COPY

Human Genome news

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

ISSN: 1050-6101

Vol. 5, No. 6, March 1994

DOE Funds Judicial Reference Books

Desk Books To Help Judges Understand, Apply Scientific Principles

In response to the rapidly expanding number of cases involving complex scientific and genetic data, U.S. agencies are funding the development of a series of primers to assist judges and other court personnel in processing these cases. A set of five judicial reference books is being produced by the project on Court-Adjudicated and Court-Ordered Health Care, directed by Franklin Zweig at the Center for Health Policy Research, George Washington University (GWU). These volumes describe case law and complicated adjudication topics in which accurate, reliable technical information from the health sciences is critical. (For more information on the project, see side bar on right and accompanying box, p. 2.)

The Hon. Sherman G. Finesilver (Chief Judge, U.S. District Court for the District of Colorado) said of the desk books, "We are living in an increasingly scientific and technical world in which judges are expected to be the gatekeepers of science as it interfaces with society. The principles set forth in these books go beyond DNA and genetics and provide us with the tools we need to understand and apply these principles to other litigation centered on scientific data. Ultimately, this knowledge will make judges more articulate in searching for truth." Chief Judge Finesilver also pointed out that DNA data does not stand alone but is considered along with other evidence presented in court.

This project is supported by the Ethical, Legal, and Social Issues component of the DOE Human Genome Program, the State Justice Institute, the National Institute of Justice, and the Federal Bureau of Investigation (FBI). The project's consortium approach is guided by an Advisory and Review Committee, chaired by the Hon. Shirley S. Abrahamson (Justice, Wisconsin Supreme Court) and composed of judges, scientists, and lawyers representing a full spectrum of legal interests.

Justice Abrahamson stressed that development of the desk books will also benefit the public. "People expect the courts to treat all citizens fairly," she said. "Better judicial understanding of complex scientific data cannot help but lead to fair and just results, both within a given court system and across jurisdictions." She further noted that judges familiar with scientific concepts will be better equipped to minimize delays in litigation based on such concepts.

Workshops connected with the project's first two books have already been held. Selected discussion highlights are given below.

Workshop on Adjudication of DNA Forensic Technology

To gather information for the first book, attendees at the Workshop on Adjudication of DNA Evidence in Criminal Cases, chaired by Justice Abrahamson, focused on DNA evidence, especially as it relates to murder and rape. The following background information was furnished to participants.

When cases depend on such sophisticated scientific and technical evidence, special safeguards are needed to ensure a fair trial. The trial court must have a clear understanding of the scientific foundation on which the evidence is based and the technical means by which it was discovered, collected, processed, tested,

Project Goals

- Orient state and federal judges on possible litigation issues involving biomedical science, especially new discoveries in molecular and population genetics, genetic testing, and gene therapy.
- Provide a conceptual base and essential vocabulary so cases will be easier to understand and manage when they arise.
- Link cases and statutory law to a basic understanding of relevant science.
- Assist judges in screening the validity of scientific evidence presented in genetic-testing and gene-therapy cases.

In This Issue. . .

Genome News

Page 1 — DOE Funds Judicial Reference Books
3 — *CHLC Report* Updates Projects, Genetic Maps
4 — Data Fair Held at Genome Sequencing and Analysis Conference
4 — IBC Explores Bioethics Pact
5 — Moyzis Wins DOE Lawrence Award
6 — Conference Examines DNA Patenting, Tech Transfer Issues
8 — Third Transcribed Sequences Workshop
9 — *GDB Forum:* User Support, Registration, Training; Genethon YAC Data

For Your Information

5 — *Resource:* New Panels for Mapping Mouse Loci
10 — Calendar of Genome-Related Events; Training Calendar
11 — Funding Announcements (also pp. 3 and 4), Guidelines for U.S. Genome Research
12 — HUGO Travel Awards; Calendar Acronyms

Genome News

Judges Must Ensure Evidence Is Valid, Reliable, Scientifically Acceptable

and reported. In ruling on the admissability of DNA evidence for presentation to a jury, the judge must ensure that it is valid and reliable; scientifically acceptable; sufficiently valuable when weighed against its capability to confuse or prejudice a jury; and manageable in harmony with other procedures—pre-trial, at trial, and post-trial.

