Hold Minority Programs Symposium

The 1991 Minority Programs Symposium, sponsored by the NIH National Institute of General Medical Sciences, will be held November 3–6 in Washington, D.C.

The symposium, the largest U.S. gathering of minority scientists and students, is designed to promote minority involvement in ongoing biomedical research by presenting a vast array of career opportunities and available graduate-level educational experiences. The meeting also provides the opportunity for exhibiting organizations to meet qualified minority prospects for doctoral and other educational programs.

- Attendance and exhibitor information: Mark Brown (TASCON, Inc.), 301/907-3844. ◇

Newsletter To Feature Genome Data Base

The November *Human Genome News* will be largely focused on GDB, now jointly sponsored by NIH and DOE, and future issues will feature a page for GDB news and information. ◇

DOE OHER Proposes Guidelines for Access to Its Human Genome Program Data and Material Resources

The information and resources generated by the U.S. Department of Energy Office of Health and Environmental Research (DOE OHER) Human Genome Program have become sizeable, and the number of collaborations is growing steadily. Because of this, DOE OHER is planning to adopt the following guidelines to govern access to DNA mapping and sequencing data and the sharing of materials. It is expected that adoption of these guidelines will be an agenda item of the next DOE-NIH Joint Subcommittee on the Human Genome, which will meet in Irvine, California, in January 1992.

Data-Sharing Guidelines Proposed for Awardees, Contractors, and Grantees

Although the desire of DOE OHER is to maximize outreach to the scientific community, there is also an acute awareness of the investigator's need to maintain an edge in the present competition-driven environment. Genetic materials and information are being accumulated rapidly, and much of it is deposited in and available through various repositories (American *Type Culture* Collection, Genome Data Base, GenBank®, etc.).

For materials and information not yet in repositories, the following sharing guidelines for DOE Human Genome Program awardees, contractors, and grantees have been developed. These guidelines are the result of much internal discussion and consultation with investigators at several laboratories dealing with these issues; these guidelines were carefully considered by the DOE Human Genome Coordinating Committee.

Published Data

Information and materials either developed by or provided to a DOE awardee, contractor, or grantee and published in the open literature should be made freely available to the scientific community. Reasonable requests for information and materials should be honored to the extent that the DOE investigator has the resources to accommodate them.

Recipients should abide by any donor laboratory's requirements pertaining to further distribution, nomenclature, or proprietary rights. Proper acknowledgement of the donor laboratory should be made by the recipient in any subsequent publications and reports. There may be exceptions to this sharing policy for materials not originating in the laboratory of the DOE awardee, contractor, or grantee and covered under a separate third-party agreement.

Collaboration

Collaboration between an awardee, contractor, or grantee and a requestor is encouraged as a means of advancing the science and protecting the proprietary rights of the laboratory originating the data. The awardee should provide to collaborators, upon request, those materials (clones, cell lines, probes, etc.) relevant to the region of mutual interest and information on the status of the corresponding region of the larger physical/genetic map.

Suitable Delay

Unpublished information and materials also should be made available to the scientific community after a suitable delay that will give the originating scientist(s) time to do follow-up work. Specifically, data generated internally by the awardee, contractor, or grantee or through external collaboration should be entered into a database once the information is felt to be useful to the scientific community. At the time of entry, these data should be encoded with a time stamp. *Information* stored in the database should be made accessible no later than 6 months after data entry. *Materials* (cell lines, clones, probes, etc.) associated with the data should also be made accessible no later than 6 months after data entry.

The DOE awardee, contractor, or grantee should endeavor to accommodate the desires of all requestors. It is understood that, at times when this cannot be done, exceptions will have to be made.

All information and material resources ultimately should be available in a public database and/or repository. In addition, data of value to collaborators and other investigators but too detailed to be stored in central archives should be translated into machine-readable form and made directly accessible using standard methods and data query protocols via Internet. ◊

If there are any questions or if concerns arise about these guidelines, please contact

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Genome News

Grantees, PACHG Recommend Annual Grantee Workshops

Physical Mapping, YACs Are Featured Topics at First NCHGR Grantee Workshop

On June 24 the National Center for Human Genome Research (NCHGR) held its first Grantees Workshop in Bethesda, Maryland, in conjunction with the semiannual meeting of the Program Advisory Committee on the Human Genome (PACHG). Over 125 grantees, advisors, scientists, and invited guests attended the 1-day workshop to discuss the state of physical mapping, assess progress toward the Human Genome Project's 5-year goals for physical mapping, and address future mapping directions and needs. Oral and poster presentations were given on work performed under more than 50 active physical mapping and mapping technology development grants.

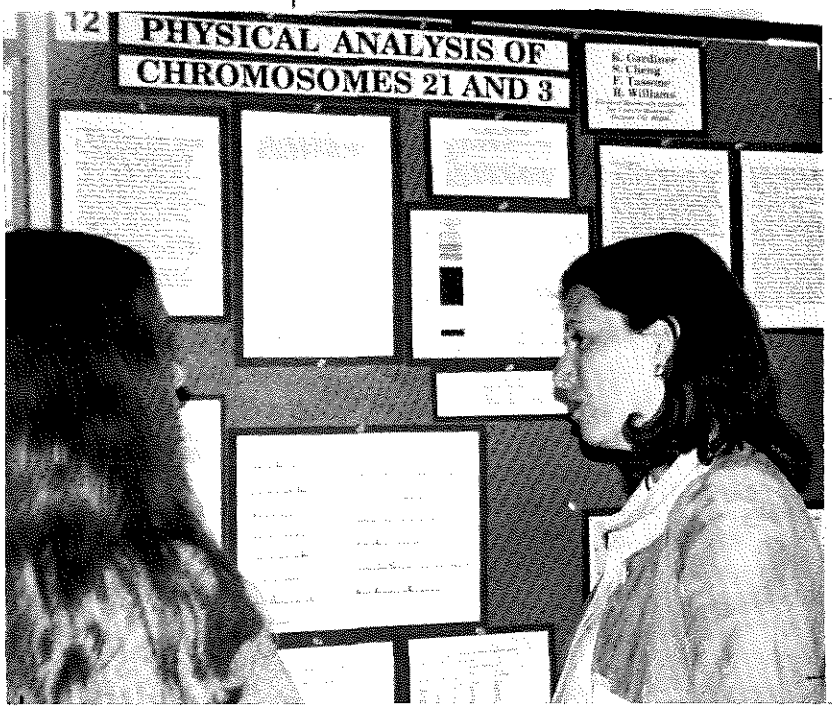
After welcoming remarks by NCHGR Director James Watson and PACHG Chair Paul Berg, the morning program focused on technology development for physical mapping.

- Maynard Olson (Washington University) gave a keynote talk on the development of current approaches to large-genome physical mapping.
- David Patterson (Eleanor Roosevelt Institute) reported on the human chromosome 21 Joint YAC Screening Effort, which is a community-wide collaboration for central screening of the St. Louis yeast artificial chromosome (YAC) library to identify clones derived from chromosome 21.
- David Ledbetter (Baylor College of Medicine) discussed his laboratory's work on the use of repeat-sequence polymerase chain reaction methods in human chromosome 17 physical mapping.
- Jeanne Lawrence (University of Massachusetts) described her efforts to develop fluorescence in situ hybridization of metaphase and interphase chromosomes as a tool for mapping and genome characterization.
- Paul Meltzer (University of Michigan) talked about using chromosome microdissection applications to establish a human chromosome 6 physical map.
- Scott Strobel (California Institute of Technology) described his work in Peter Dervan's laboratory on site-specific enzymatic cleavage of a human chromosome mediated by triple-helix formation.

Grantees presented summaries of their work at poster sessions, where they had the opportunity to talk with other grantees and advisors. A panel composed of PACHG members and chaired by Norton Zinder (Rockefeller University) led discussions on the state of physical mapping, primarily on improvements in the resolution of in situ hybridization and other mapping studies. Additional topics were YAC technology limits, existing YAC libraries' status, and potential ways to improve the YAC system.

Grantees and advisors concluded that the workshop provided a useful forum for NCHGR-supported investigators to discuss their work and meet with others in the field. PACHG members strongly recommended that similar workshops be held annually. ◊

Reported by Mark Guyer
Assistant Director for Program Coordination
and
Joyce Rudick
Program Assistant
NIH NCHGR



NCHGR grantees (from left) Katheleen Gardiner (Eleanor Roosevelt Institute) and Julie Korenberg (Cedars-Sinai Medical Center) discuss procedures at the Grantee Workshop in Bethesda, Maryland, on June 24.

NIH-DOE Joint Subcommittee, NIH Program Advisory Committee Hold Meetings

The NIH-DOE Joint Subcommittee on the Human Genome and the NIH Program Advisory Committee on the Human Genome (PACHG) met in Bethesda, Maryland, on June 25. Discussions at the subcommittee meeting centered around policies for joint meetings with PACHG, future meeting dates, and reports on working groups and international genome programs.