Criminal investigations using DNA forensic analysis began in England in 1985 after two cases, both involving rape and murder, yielded semen samples that were matched to collected DNA evidence. From 14 U.S. cases in 1987, DNA samples in an estimated 12,000 cases had been sent to laboratories by mid-1993. This momentum has been fueled by the hope of law enforcement officials that DNA testing, profiling, and typing will provide personal identification evidence even more useful than fingerprinting. The result has been expanded use of DNA tests amid rapidly changing technology.

About equal numbers of DNA samples are sent to FBI and private laboratories. Most samples are blood or semen, but other tissues may be tested when cells can be recovered, for example, in saliva, hair follicles, and bone. Earlier DNA-based forensic technology produced X-ray films (autoradiographs) of DNA fragments through restriction fragment length polymorphic (RFLP) analysis. The new generation of analysis uses polymerase chain reaction techniques, some of which are considered less sensitive than RFLP analysis but have important advantages for investigating small or degraded evidence samples. To maximize the best features of each approach, the FBI laboratory is turning to a combination of methods.

Critics charge that DNA forensic technologies have been rushed into service before the standardization necessary for quality assurance and interpretation has been established; also, DNA analysis is still evolving into well-understood, well-validated forensic techniques. Defenders state that any forensic method is subject to error. Standard-based protocols, quality assurance, and monitoring of laboratory and personnel proficiency can reduce flawed or skewed DNA test results based on technical error in collecting and processing evidence.

In addition, members of the scientific community disagree on the interpretation of statistical methods used to calculate the probability that two DNA samples (i.e., suspect DNA and evidence DNA) came from the same source. Probabilities against a random match are estimated to range between hundreds and billions to one.

Patricia Riley, Chief of the U.S. Attorney's Sex Offense Unit in the District of Columbia, reported that the admissibility of DNA evidence was upheld in 95% of appellate cases. Her research also found that courts are raising other considerations related to DNA evidence, including pre-trial hearings on admissability, court-appointed experts for the defense, chain of custody, and appropriate jury instructions.

Workshop on Adjudication of Genetic-Testing Evidence

The Workshop on Adjudication of Genetic-Testing Evidence in Health-Care Cases, held in connection with the second book and chaired by Chief Judge Finesilver, dealt with legal, scientific, ethical, and philosophical aspects of cases involving genetic testing and gene therapy.

A hypothetical case was considered in which a judge was asked to rule on the state's request for maternal and fetal genetic testing of a 14-year-old ward of the state who was pregnant by a young man with an expressed genetic disease. This presentation by Laurinda Harman (GWU Medical School) was very provocative in regard to numerous ethical and legal issues that could confront the courts in the near future.

Chief Judge Finesilver said future genetic testing will probably be used in cases involving such controversial factors as electromagnetic fields and cellular telephones as carcinogenic agents, contaminated blood, and silicone gel breast implants. He cited the Americans with Disabilities Act (ADA), its effects on the courts, and the impact of medical science and technology on the development of ADA law. For example, these cases could raise the issues of what constitutes a disability and whether a genetic trait or predisposition can qualify as a disability. Chief Judge Finesilver also noted that genetic data is most likely to affect the judicial system in cases involving confidentiality and

(see Judicial Books, p. 3)

Judicial Reference Book Project

The reference book project operates in five steps for each subject area. A draft book for each area is produced by project staff, with assistance from expert consultants as needed. A workshop is then held for judges, lawyers, scientists, and other interested persons to review each book for accuracy, objectivity, balance, clarity, usefulness, and completeness. After workshop revisions are incorporated, the near-final book is circulated to workshop panelists and advisory committee members for further review and revision. The completed books, which will be distributed in late 1994 and early 1995 at basic cost to state and federal courts, will be useful not only as references for judges but also as curriculum sources for judicial educators.

Tentative book titles are noted below. Workshop sites and dates are listed within brackets with the names of presiding judges.