The afternoon PACHG meeting included discussions on training, physical mapping, and genetic test evaluation. [See box, p. 10 for list of each meeting's attendees; for a list of subcommittee and PACHG members and their affiliations, see *HGN* **2**(3), 7 (September 1990) and *HGN* **3**(1), 9–10 (May 1991).]

Joint Subcommittee Meeting

The subcommittee discussed the agenda for the joint DOE-NIH staff retreat in California and heard reports from the joint working groups.

Dieter Soll (Yale University) presented the Joint Informatics Task Force report. He summarized the group's recent efforts, emphasizing that its organization has improved as its purpose has been refined. He attributed this improvement particularly to the efforts of David Benton (NCHGR) and Robert Robbins (Johns Hopkins University) in his role as DOE Human Genome Program informatics detailee while at the National Science Foundation. The working group established a January 1992 target date for production of a resource report defining the scope and nature of genome informatics.

Nancy Wexler highlighted the report of the Working Group on Ethical, Legal, and Social Issues (ELSI) related to data produced in the Human Genome Project. She noted that grants for pilot projects in cystic fibrosis (CF) testing would be awarded soon. Wexler detailed four major ELSI working group priorities:

- public and professional education,
- genetic test quality and access,
- fair use of genetic information by employers and insurers, and
- privacy issues involving genetic information.

The ELSI Working Group has created an insurance task force to consider insurance practices related to CF and will be reviewing privacy issues. After Wexler discussed the Americans with Disabilities Act of 1990, the subcommittee agreed to make a statement consistent with ELSI Working Group recommendations to the Equal Employment Opportunity Commission, which will interpret and implement the act (see ELSI Working Group Statement, pp. 12–13). Subcommittee members also discussed NIH and DOE regulations governing such statements about legislation and regulations; although NIH and DOE cannot present comments, individual advisory groups may do so.

Subcommittee members asked about various mapping workshops in the United States and abroad. Elke Jordan noted that a chromosome workshop summary was included in the handout material, and Benjamin Barnhart reported on an upcoming mapping workshop on chromosome 16 in Adelaide, Australia.

Members generally agreed that model-organism mapping and single-chromosome workshops have had a measurable impact on mapping standards. Phillip Sharp suggested that an annual report be produced to summarize progress in mapping individual chromosomes.

Mark Guyer (NCHGR) noted that grants for mapping index markers have been awarded by NCHGR and investigators have begun their projects. [For a list of projects and awardees, see *HGN* **3**(2), 1–2 (July 1991).] He also reported on the first meeting of the NCHGR Framework Map Collaborative Working Group.

Verne Chapman (Roswell Park Cancer Institute) presented the report of the Joint Working Group on the Mouse [see *HGN* **3**(2), 4–5 (July 1991)]. He said the mouse's main strengths are its inbred strains representing defined fixed genotypes and the large number of recombinant inbred strains. Mouse genetic mapping resources are equivalent to fully informative human families for almost any functional gene under study, Chapman said, necessitating ongoing communication between the mouse genetic research community and human genome mappers.

(continued)

Subcommittee Considers Joint Meetings with PACHG

Joint Working Groups Take Action

- **JITF Sets January 1992 Target Date for Resource Report**
- **ELSI Creates Insurance Task Force**

Genome News

NIH-DOE Joint Subcommittee on the Human Genome*

Cochairs: Paul Berg and Sheldon Wolff	Charles Cantor	Robert Moyzis	Mark Pearson
	Anthony Carrano	Maynard Olson	Diane Smith
	Leonard Lerman	MaryLou Pardue	Nancy Wexler

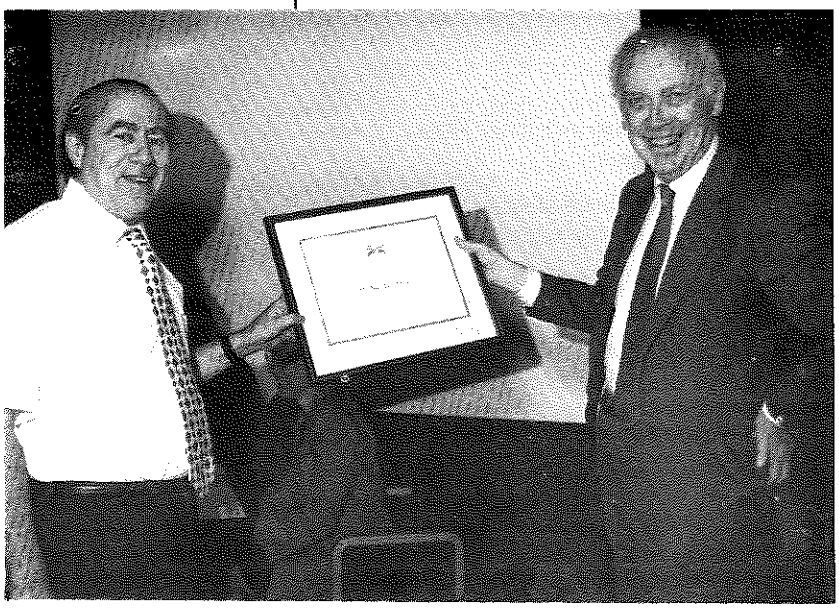
NIH Program Advisory Committee on the Human Genome*

Chair: Paul Berg	Elke Jordan	Mark Pearson	**Other Participants:**
Bruce Alberts	Victor McKusick	Phillip Sharp	Norton Zinder
	Maynard Olson	Nancy Wexler	Benjamin Barnhart

*Members attending meeting.

NLM To Administer GenBank® Beginning 1992

Norton Zinder (Rockefeller University), on left, receives a certificate in recognition of his leadership and outstanding contributions as the first chair of the NIH Program Advisory Committee on the Human Genome. Presenting the commendation is James Watson, Director of the NIH National Center for Human Genome Research.



Reports on International Genome Programs

Michele Durand (Science Attache, French Embassy) explained the structure and organization of the French human genome research program. She noted that the first French human genome laboratory was to be established this summer in Paris.

Bronwen Loder [European Communities (EC)] said the EC genome program Eurogem has called for research proposals in three research areas; the EC commission is investigating the limited response in the informatics area. She announced that the new Biomedical and Health Research Program should be approved in the fall of 1991 and would continue through 1994. Questioned about patents for cDNA sequences, Loder explained that EC provisions prohibit exclusive rights to a particular cDNA sequence.

Charles Cantor reported on the restructuring of the Human Genome Organization (HUGO) to establish an office in Moscow (see article, p. 14). The major mission of HUGO – coordinating worldwide single-chromosome mapping – would merge HUGO activities with the organizational and committee structure of the human gene mapping workshops. Cantor noted that reasonable workshop locations would be geographic areas where the majority of research on specific chromosomes is taking place.

David Lipman [National Center for Biotechnology Information, National Library of Medicine (NLM)] outlined various cooperative ventures, including genome research activities, being pursued by NLM. He said that NLM would assume responsibility for GenBank® in 1992 and that the transition is progressing smoothly.

David Galas (DOE Human Genome Program) updated the subcommittee on the DOE cDNA initiative; $1.4 million has been devoted this year to six initial cDNA projects, which emphasize generating cDNA libraries and sequence tagged sites (STSs) and mapping and sequencing cDNAs. He also reported that the U.S. House of Representatives and Senate have approved the requested 1992 DOE budget of $59 million for its Human Genome Program.

Galas briefly highlighted recent DOE activities, which include substantial progress in physical mapping, informatics, and technology development. Anthony Carrano (Lawrence Livermore National Laboratory Human Genome Center) said that the chromosome 19 map is about 70% (41 Mb) covered in cosmid contigs. Robert Moyzis (Center for Human Genome Studies, Los Alamos National Laboratory) reported that a 90% coverage (90 Mb) of chromosome 16 has been achieved, with closure anticipated in the next few years (2-Mb contigs, 0.1-Mb spacing of STSs).

NIH PACHG Meeting

Paul Berg, the new chairman of NIH PACHG, welcomed participants. Elke Jordan (NCHGR) reported on several items of general interest as well as the NCHGR budget, which is awaiting action from the Senate. The House approved an NCHGR budget of $93 million, down from $110 million requested by the President. She noted that the budget cut was designed to maintain the current level of program activity and included a cost-of-living increase.

Jordan stated that the disappointing response to a recent training grant solicitation might be the result of several factors, such as lack of information and relatively low stipends. Bettie Graham (NCHGR) also noted the small number of respondents as she outlined recent training activities and described various institutional training grant awards. Graham asked PACHG members for input on possible training course topics, emphasizing that the purpose is rapid introduction of new laboratory technology.

Jordan explained the purpose and objectives of the new K01 career award, and PACHG members approved a concept paper that Graham presented for a solicitation on a Special Emphasis Research Career Award (K01). Graham expressed the hope that the $50,000 annual stipend would attract qualified applicants from nonbiological disciplines.

The committee noted that the NIH-DOE Joint Mapping Working Group needs to meet soon to discuss physical and genetic mapping progress; Sharp stressed the need to establish some standard by which mapping progress can be measured.

Eric Juengst (NCHGR) discussed genetic testing evaluation for CF and enumerated six research areas for consideration: public understanding of the issues, optimum pretest education levels, effective posttest counseling, optimum test settings, confidentiality concerns, and test accuracy and cost-effectiveness.

PACHG also received an update on CF activities and discussed the status of p53 testing. ◊

1992 PACHG, Subcommittee Meetings Planned for January 3–4 and June 22–23

Genome Study Section Established at NIH

The NIH Division of Research Grants Genome Study Section held its first meeting on June 20–21 in Washington, D.C. Members (listed in box) reviewed grant applications and were oriented on NIH procedures.They advise NIH on grant applications for research on the characterization of the genomes of human and other organisms.

The study section meets three times a year to consider applications for several types of grant mechanisms: R01s (traditional research projects), R21s (pilot projects), R29s [First Independent Research Support and Transition (FIRST) Awards], and K04s (Research Career Development Awards).

Research areas include

- genetic map expansion;
- physical map development;
- DNA sequence determination;
- map and DNA sequence management and analysis; and
- innovative development of technology, tools, and resources in genetics, molecular biology, chemistry, and biophysics required to achieve these goals.

The NIH Director appoints Genome Study Section members from the fields of cytogenetics, human genetics, molecular genetics, quantitative genetics, somatic cell genetics, molecular biology, biochemistry, chemistry, biophysics, physics, and computer science. ◊

Reported by Cheryl M. Corsaro
NIH Division of Research Grants

GENOME STUDY SECTION

Chair:
Frank H. Ruddle
Yale University

Elbert W. Branscomb
Lawrence Livermore National Laboratory

Neal Castagnoli, Jr.
Virginia Polytechnic Institute

Aravinda Chakravarti
University of Pittsburgh Graduate School of Public Health

Louise B. Clarke
University of California, Santa Barbara

Walter Gilbert
Harvard University

Steven Henikoff
Howard Hughes Medical Institute; Fred Hutchinson Cancer Research Center

Michael Litt
Oregon Health Sciences University

Marcos F. Maestre
Lawrence Berkeley Laboratory

Joachim Messing
Rutgers University Waksman Institute

Barbara R. Migeon
Johns Hopkins University School of Medicine

Orlando J. Miller
Wayne State University School of Medicine

Webb Miller
Pennsylvania State University

Robert K. Moyzis
Los Alamos National Laboratory

Lee M. Silver
Princeton University

Mark H. Skolnick
University of Utah Medical Center

Nat Sternberg
Du Pont/Merck Pharmaceutical Co.

Dorothy P. Warburton
Columbia University College of Physicians & Surgeons

Carol A. Westbrook
University of Chicago

Barbara J. Wold
California Institute of Technology

Scientific Review Administrator:
Cheryl M. Corsaro
NIH Division of Research Grants

Genome News

ELSI Working Group Studies Genetic Bias

ELSI Statement Recommends Revisions to Americans with Disabilities Act

The NIH-DOE Working Group on the Ethical, Legal, and Social Issues (ELSI) related to data produced by the Human Genome Project held its fifth meeting on April 29–30 at Los Alamos National Laboratory. The agenda included consideration of regulations proposed by the Equal Employment Opportunity Commission (EEOC) to implement Title I of the Americans with Disabilities Act (ADA), as well as a workshop on genetic discrimination.

With the assistance of Mark Rothstein (University of Houston Health Policy Institute), the working group recommended revisions in the EEOC guidelines designed to prohibit employment discrimination against individuals with disabilities. In its advisory capacity, the ELSI working group forwarded the text to its parent organization, the NIH-DOE Joint Subcommittee on the Human Genome; the subcommittee made a statement consistent with the recommendations. [See report to the subcommittee by Nancy Wexler (Chair, Joint ELSI Working Group), p. 9.] DOE and NIH cannot issue statements about legislation and regulations, but the subcommittee, as advisor to these agencies, may do so. (See box below and on p. 13 for full text of the statement.) The final ADA regulations published by EEOC on July 26 did not address the subcommittee's recommendations. (See *Federal Register* **56**, 35726–56.)

The recommendations were

- to prohibit discrimination against unaffected heterozygous carriers of recessive autosomal or X-linked genetic disorders that might affect their offspring (the regulations do cover discrimination against employees who are themselves affected by genetic disorders) and
- to limit employment entrance medical examinations to the assessment of job-related physical and mental conditions.

The working group also recommended that EEOC develop requirements to maintain confidentiality of employee medical records in connection with job-related medical assessments and health insurance claims.

Workshop on Genetic Discrimination

Marc Lappe (University of Illinois College of Medicine), the first speaker in the workshop on genetic discrimination, discussed racial myths and noted that socioeconomic factors have been found to be a much stronger indicator of certain health outcomes than race. He predicted that the

Statement of Recommendations by the Joint Working Group on Ethical, Legal, and Social Issues (ELSI) Concerning Genetic Discrimination and ADA Implementation

The Joint Working Group on Ethical, Legal, and Social Issues in Human Genome Research met at Los Alamos National Laboratory on 29 April 1991. This working group is sponsored by the Human Genome Program, U.S. Department of Energy, and the National Center for Human Genome Research, National Institutes of Health. The Joint Working Group brought together experts from law, human genetics, voluntary health organizations, and other fields to discuss the Americans with Disabilities Act (ADA).

The effort to map the human genome will, over the coming decade, create the tools to analyze human genetics in enormously greater detail than hitherto possible. The joint NIH-DOE five-year goals for human genome research, for example, call for a set of index markers that span all the human chromosomes in the next several years and a high-resolution map of the entire genome within five years. Such a map will greatly enhance our ability to identify genetic factors that influence disease and disability. New technologies will introduce new choices for individuals, and also difficult public policy choices. The rapidly expanding power of human molecular genetics promises great benefits, but also raises the specter of genetic discrimination — that is, the use of genetic information to classify persons into groups, some of which are denied opportunities offered to other groups.

Access to jobs is a central concern. The ADA is intended to address potential issues of great concern to those who might be subject to discrimination on the basis of genes they bear. These comments do not reflect on past actions or policies of the sponsoring agencies or other groups. They are recommendations intended to bring this issue to the attention of the Equal Employment Opportunity Commission (EEOC).

I. Coverage of Genetic Conditions

Although individuals who already manifest symptoms of a severe genetic disease and individuals at increased risk of a severe genetic disease are covered by Section 3(2) and Section 1630.2, the proposed regulations do not expressly state that unaffected heterozygote carriers of recessive disorders and X-linked disorders are covered when the basis for their exclusion is the fear that the individual is at risk of parenting a child who will have the condition. Congress sought to prohibit discrimination based on associations in enacting Section 102(b)(4). Because of the substantial economic incentives for employers to engage in this form of discrimination, EEOC should revise its proposed Section 1630.21 to provide that "is regarded as having such an impairment" includes action based on an individual's genotype.

II. Job-Related Employment Entrance Examinations

Proposed Section 1630.14(b)(3) provides that an employment entrance examination administered after a conditional offer of employment need not be job-related, although only job-related criteria may be used as the basis for screening out otherwise qualified individuals. In effect, employers are permitted to require, as a condition of employment, that individuals accede to medical examination, including genetic tests, whose results may not be used for screening purposes.

While purporting to prohibit discrimination, the regulation facilitates discrimination because neither the ADA nor the EEOC regulations have yet altered the existing common law of employment relations, which provides that: conditional offerees have no right to know what medical tests are being performed (e.g., the specific tests being run

Human Genome Project will uncover many disease polymorphisms transcending race and thus will help to blur artificial racial distinctions.

Lappe questioned the relative importance accorded to genetic identity as a predictor of somatic identity, because many body systems have mechanisms that allow genetic change and are highly mutable. He noted that genetic susceptibility to disease can be demonstrated in some cases only under exposure to constant environmental conditions. Further, Lappe discussed evidence that the germ line is susceptible to environmental insults, and he looked to the Human Genome Project to shed light on this vulnerability. Finally, he warned against using genetic data to define normalcy as opposed to identifying deviancy.

Paul Billings (Pacific Presbyterian Medical Center) spoke on genetic discrimination in insurance and employment, which he suggested is fairly widespread. Billings related some of the 37 cases of genetic discrimination that he has reviewed, and he described his proposed 5-year moratorium on the use of genetic information by insurers and employers.

Sue Levi-Pearl (Tourette Syndrome Association) said her organization has received scores of reports that health insurance was denied on the basis of Tourette syndrome diagnosis, although most individuals affected by this disorder have mild cases that never require medical attention. She said insurers are acting not on the basis of knowledge but on the unfounded fear that Tourette syndrome will cause significant medical expenses.

Levi-Pearl also touched on several other issues of concern to those affected by genetic disorders, including protection of privacy, employment discrimination, insufficient genetic counseling resources, and potential misuse of genetic testing.