- *Adjudication of Forensic DNA Evidence in Criminal Cases* [Washington, D.C., June 1993; **Hon. Shirley S. Abrahamson** (Justice, Wisconsin Supreme Court)].
- *Adjudication of Genetic-Testing and Gene-Therapy Cases* [Washington, D.C., December 1993; **Hon. Sherman G. Finesilver** (Chief Judge, U.S. District Court for the District of Colorado)].
- *Neuroscience Evidence in Competency and Guardianship Adjudication of the Senile Dementias* [Scheduled for April in Sarasota, Fla.; **Hon. Stephen L. Dakan** (Presiding Judge, 12th Circuit Court of Florida)].
- *Medical Practice Guidelines as Scientific Evidence in Health-Care Cases* [Scheduled for May in Milwaukee, Wis.; **Hon. Patrick T. Sheedy** (Chief Judge, Circuit Court of Milwaukee County)].
- *Neuroscience Evidence in Criminal Adjudication of Addictive Disorders* [Scheduled for November in Houston, Tex.; **Hon. Thomas J. Stovall** (Presiding Judge, Second Administrative Judicial Region) and **Hon. Miron Love** (Presiding Judge, Courts of Harris County, Texas)].

Genome News

CHLC Report Updates Projects, Genetic Maps

Linkage Center Publication Also Features Online Access, Outreach

The Cooperative Human Linkage Center (CHLC), directed by Jeffrey Murray, has published the second issue of *CHLC Report*. In addition to individual updates on the five CHLC constituent projects at the University of Iowa (UI), Harvard Medical School, Marshfield Medical Research Foundation (MMRF), and Fox Chase Cancer Center (FCCC), the newsletter contains an updated version of the skeletal genetic maps described in its first issue [see *HGN* **4**(4), 3 (November 1992) and **5**(3), 13 (September 1993)]. These maps continue to integrate markers genotyped by Centre d'Etude du Polymorphisme Humain (CEPH) collaborators and, for the first time, include a substantial body of markers developed by CHLC. Significant numbers of tri- and tetranucleotide repeats are provided to complement efforts of other groups using polymorphisms based on the polymerase chain reaction. Selected information from the report is highlighted below.

Online access to CHLC maps, which are continually updated, continues to be supported through the Informatics Core at FCCC. Initial access can be obtained by sending a message to *info-server@chlc.org*. The online reply provides (1) detailed instructions on using the ftp server and Gopher services and (2) an overview of available information. This includes not only skeletal and framework maps, but also genotypes, information on mapping methodologies, primer sequences, sequences from which primers were developed, and mapping data on the initial battery of markers. The primers are available from Research Genetics; 2130 Memorial Parkway; Huntsville, AL 35801 (800/533-4363, Fax: 205/536-9016).

CHLC outreach activities include opportunities for linkage mapping of markers associated with diseases. Interested individuals may spend up to 3 months at the CHLC laboratory, using the laboratory's reagents, maps, and protocols on their own material. Another core activity provides onsite support for 1- to 2-month stays by secondary school science teachers to gain direct experience with the technology of the genome project and participate in studies of ethical, legal, and social issues (ELSI). Over the next year, this program will be expanded to assist the ELSI Core in providing similar experiences for the ELSI fellows. [Contact: Jeff Murray; CHLC; University of Iowa; Iowa City, IA 52242 (319/356-3508, Fax: /335-6970, Internet: *jmurray@umaxc.weeg.uiowa.edu*)].

Investigators at MMRF are genotyping new polymorphisms developed at the center through the CEPH reference families. A major goal continues to be improvement of technology used to genotype short tandem repeat polymorphisms. The simple program (*geno*) for entering genotypes offers advantages over systems for standard data entry and sophisticated, semiautomated image analysis. Program access: anonymous ftp to *dgabby.mfldclin.edu*.