Troy Duster (University of California, Berkeley) rebutted the assumption that information from the Human Genome Project will simply penetrate society, producing important health outcomes. Instead, he said, some groups may incorporate genetic information in a collective process, as in Tay-Sach's screening, while other groups may be fragmented by the information, as in thalassemia testing in Greece. Genetic information cannot be simply dropped into the social realm without assessing its implications for the affected group, he said, particularly a group at the base of the social order and with few resources. For the Human Genome Project to produce effective health interventions, he continued, we must study how genetic information is received.

(see ELSI, p. 14)

on a blood sample); conditional offerees have no right to know the results of genetic and other medical tests; and conditional offerees have no right to know why a conditional offer of employment was withdrawn. Because this information is only discoverable, if at all, after the filing of a discrimination claim, it facilitates surreptitious testing and discriminatory reliance upon non-job-related criteria in making decisions.

Equally important, the ADA seeks to promote autonomy and confidentiality. Even genetic and other medical examinations of employees of some efficacy in promoting employee health generally, such as mandatory, comprehensive annual physicals, should not be permitted unless they are job-related or voluntary. Section 102(c)(4). When medical disclosures are made, they must be confidential. Section 102(c)(3).

Under this proposed regulation, employers would be permitted to perform genetic testing, HIV testing, and other non-job-related medical examinations of conditional offerees. This could not have been intended by Congress.

EEOC should amend Section 1630.12(b)(3) to provide that post-offer, employment entrance medical examinations must be limited to assessing job-related physical and mental conditions.

III. Access to Genetic Information in Medical Records and Health Insurance Claims

A. Medical Records

Employers conducting lawful, job-related medical assessments may need to obtain information about the individual's medical condition. Current practice is for employers to require that the individual sign a release authorizing the health care provider to release the records. Hospital records and medical records of an individual's treating physician often contain much information of a highly confidential, non-job-related nature, including genetic information. It is infeasible for the health care provider to "sanitize" the records before disclosure.

B. Health Insurance Claims

A significant, but largely unrecognized, threat to the confidentiality of employee genetic and medical information exists in the method of paying employee health insurance claims. Perhaps most pronounced at large, self-insured companies, these breaches of confidentiality are very common. When a health care provider submits a bill for payment, it will customarily contain an explanation of the nature of the services rendered, either by description or code number. These bills are processed by the benefits office, not the medical department, and access to the information may be widespread.

EEOC should initiate rulemaking proceedings to determine the most effective way of protecting the privacy of health insurance claims information. One possible option is for each employee to have a separate medical claims number and have claims submitted by number only. ◊

Signatories to the Joint ELSI Working Group Statement to EEOC

Joint ELSI Working Group Chair:
Nancy S. Wexler
Columbia University; Hereditary Disease Foundation

Jonathan Beckwith
Harvard Medical School

Robert M. Cook-Deegan
Institute of Medicine
National Academy of Sciences

Patricia King
Georgetown University Law Center

Robert F. Murray, Jr.
Howard University College of Medicine

Thomas H. Murray
Case Western Reserve University

Genome News

HUGO Establishes Office in Moscow

Soviet Union Genome Program Numbers 1000 Researchers in 100 Laboratories

The Human Genome Organization (HUGO) and the Soviet Union have agreed on a Moscow HUGO office as a satellite of the London-based regional office, HUGO Europe. This accord grew out of June meetings in Moscow among representatives of HUGO and three Soviet organizations: Academy of Sciences, State Committee for Science and Technology, and Council of the Human Genome Program.

The Moscow HUGO office, which officially came into existence on July 1, will encourage Soviet genome scientists to become integrated more fully into the global Human Genome Project. As the project's international coordinating body, HUGO will both facilitate and be implemented by the development of communication links, the exchange of scientists, the improved flow of genome-related information, and the spread of new technologies between the Soviet Union and other countries.

The Soviet Union has a substantial human genome program involving 60 different research centers, 100 laboratories, and 1000 scientists. Public opinion is described by some of the scientists involved as "very positive." The program received generous government support during its initial 3-year period with total funding of nearly 90 million rubles, including 32 million rubles for the current year. This year also marks the beginning of a shift from basic funding of Academy of Science institutes to support through grants.

During discussions in Moscow, Academician Nikolay Laverov (Deputy Prime Minister and Chairman of the Soviet State Committee for Science and Technology) expressed his government's wholehearted support for the establishment of the HUGO office. He promised to work through the Soviet/American Cooperation Committee to establish satellite links for data exchange and to overcome problems relating to importing computer hardware into the Soviet Union. ◇

Reported by Liz Evans
HUGO Europe

ELSI *(from p. 13)*

Duster noted that genetics and biology were rejected at midcentury as explanations of socioeconomic status and behavior. Within the past 20 years, however, genetics at the molecular level has inspired genetic explanations of alcoholism, crime, mental illness, and intelligence through correlations with population statistics. These genetic theories, Duster fears, may result from studying populations in which certain groups of individuals are overrepresented for social reasons. Duster also cautioned against concentrating on genetic components of multifactorial conditions.

Camille Limoges (University of Quebec, Montreal) identified several areas that should receive the attention of ELSI programs. In addition to "downstream issues," such as regulating the use of genetic test information, attention should be paid to "upstream issues," such as the concepts of normalcy and causality, the unity and diversity of the human species, the conceptualization of scientific research, and the relationship between scientific and public discourse. Limoges noted the need for ethnographic approaches in fields such as genetic screening, where hypothesis testing would be difficult because there is little current knowledge. He emphasized the need to communicate the scientific and social issues of the Human Genome Project and suggested that projects involve science journalists, who are "multipliers" of information. Finally, he recommended an effort to involve graduate students in ELSI projects to ensure a new generation of social analysts, who, Limoges said, will surely be needed. ◇

Reported by Michael S. Yesley
Coordinator, DOE ELSI Program
Los Alamos National Laboratory

NCHGR Position Available

NIH is seeking outstanding candidates for a position with the National Center for Human Genome Research in Bethesda, Maryland. Duties include administration of a portfolio of research, center, and training grants.

- Qualifications: Ph.D., M.D., or equivalent; human genetics, molecular biology, or genetics research experience; minimum 1 year postdoctoral training; significant scientific experience; and U.S. citizenship.
- Salary: $37,294–$68,129.

To apply: Submit a curriculum vitae and three reference names to

- Jane Peterson; NIH; Building 38A, Room 610; 9000 Rockville Pike; Bethesda, MD 20892. ◇

Second International Workshop on Chromosome 3

The Second International Workshop on Human Chromosome 3, sponsored by the DOE Human Genome Program, the NIH National Center for Human Genome Research, and the Eleanor Roosevelt Institute, was held April 4–5 in Denver, Colorado. With 43 participants representing 8 nations, the workshop focused on whole-chromosome resources including probes, polymorphic markers, hybrids, yeast artificial chromosomes (YACs), and genes, and on efforts in genetic linkage and region-specific physical mapping. Two major workshop goals were to identify sets of common reference DNA markers and somatic cell hybrids.

Whole-Chromosome Resources

Cloned DNA markers were described by David Smith (Wayne State University), Harry Drabkin (University of Colorado Health Science Center, Denver), Eugene Zabarovsky (Karolinska Institute, Stockholm, and Engelhart Institute of Molecular Biology, Moscow), Lakshmi Atchison (Fox Chase Cancer Center), and Kazuhiro Yamakawa (Cancer Institute, Tokyo). The total number of clones isolated in their respective laboratories exceeds 12,000, of which about 1400 have been regionally localized.

Localization of DNA markers by fluorescence in situ hybridization analysis was reported by Yamakawa, William Modi (PRI/Dyncorp), and Pamela Rabbitts (Medical Research Council, Cambridge, U.K.).

Somatic cell hybrids useful for localizing DNA markers or isolating specific chromosomal regions were reported by Drabkin, Atchison, Susan Naylor (University of Texas Health Science Center, San Antonio), and Tom Glover (University of Michigan, Ann Arbor).

Isolation of YAC clones specific for chromosome 3 was reported by Mike Mendez (Eleanor Roosevelt Institute). Phyllis McAlpine (University of Manitoba, Winnipeg) described a chromosome 3–specific YAC library.

Manfred Zorn (Lawrence Berkeley Laboratory) demonstrated the Chromosome Information System, which is computer software for entering and storing mapping data.

Genetic Linkage Maps

Polymorphic loci including C-A repeat clones and primer sets for polymerase chain reaction–based allele assays were reported by several groups, including those of Drabkin, Rabbitts, and Naylor.

Several genetic linkage maps with various degrees of coverage were described. The linkage map reported by Yamakawa contained 41 continuously linked markers and extended for a sex-averaged distance of 314 cM. Margaret Pericak-Vance (Duke University Medical Center) and Jonathan Haines (Massachusetts General Hospital) described a 43-loci map that extended 156 cM in males and 203 cM in females. Kalman Tory [NCI-Frederick Cancer Research Facility (FCRF)] reported on a map that included 20 3p loci covering a sex-averaged distance of 130 cM. Vince Stanton (Massachusetts Institute of Technology) described the use of denaturing gradient gel electrophoresis

A more detailed report of resources and mapping information presented at the workshop will be published in *Cytogenetics and Cell Genetics*.