Collaborative efforts in mapping disease genes are continuing at MMRF. During the first grant year, genes responsible for colon cancer, familial expansile osteolysis, and a form of pseudoachondroplasia were mapped through these collaborative efforts. Those interested in collaborating on gene-mapping projects should contact James Weber at MMRF; Marshfield, WI 54449 (715/387-9179, Fax: /389-3808, Internet: *weberj@dgabby.mfldclin.edu*). ◊

To subscribe to *CHLC Report* in hard copy, send name, affiliation, and address to CHLC Administration; #431 EMRB; University of Iowa; Iowa City, IA 52242. The report is available online through the following addresses:

- **ftp:** ***ftp.chlc.org***
- **gopher:** ***gopher.chlc.org***

Judicial Books *(from p. 2)*

discrimination, employment, insurance, medical standards, wrongful birth, patents, testing, and court-appointed experts.

Summary

In commenting on the usefulness of the workshops, Zweig said, "Courts usually have to wait for litigation filed in great numbers before they confer about it. In these genetic cases, it is possible to get ahead of the curve and become familiar with some very complex scientific information on the developing margins so that case management will proceed effectively."◊

NCHGR Funding Opportunies

Request for Applications (applications due April 22)

- **HG-94-01 (R01, R03).** The NIH National Center for Human Genome Research (NCHGR), National Cancer Institute, National Institute of Mental Health, and the National Institute of Nursing Research invite applications for projects to examine the psychosocial and clinical impact of using gene-based diagnostic tests in families with heritable forms of breast, ovarian, and colon cancer. The program is designed to assess public knowledge and attitudes about genetic testing for cancer risks and to gather information useful in establishing clinical protocols for these risk-assessment technologies. Application receipt date: April 22. For additional information or to discuss proposals (strongly recommended), contact Elizabeth Thomson; Ethical, Legal, and Social Implications Branch; NCHGR; Bldg. 38A, Room 617; 9000 Rockville Pike; Bethesda, MD 20892 (301/402-4997, Fax: /480-2770, Internet: *exx@cu.nih.gov*).

Program Announcements (applications due June 1, October 1, and February 1)

Telephone, electronic, and written inquiries are strongly encouraged. [NIH NCHGR: Bldg. 38A, Room 610; 9000 Rockville Pike; Bethesda, MD 20892 (301/496-7531, Fax: /480-2770).]

- **PAR-94-046.** *Pilot Projects or Feasibility Studies for Genomic Analysis (R21)*: Novel, creative approaches that will provide significant advances but are not developed enough to compete successfully for a standard R01 grant. Areas of concentration are physical map annotation, DNA sequencing, high-throughput genotyping, gene identification, and informatics. [Bettie Graham (Internet: *bettie_graham@occshost.nlm.nih.gov*)]
- **PA-94-045.** *New and Improved Technologies for Genomic Research and Analysis (R01, R21, and R29)*: Research that will significantly advance progress toward the extended scientific goals of the Human Genome Project, particularly in mapping, sequencing, informatics, and gene identification. (Graham, see PAR above)
- **PAR-94-044.** *Genome Science and Technology Centers (GESTECs) (P50, P01)*: Supports large-scale, multidisciplinary genomic studies in mapping and sequencing. [Jane Peterson (Internet: *jane_peterson@occshost.nlm.nih.gov*)] ◊

Genome News

ESTs from dbEST

human	16,227
C. elegans	4699
Arabidopsis	2690
rice	1023
plasmodium	831
mouse	136
goat	108
wallaby	36
maize	16

Unpublished ESTs

TIGR	16,913 (human)
G. Guellean	609 (testis)
W. Salser	526 (myeloid)
TIGR	849 (yeast)
TIGR/S. Pena	458 (schistosomiasis)
N. Miyadera	3208 (rice)
TOTAL	48,329 (15,127,080 nt)

Genomic Sequences

Homo sapiens	
E. Chen	225 kb (Chromosomes X and Y)
B. Roe	180 kb (c-abl region)
	146 kb (bcr region)
D. Smith	40 kb (Chromosome 10)
C. Martin	47 kb (Chromosome 8)
S. cerevisiae	
J. Mulligan	420 kb (Chromosome 5)
M. leprae and tuberculosis	
D. Smith	690 kb
Drosophila	
C. Martin	77 kb
E. coli	
F. Blattner	620 kb
C. elegans	
R. Wilson	2200 kb
TOTAL	4,645,000 nt