Chromosome 5 Update

Colon Cancer Gene Discovered

New Diagnostic Test Possible

Investigators have found the gene responsible for familial adenomatous polyposis (FAP), an inherited form of colon cancer. The gene, called APC for adenomatous polyposis coli, is believed to act as a tumor suppressor. However, individuals who inherit a damaged version of the gene may develop hundreds of thousands of tiny colon polyps that very often become malignant before the person reaches the age of 30. About 1 in 5000 people suffer from FAP.

"This is a gene discovery that can have direct impact for the patient. Early diagnosis and removal of polyps can prevent colon cancer," said investigator Raymond White, whose group reported its findings in the August 9 issue of *Cell*. Similar results were reported in the August 9 issue of *Science* by Bert Vogelstein of Johns Hopkins University and Yusake Nakamura of the Cancer Institute in Tokyo. Nakamura contributed to earlier polyposis research in White's laboratory at the University of Utah. The work was funded in part by the NIH National Center For Human Genome Research.

Discovery of the polyposis gene not only allows early detection of colon tumors but has enabled the development of a simple blood test to identify family members who have inherited the mutant gene. Affected individuals can be watched closely, and intervention may become possible at an earlier stage of the disease.

Colorectal cancer is second only to lung cancer as a cause of death by malignancy. Over 150,000 people will contract the disease this year, and over 60,000 will die of it. At least 20% of these cases, perhaps many more, are attributed to genetic causes. ◇

Meeting Reports

Chromosome 3 Workshop Set for Boston in 1992

to detect large numbers of polymorphisms for markers that are otherwise noninformative.

Von Hippel-Lindau (VHL) disease (3p25-p26)

Several groups described the current status of linkage between VHL and polymorphic markers on 3p. Using 36 VHL families, Eamonn Maher (Cambridge University, U.K.) found linkage to RAF1 at 6 cM and with D3S18 at 0 cM. Multipoint linkage analysis gave the order CEN-THRB-RAF1-(VHL,D3S18)-D3S191. Berton Zbar (NCI-FCRF) presented data on 41 VHL families and placed VHL between RAF and D3S18 with a marker order of D3S571-RAF-VHL-D3S18-D3S191-D3S627. Zbar also tested these markers for risk determination. Bernd Seizinger (Massachusetts General Hospital) and colleagues found marker order to be RAF1-(c233E2,VHL)-c479H4-c64E2. Several new C-A repeat polymorphisms near VHL were developed, and construction of a long-range restriction map of the VHL region has begun.

3p Syndrome (3p25-pter)

Modi reported on the physical mapping of 15 polymorphic loci near the deletion breakpoint at 3p25.

Small-Cell Lung Carcinoma (SCLC) and Renal Cell Carcinoma (RCC) (3p13-p23)

Data focusing on 3p13-p23, a region commonly found deleted in cancer, was presented by many groups, including Ferenc Boldog (University of Nebraska, Omaha), Charles H.C.M. Buys (University of Groningen, the Netherlands), Drabkin, Bob Gemmill (Eleanor Roosevelt Institute), Gyula Kovacs (NCI-FCRF), York Miller (Veterans Administration Hospital, Denver), Smith, and Yamakawa. The data presented included

- several hybrid cell lines deleted for specific regions within 3p (Boldog);
- a study on loss of heterozygosity, which suggested that one putative RCC gene was flanked by D3S2 and THRB (Buys);
- fine structure mapping of 100 markers into 3p14-p21 and identification of 8 deleted probes in the SCLC cell line U2020 (Drabkin);
- pulsed-field gel linkage and YAC contigs from within 3p14-p21 including linkage of 7 probes within the U2020 deletion (Gemmill);
- the loss of 3p sequences and duplication of 5q in RCC (Kovacs);
- lack of ACY1 expression in many SCLC cell lines (Miller);
- identification of several potential genes within 3p21.1 and isolation of the t(3;6)(p14.3;p11) breakpoint (Smith); and
- a study of RCC suggesting that two commonly deleted regions exist at 3p12-14 and 3p21.3 (Yamakawa).

INV(3)(p25;q21)

McAlpine placed both TF and PCCB outside the inversion (distal on 3q), reducing the interval for PCCB to 3q21-q22.

Workshop discussions covered designation of a common reference marker set, common somatic cell hybrids, and a joint YAC screening effort. The DNA markers and somatic cell hybrids are to be deposited with the American *Type Culture* Collection and the Coriell Institute, respectively. The Drabkin and Gemmill laboratories will seek supplemental funding to permit distribution of purified DNA from these hybrids. A joint YAC screening effort was discussed and received favorable response.

Seizinger will host the next chromosome 3 workshop to be held in Boston in 1992.

Reported by Bob Gemmill
Eleanor Roosevelt Institute

HGMIS Lists Genetic Disease Groups

On receiving requests for information on genetic disease groups, HGMIS refers inquirers to the sources below, all of which will direct callers to other groups that may meet the caller's needs. The list is printed here as an aid to readers who may also receive these requests. Please contact HGMIS (see contact information, p. 20) to share information on other comprehensive genetic disease groups or sources.

National Organization of Rare Disorders (NORD)
P.O. Box 8923
New Fairfield, CT 06812
203/746-6518

NORD is a clearing house for information on rare disorders that also supplies a list of applicable support groups.

Alliance for Genetic Support Groups (AGSG)
38th & R Streets, NW
Washington, DC 20057
800/336-4363

AGSG has a comprehensive list of support groups for many diseases and a regional list of genetic counselors to whom people can be referred.

National Health Information Center (NHIC)
P.O. Box 1133
Washington, DC 20013-1133
800/336-4797

NHIC is a referral service that gives the names and numbers of government agencies or national organizations having information on particular diseases. ◊

First International Chromosome 4 Conference

A 2-day conference incorporating three meetings on the genetic and physical maps of human chromosome 4 was held June 22–23 in Philadelphia. Some 25 participants from 5 countries attended the conference, which was sponsored by the Centre d'Etude du Polymorphisme Humain (CEPH), NIH, and the Fox Chase Cancer Center.

The CEPH consortium group developing the genetic linkage map of chromosome 4 discussed marker inclusion, map development, significance criteria, and checks for genotyping errors. From CEPH data, Ken Buetow (Fox Chase Cancer Center) generated a preliminary 33-point multilocus map that encompassed all of chromosome 4 at an average resolution of about 8 cM.

Preliminary 33-point map generated with average resolution of 8 cM.

The facioscapulohumeral muscular dystrophy consortium discussed recent data pooling for linkage analysis of this disorder, which has been mapped to 4q35-4qter.

In the plenary meeting, Peter Pearson (Johns Hopkins University) gave an overview of consensus vs component maps; he made the Genome Data Base (GDB) available to investigators during the conference. A number of individual presentations described chromosome 4 genetic and physical maps and specific loci or genes:

- mouse homologies and human DNA variants associated with the *c-kit* oncogene and pigmentary abnormalities [Maja Bucan (University of Pennsylvania) and Richard Spritz (University of Wisconsin)];
- evolution of the glycophorin gene family and an extensive physical map based on cosmid walking [Shinichi Kudo (La Jolla Cancer Research Foundation)]; and
- identification of cDNAs in the 4p16.3 region [Olaf Riess (University of British Columbia), Leon Carlock (Wayne State University), Gert-Jan Van Ommen (Leiden University, Netherlands), and Richard Myers (University of California, San Francisco {USCF})].

Discussions included human chromosome 4 mapping resources now being developed and made available both by individual investigators and through the human genome center headed by Myers at USCF. These resources will help to generate high-resolution maps of regions near identified chromosome 4 genes and to develop chromosome 4 maps (radiation, genetic, and clone-based) not based solely on genes and genetic disorders.

Participants discussed organization of future workshops around GDB. The second chromosome 4 conference will be held June 13–14, 1992, in Leiden, Netherlands. ◇

Reported by Jeffrey C. Murray
University of Iowa

For complete proceedings of the conference, contact

- **Jeffrey C. Murray**
  Department of Pediatrics
  Division of Medical Genetics
  University of Iowa
  Iowa City, IA 52242
  319/356-2674
  Fax: 319/356-3347

For information on the next chromosome 4 workshop, contact

- **Gert-Jan Van Ommen**
  Leiden University
  Netherlands
  (Int.) 31/71-276075

Biotechnology Resource Lists Researcher Information

Biotechnology Research Faculty Profile, a new database of up-to-date information on more than 4300 U.S. biotechnology researchers, was compiled from a survey conducted this year by the North Carolina Biotechnology Center, a nonprofit corporation funded by the N.C. General Assembly. [For survey announcement, see *HGN* 2(6), 6 (March 1991)].

The database, which can be purchased on computer disks, contains respondents' contact information, institutional affiliation, and area of scientific interest; it also includes their laboratory's research technique expertise, organisms most frequently used, funding sources, and biotechnology research being conducted. The data are available in printed form as the *Biotechnology Research Directory: 4000 Faculty Profiles.*

The database and directory are expected to have a wide variety of uses, especially in technology transfer or in interactions between industry and researchers. Sales proceeds will be used to support information collection on an annual basis; future editions will include researchers at federal laboratories and private research institutions.

- Disks, $1200; printed directory, $125. Database and directory information: Biotechnology Information Division; North Carolina Biotechnology Center; P.O. Box 13547; Research Triangle Park, NC 17709; 919/541-9366. ◇

Meeting Reports

Second International Workshop on Chromosome 21

54 YACs Isolated, Distributed to Requesting Investigators

The Second International Workshop on Chromosome 21 was held April 10–11 at the Eleanor Roosevelt Institute in Denver, Colorado. The workshop was sponsored by the NIH National Center for Human Genome Research and the DOE Human Genome Program.

Fifty-two investigators from eight countries met to produce a current integrated physical, genetic, and cytogenetic map of chromosome 21 and to determine what is needed to complete the map.

Participants in the Joint Yeast Artificial Chromosome (YAC) Screening Effort, established at the First International Workshop on Chromosome 21 in April 1990 in Bethesda, Maryland, reported that 54 YACs have been isolated and distributed to requesting investigators. Others described the isolation of chromosome 21–specific YACs; Eiichi Soeda (Riken Gene Bank) reported that an additional 17 YACs will be made available after publication.

The following have isolated and mapped chromosome 21–specific YACs in various stages of characterization and availability:

- Mary Kay McCormick [Los Alamos National Laboratory (LANL)];
- Marie-Claude Potier [Medical Research Council (MRC) Laboratory of Molecular Biology, U.K.];
- Joe Gray [formerly Lawrence Livermore National Laboratory (LLNL), now University of California, San Francisco (UCSF)]; and
- Jeffrey Gingrich [Human Genome Center, Lawrence Berkeley Laboratory (LBL)].

About 20% of the long arm of chromosome 21 is estimated to be represented in YACs.

A more detailed report of resources and mapping information presented at the workshop will be published in *Cytogenetics and Cell Genetics.*

New Technologies for Chromosome 21 Mapping

Discussions focused on

- new types of DNA polymorphisms and their use in generating a genetic linkage map [Stylianos Antonarakis (Johns Hopkins University School of Medicine)];
- microdissection and microcloning to create large numbers (10^6) of usable chromosome 21 DNA markers and methods for rapidly converting them to YACs or cDNAs [Fa-Ten Kao (Eleanor Roosevelt Institute)]; and
- two-color fluorescence in situ hybridization for ordering and localizing DNA probes, including YACs (Gray).

Creation of a Chromosome 21 Gene Map

David Cox (UCSF) presented an exon trapping approach to cloning genomic DNA fragments containing coding regions. Michael Siciliano (M.D. Anderson Cancer Center) and Miles Brennan (Mount Sinai School of Medicine) described two approaches to cloning transcribed regions of chromosome 21.

Recent Mapping to Chromosome 21 of Genes Related to Specific Human Diseases

Presentations were made on

- genetic linkage of a gene responsible for some cases of familial amyotrophic lateral sclerosis to the marker D21S58, located in the 21q22.1 region [Teepu Siddique (Duke University Medical Center)];
- genetic linkage of a gene coding for progressive myoclonus epilepsy (EPM1) of the Unvericht-Lundborg type to 21q22.3 [Anna-Elina Lehesjoki (University of Helsinki)]; and
- specific mutation in exon 17 of the amyloid precursor gene in some familial Alzheimer's disease (AD) pedigrees [Mike Mullen (St. Mary's Hospital Medical School, London)]. Because this mutation is not found in all families with linkage of AD to chromosome 21, Jonathan Haines (Massachusetts General Hospital) discussed the possibility of two AD loci on chromosome 21.

Harry Drabkin (University of Colorado and Eleanor Roosevelt Institute) and Misao Ohki (Saitama Cancer Center Research Institute, Japan) each presented the cloning of an 8;21 translocation breakpoint

associated with acute myelogenous leukemia. This represents the third chromosome 21 translocation breakpoint detected by physical methods and used as a landmark to relate the physical and cytogenetic maps.

Julie Korenberg (Cedars-Sinai Medical Center) and Jean Delabar (Necker Hospital, Paris) reported on the use of chromosomes from individuals with partial trisomy or partial monosomy; they are also beginning to create a phenotype map in which chromosomal regions defined by the physical map can be associated with specific clinical phenotypes.

Roger Reeves (Johns Hopkins University), Chair of the Committee on Mouse Chromosome 16, and Muriel Davisson (Jackson Laboratory) described progress in mouse genome physical mapping emphasizing mouse chromosome 16; significant homology appears not only between mouse chromosome 16 and human 21 but also between human 21 and mouse chromosomes 10, 17, and perhaps 3.

Manfred Zorn (LBL) presented an update and demonstrations of the LBL Chromosome Information System, including the latest data from the Genome Data Base (GDB) at Johns Hopkins University, made available by Peter Pearson (GDB). Ray Hagstrom (Argonne National Laboratory) demonstrated a Prolog-based alternative for development of a genome database.

A consensus genetic linkage map (1000:1 odds) was constructed at the workshop, using 29 markers from the standard Centre d'Etude du Polymorphisme Humain reference panel and the Venezuelan reference panel. Several new markers included in this map are highly polymorphic polymerase chain reaction markers; most new markers to be added are expected to be this type. Both sources agree on locus order for the common markers; however, in some areas, differences in distance may indicate heterogeneity between the mapping resources. A highly provisional corrected map length of 75 cM (50 cM male and 100 cM female) for the D21S13-CD18 interval was suggested. A current, but highly provisional, combined genetic linkage and physical map of chromosome 21 was also produced at the workshop.

Workshop participants decided to expand *FAX on the YACs* into a more inclusive chromosome 21 newsletter to disseminate information as rapidly as possible. David Patterson (Eleanor Roosevelt Institute) will serve as editor and be responsible for ordering markers on the physical map. Sue Rider (UCSF) and Rudolph Tanzi (Massachusetts General Hospital) will be responsible for YAC data. Dean Nizetic and Gunther Zehetner (both at Imperial Cancer Research Fund, London) will report on cosmid screening, and Aravinda Chakravarti (University of Pennsylvania) and Antonarakis will assume editorial responsibility for the genetic linkage map aspects of the newsletter. Antonarakis was chosen to organize the next chromosome 21 workshop. ◊

Reported by David Patterson
Eleanor Roosevelt Institute

Genome Publications

¶As time and space permit, *Human Genome News* will publish information about books and journals that may be of interest to our readers. This is not a comprehensive list, and announcements will be taken from material at hand. We welcome news from authors and publishers about new publications.

BOOKS

The Genome, by Ram Sagar Verma (Long Island College Hospital and State University of New York Health Science Center), covers a wide spectrum of topics, including a comprehensive introduction; an anatomy of the genome; the molecular biology of heterochromatin, kinetochores, and centromeres; meiotic chromosomes; dosage compensation and sex determination; sister chromatid exchange; the aberrant human genome; the mitochondrial genome; genomic diversity in neoplasia and the retroviral genome; and the unfolding genome. An extensive bibliography is included. 1990, $75. [VCH Publishers; 220 East 23rd St.; Suite 909; New York, NY 10010; 800/422-8824.]

Electrophoresis, Supercomputing, and the Human Genome: Proceedings of the First International Conference, Tallahassee, Florida, 10–13 April, 1990, edited by Charles R. Cantor (Lawrence Berkeley Laboratory) and Hwa A. Lim (Florida State University), contains 15 papers on the initiation of human genome research and the supporting technologies of electrophoresis and computing. 1991, $75. [World Scientific Publishing Company, 687 Hartwell Street; Teaneck, NJ 07666-5309; 800/227-7562 or 201/837-8858; Fax: 201/837-8859. Europe only: 73 Lynton Mead, Totteridge, London N20 8DH; (Int.) 1/446-2461; Fax: (Int.) 1/446-3356.]

Medical Genetics and Society is based on the International Panel Discussion on Education and Ethics in Medical Genetics held August 3, 1990, in Fukui, Japan, under the auspices of the Council for International Organizations of Medical Sciences (CIOMS). [For a report on the CIOMS meeting, see *HGN* 2(4), 7 (November 1990).] The 107-page softcover book also contains short summaries of the

(see Publications, p. 20)

Resources

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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Publications *(from p.19)*

International Association of Human Biologists Conference on Isolation and Migration, the 35th Meeting of Japan Society of Human Genetics, and the CIOMS conference.

The book contains complete papers from the two panel discussions presented at the meeting: (1) Panel on Education in Medical Genetics and (2) Panel on Ethics in Medical Genetics.

1991, $35. [Kugler Publications; U.S. and Canada: P.O. Box 1498; New York, NY 10009-9998; 212/477-1970; Fax: 212/477-0181.]

Introduction to Protein Structure by Carl Branden (Swedish University of Agricultural Sciences, Uppsala) and John Tooze (European Molecular Biology Organization, Heidelburg) features full-color illustrations and explains for both biologists and chemists the structural and functional logic emerging from the latest data on protein structures. The authors identify recurring structural motifs and show how proteins with unrelated functions are built up from combinations of these structures. They discuss how common basic structures can be enhanced to fulfill different functions and how the same biological function can have more than one structural solution.

350 pp., 1991. Hardcover, $49.95; paper, $27.95. A set of 100 color slides of the most important illustrations in the text is also available. [Garland Publishing; 136 Madison Avenue; New York, NY 10016; 212/686-7492; Fax: 212/889-9399. Europe: European Book Service/ PBD; 63 Strijkviertel; 3454 PK de Meern, Netherlands.]

JOURNALS

Methods, a companion journal to the book series, *Methods in Enzymology*, is edited by John N. Abelson and Melvin I. Simon (California Institute of Technology). The journal is composed of topic-oriented issues, each organized by a special editor and consisting of a set of invited articles on a specific new technique or approach and its theoretical basis. Emphasis is placed on clear descriptions of protocols that allow application of these methods in a number of disciplines.

Topics of issues published this year include DNA sequencing, edited by Bruce A. Roe (University of Oklahoma), and polymerase chain reaction, edited by Norman Arnheim (University of Southern California). Six issues yearly, $86. [Academic Press, Inc.; Journal Promotion Department; 1250 Sixth Avenue; San Diego, CA 92101; 619/699-6742.]

Proteins: Structure, Function, and Genetics, now published monthly, concentrates on advances in all areas of protein biochemistry. Original research articles, timely reviews, and brief research communications are features of this journal, which highlights color illustrations and computer-generated graphics of protein structure. Twelve issues yearly, $95. [John Wiley & Sons, Subscription Department; 605 Third Avenue; New York, NY 10158-0012; 212/850-6543. Europe, United Kingdom, and Africa: John Wiley and Sons; Baffins Lane; Chichester; Sussex PO19 1UD; England.]

PCR Methods and Applications,devoted exclusively to amplification methods and their use, aims to serve as a central source of reliable, independent, and up-to-date information about the principles, practice, and application of amplification methods. The editorially independent journal will be published quarterly with the support of Perkin-Elmer Cetus and will include a combination of peer-reviewed research reports, commissioned review articles and commentaries, letters, and other items of interest to polymerase chain reaction users. The journal's Board of Associate Editors includes Richard Myers (University of California, San Francisco), Richard Gibbs (Baylor College of Medicine), Eric Green (Washington University School of Medicine), and David Bentley (Guy's Hospital, London). Four issues yearly, $40. [Cold Spring Harbor Laboratory Press; 10 Skyline Drive; Plainview, NY 11803-9729; Continental United States 800/843-4388; all other locations: 516/349-1930; Fax: 516/349-1946.] ◇

Mammalian Genome is the official journal of the International Mammalian Genome Society. It is published quarterly and edited by Lee M. Silver (Princeton University), Joseph H. Nadeau (Jackson Laboratory), and Jan Klein (Max Planck Institute for Biology). The journal is devoted entirely to studies of the mammalian genome from a molecular perspective and will serve as a forum for the community of mammalian geneticists and as a means for disseminating genetic information through reports, reviews, and original papers. Special emphasis is placed on genetic and physical maps, analysis of gene complexes and complex traits, DNA sequencing as related to genome organization, comparative gene mapping, new techniques, informatics, and genetic analysis of human genetic disorders and animal models. The first issue focuses on molecular studies. Four issues annually, $65. [Springer-Verlag New York, Inc.; 175 Fifth Avenue; New York, NY 10160-0266; 800/777-4643 or 212/460-1500.]

For Your Information

NCHGR Invites *Drosophila* Applications

■ **RFA HG-91-05**

The National Center for Human Genome Research (NCHGR) invites applications for research assistance awards for the following projects focusing on *Drosophila melanogaster*: high-resolution physical map development, feasibility studies for large-scale DNA sequencing of biologically interesting regions, and development of new technologies to detect all the expressed-gene coding regions in genomic DNA.

Project emphasis will be on whole-genome characterization, use of state-of-the-art technology, and cost- and labor-efficiency.

Timetable

- Letter of intent due: October 18.
- Application due: November 15.
- Application review: March–May 1992.
- Granting of Awards: July 1, 1992.

Prospective applicants are encouraged to contact NCHGR staff very early in the planning phase. **For more information or to request the complete RFA**, contact

- Bettie J. Graham (301/496-7531); NCHGR; Building 38, Room 613; NIH; Bethesda, Maryland 20892. ◇

NCBI Seeks GenInfo Enhancement

■ **BAA/RFP NLM-92-101/AJM**

The National Center for Biotechnology Information (NCBI) invites proposals for enhancing GenInfo coverage and for developing linking databases. BAA/RFP release will be in October; responses will be due in early 1992.

NCBI is developing the GenInfo database to link with other sequence databases and to serve as an integrated nucleic acid and protein sequence database derived from the published literature and direct author submissions. Sequence, structural, genetic, bibliographic, and other databases will be connected, and data will be represented in a standard description language.

Written requests for a copy of BAA/RFP NLM 92-101/AJM should be sent to

- Anthony Murray, National Library of Medicine; Office of Acquisitions Management; 8600 Rockville Pike; Building 38A, Room B1N17; Bethesda, MD 20892. ◇

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, 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.

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 log in via modem to NIH Grant Line – call John James, 301/496-7554.
- Listserver computer network subscription – call Dottie Baker, 919/966-5625; BITNET: "pjones@uncvx1.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, MD (301/496-0844).

DOE Human Genome Program

Solicitations for proposals will be published in February 1992 issues of the *Federal Register* and *Science*. Formal proposals are due in August 1992.

For further information, contact the program office via

- 301/353-5037 or FTS 233-5037; Fax: 301/353-5051 or FTS 233-5051; or Internet: "genome@oerv01.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: spring 1992. For more information, contact

- Samuel Barish; SBIR Program Manager, ER-16; DOE; Washington, DC 20585; 301/353-5707.

Human Genome Distinguished Postdoctoral Fellowships
Next deadline: February 1, 1992. For further information, see *HGN* **2**(3), 11 (September 1990) or contact

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

Calendar of Genome Events*

October	2–4	***DOE Human Genome Program Proposal Review Panel**; Washington, DC
	5	**International Gathering of Networks of Support Groups**; Washington, DC [*J. Weiss, 800-336-GENE or 202/331-0942*]
	6–11	**Third International Congress for Plant Molecular Biology**; Tucson, AZ [*Woo Wester Conference Consultants, 213/322-1016, Fax: 213/322-4974*]
	6–11	**8th International Congress of Human Genetics**; ASHG, Washington, DC [*M. Ryan, ICHG, 301/571-1825, Fax: 301/530-7079*]
	14–18	**Fifth International Workshop on Mouse Genome Mapping**; Lunteran, Netherlands [*M. Sonne, (Int.) 31/20-512-1990, Fax: (Int.) 31/20-617-2625*]
	16–19	***Workshop on the Genome of *E. Coli***; Cold Spring Harbor, NY
	17	**NCHGR Lecture Series: The Human Genome Project and Its Social Impact**; Bethesda, MD [*C. Dahl, 301/402-0838*]
	18–19	**The Societal Impact of Human Genetic Engineering**; Oak Ridge, TN [*N. Brown, 615/483-4357*]
	21–23	**Human Genome III: The International Conference on the Status and Future of Human Genome Research**; San Diego, CA [*Scherago Associates, Inc., 212/730-1050, Fax: 212/382-1921*]
	24	***DOE Human Genome Coordinating Committee**; San Diego, CA
	26	**Science and Journalism III. Genes and Human Behavior: A New Era?** Boston, MA [*J. Beckwith, 617/432-1920*]
November	3–6	**1991 Minority Programs Symposium**; Washington, DC (Exhibitor registration deadline: Oct. 1) [*M. Brown, 301/907-3844*]
	4	**Applied Biosystems Seminar: The Genetic Analysis Revolution**; Washington, DC (also during November in Philadelphia, San Francisco, Chicago, Boston, New York City, and Research Triangle Park, NC) [*ABI registration: 800/874-9868, ext. 7600*]
	8–9	**Justice and the Human Genome**; Chicago, IL [*Conference Registrar: 312/996-5225, Fax: 312/996-5227*]
	10–15	**Nanometer Scale Science/Technology (NST) AVS 38th Annual Symposium**; Seattle, WA [*J. Murday, 202/767-3026, Fax: 202/404-7139*]
	20	**NCHGR Lecture Series: New Computational Methods for Genome Analysis**; Bethesda, MD [*see contact: Oct. 17*]
	20–22	**Bioinformatics in the 90s**; Maastricht, Netherlands [*J. Franklin, (Int.) 31/2993-72751, Fax: (Int.) 31/2993-72877*]
December	8–11	**Human Genetics and Genome Analysis: A Practical Workshop for the Nonscientist**; Cold Spring Harbor, NY [*J. Witkowski, 516/549-0507*]
	19	**NCHGR Lecture Series: Genetic Mapping of Human Breast Cancer**; Bethesda, MD [*see contact: Oct. 17*]
January 1992	3–4	**DOE/NIH Joint Subcommittee on the Human Genome; NIH Program Advisory Committee on the Human Genome**; Irvine, CA [*J. Ades, 301/402-2205, Fax: 301/402-2218*]
	4	***DOE Human Genome Coordinating Committee**; Irvine, CA
	7–10	**"Biotechnology Computing Minitrack" at the Hawaii International Conference on System Sciences-25**; Kailua-Kona, HI [*L. Hunter, 301/496-9300, Fax: 301/496-0673, E-mail: "hunter@nlm.nih.gov"*]
	25–Feb. 1	**Keystone Symposia Meeting: Molecular Mechanisms in DNA Replication & Recombination**; Taos, NM (abstract deadline: Sept. 25) [*Keystone Symposia, 303/262-1230, Fax: 303/262-1525*]
February	7	***National Advisory Council for Human Genome Research**; Bethesda, MD
	26–28	**Chromosome 16 Workshop**; Adelaide, Australia [*E. Hildebrand, 505/667-2746, Fax: 505/665-3024 or G. Sutherland, (Int.) 61/8-267-7284, Fax: (Int.) 61/8-267-7342*]
March	13–15	***Second Invitational Conference on Genetics, Religion, and Ethics**; Houston, TX [*R. Nelson, 713/797-0600, Fax: 713/797-9199*]
	15–18	**30th Annual Meeting of the American Cytogenetics Conference**; Virginia Beach, VA [*A. Brothman, 804/446-5670, Fax: 804/624-2255 or P. Jacky, 503/652-2880, Fax: 503/652-5783*]

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

Calendar of Genome Events*

March	19	**NCHGR Lecture Series: Social Implications: Genetics and Popular Culture**; Bethesda, MD [*See contact, Oct. 17*]
April 1992	3–10	**Keystone Symposia Meeting: Molecular Biology of Human Genetic Disease**; Copper Mountain, CO; abstract deadline: Dec. 4 [*Keystone Symposia, 303/262-1230, Fax: 303/262-1525*]
	27–28	**Annual Biotechnology Patent Conference**, ATCC, Washington, DC [*ATCC Workshop Manager, 301/231-5566, Fax: 301/770-1805*]
	27–29	**Third European Workshop on Cytogenetics and Molecular Genetics of Human Solid Tumors**; Porto, Portugal [*S. Castedo, 351.2.497833, Fax: 351.2.4103940*]

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

Training Calendar: Workshops and Coursework**

October	7–12	**cDNA Libraries Techniques**; LTI, Germantown, MD (also offered Jan. 27–Feb.1)[*L. Kerwin, 800/828-6686 or 301/921-2250, Fax: 301/258-8212*]
	9–11	**Recombinant DNA Methodology**; Columbia, MD (also offered Nov. 4–8) [*Exon-Intron, Inc., 301/730-3983*]
	14–16	**PCR Techniques**; CUA, Lake Tahoe, NV (also offered Jan. 3–5 in Washington, DC) [*M. Miller, 202/319-6161, Fax: 202/319-5721*]
	14–16	**Recombinant DNA Methodology**; CUA, Lake Tahoe, NV (also offered Jan. 6–10 and Mar. 2–6 in Washington, DC) [*see contact: Oct. 14–16 above*]
	28–Nov. 1	**DNA-Protein Techniques**; LTI, Germantown, MD (also offered Mar. 9–13) [*see contact: Oct. 7–12*]
	28–Nov. 1	**Recombinant DNA: Techniques and Applications**; ATCC, Rockville, MD (also offered Nov. 4–8) [*ATCC Workshop Manager, 301/231-5566, Fax: 301/770-1805*]
	28–Nov. 15	**Carolina Workshop on Molecular Techniques for Human/Mammalian Genome Analysis**; Chapel Hill, NC (application deadline: Sept. 1) [*W. Litaker, 919/966-1730, Fax: 919/966-6821*]
November	11	**DNA Amplification by PCR**; BTP, Ames, IA [*S. Chance, 515/232-8306 (1:00–5:00 p.m. CST)*]
	11–12	**PC/Gene**; Mountain View, CA (Registration deadline: Oct. 28) [*IntelliGenetics, Inc., 415/962-7300*]
	11–15	**Recombinant DNA Techniques I**; LTI, Germantown, MD (also offered Jan. 13–17, Mar. 23–27) [*see contact: Oct. 7–12*]
	12–15	**Basic Cloning Techniques**; BTP, Ames, IA (also offered Dec. 17–20 in Miami, FL) [*see contact: Nov. 11*]
	18–23	**Recombinant DNA Techniques II**; LTI, Germantown, MD (also offered Dec. 16–21 and Feb. 10–15) [*see contact: Oct. 7–12*]
	19–22	**Polymerase Chain Reaction (PCR) Methodology**; ATCC, Rockville, MD [*see contact: Oct. 28–Nov.1*]
December	2–6	**Cell Culture Techniques**; LTI, Germantown, MD (also offered Feb. 24–28) [*see contact: Oct. 7–12*]
	3–5	**Cytogenetics: Techniques & Applications**; ATCC, Rockville, MD [*see contact: Oct. 28–Nov. 1*]
	18–21	**IBI Recombinant DNA Workshop**; Middletown, CT [*L. Salen, 800/243-2555 or 203/786-5600*]
January 1992	6–10	**Basic Cell & Tissue Culture**; CUA, Washington, DC [*see contact: Oct. 14–16*]
March 1992	2–17	**Carolina Workshop on Yeast Molecular Genetics**; Chapel Hill, NC (application deadline: Feb. 1) [*see contact: Oct. 28–Nov. 15*]
June 1992	15–19	**Genomic Information: Ethical Implications**; Seattle, WA [*B. Brownfield, 206/543-5447, Fax: 206/685-7515*]

**Dates and course status may change; check with contact person.

Acronym List

Acronyms listed were chosen because they were either used in the text or are relevant to the human genome research community. Listed in parentheses after an organization is the branch of government or the organization to which it is responsible.

*Denotes U.S. Department of Energy organizations.
†Denotes U.S. Department of Health and Human Services organizations.

ABI	Applied Biosystems, Inc.
ADA	Americans with Disabilities Act
AD	Alzheimer's disease
APC	adenomatous polyposis coli
ASHG	American Society of Human Genetics
ATCC	American **Type Culture** Collection
AVS	American Vacuum Society
BTP	Biotechnology Training Programs
CEPH	Centre d'Etude du Polymorphisme Humain
CF	cystic fibrosis
cM	centimorgan
CSHL	Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.
CUA	Catholic University of America
DOE	Department of Energy (U.S.)
EC	European Community
EEOC	Equal Employment Opportunity Commission
ELSI	Ethical, Legal, and Social Issues
FAP	familial adenomatous polyposis
FCRF	Frederick Cancer Research Facility (NCI)
FISH	fluorescence in situ hybridization
GDB*†	Genome Data Base
HGCC*	Human Genome Coordinating Committee
HGMIS*	Human Genome Management Information System (ORNL)
HGN*†	**Human Genome News**
HHMI	Howard Hughes Medical Institute
HUGO	Human Genome Organization [International]
IBI	International Biotechnologies, Inc.
ICHG	International Congress of Human Genetics
JITF*†	Joint Informatics Task Force
LANL*	Los Alamos National Laboratory, Los Alamos, N.M.
LBL*	Lawrence Berkeley Laboratory, Berkeley, Calif.
LLNL*	Lawrence Livermore National Laboratory, Livermore, Calif.
LTI	Life Technologies, Inc.
Mb	megabase
MRC	Medical Research Council (U.K.)
NCBI	National Center for Biotechnology Information
NCHGR†	National Center for Human Genome Research (NIH)
NCI†	National Cancer Institute
NIH†	National Institutes of Health
NLM	National Library of Medicine
NSF	National Science Foundation (U.S.)
OER*	Office of Energy Research
OHER*	Office of Health and Environmental Research (OER)
ORAU	Oak Ridge Associated Universities
ORNL*	Oak Ridge National Laboratory, Oak Ridge, Tenn.
PACHG†	Program Advisory Committee on the Human Genome (NIH)
PCR	polymerase chain reaction
RCC	renal cell carcinoma
SBH	sequencing by hybridization
SBIR	Small Business Innovation Research
SCLC	small-cell lung carcinoma
STM	scanning tunneling microscopy
UCB	University of California, Berkeley
UCSF	University of California, San Francisco
VHL	Von Hippel-Lindau disease
YAC	yeast artificial chromosome

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