Data Fair Held at Genome Sequencing and Analysis Conference

For more information, contact Anthony Kerlavage at *arkerlav@tigr.org.*

The second annual Data Fair was held at the Genome Sequencing and Analysis Conference V in Hilton Head, South Carolina, on October 23–27, 1993. Scientists were offered the opportunity to use the latest sequence-analysis tools from research laboratories and commercial vendors to analyze and compare data, both published and unpublished. The fair was organized by Anthony Kerlavage [The Institute for Genomic Research (TIGR)], Jean-Michel Claverie [National Center for Biotechnology Information (NCBI)], and Fred Blattner (University of Wisconsin).

The major goal of the Data Fair was to facilitate comparison of different types of data (genomic and cDNA) from different species and provide new insights into gene expression and evolution.

All public databases available for searching were downloaded to onsite hardware including Sun and DEC workstations, Macintoshes, and a 16,000 processor MasPar. A T1 connection to the Internet allowed software to be run at remote sites. Software included Blast, FastA, Blaze, and MPSearch for sequence searching; and a variety of other clustering, filtering, and utility programs. Coding regions in ESTs were predicted using GRAIL and GENMARK and compared with translated ORFs from all genomic sequences. The recently developed MPSEARCH algorithm from John Collins (University of Edinburgh) was available on a local MasPar. In addition, on a number of electronic posters, developers of algorithms and databases demonstrated and applied the software to data brought to the fair.

Highlights of interesting results included the identification of (1) open reading frames (ORFs) in chromosome 5 of *Saccharomyces cerevisiae* by comparison with yeast ESTs and (2) a previously undetected gene in a human cosmid by comparison with human expressed sequence tags (ESTs), which are short known sequences on a cDNA.

At left is a summary of data brought to the meeting, including all ESTs present in dbEST. Researchers also made available some 20 million nucleotides (nt) for analysis and comparison.◊

DOE Human Genome Program Funding Opportunities

The DOE Office of Health and Environmental Research (OHER) invites applications in support of the following programs. Solicitations were announced in *Federal Register* 59(34), 8183–85 (February 18) and in recent issues of *Science* and other publications. Receipt date for preproposals (strongly encouraged): April 15; formal proposals: July 14.

- **Technological Advances: Program Notice 94-12.** Development of large-scale human genome sequencing that may include supportive mapping and automation; cost-effective DNA sequencing systems that promise more than a tenfold improvement in throughput; software and resources for real-time analysis and annotation of data from high-speed DNA sequencing systems; and resources for facile entry and retrieval of data in community genome maps and DNA sequence databases, including coordinated entry or retrieval across multiple, complementary databases. [Contact: David Smith, OHER, ER-72 (GTN); DOE OHER; Washington, DC 20585 (301/903-6488, Internet: *genome@er.doe.gov*).]

- **Ethical, Legal, and Social Implications (ELSI): Program Notice 94-13.** Multidisciplinary, empirical research on privacy issues arising from the creation, use, maintenance, and disclosure of genetic information, including its ownership, control, and protection. Preparation and dissemination of educational materials. Planning and implementation of OHER conferences on specific issues related to ELSI. [Contact: Daniel Drell at address above.] ◊

IBC Explores Bioethics Pact

The International Bioethics Committee (IBC) of the United Nations Educational, Scientific, and Cultural Organization (UNESCO) is working toward an ethics-based international agreement concerning human genome research and its applications. The committee, appointed to 4-year terms (1993–96) by the UNESCO Director General, is composed of 50 members from the disciplines of biology, genetics, medicine, law, philosophy, and the social and human sciences. Chaired by Noelle Lenoir, member of the Constitutional Court of France, IBC held eight workshops in 1993 to consider ethical issues associated with genome research, embryology, neuroscience, genetic therapy, and genetic tests. At the general meeting in September 1993, the Scientific and Technical Orientation Group presented a report recommending the development of an international standard-setting instrument to protect the human genome. In 1994 IBC will explore (1) the form and content of such an instrument and (2) additional topics related to implications of genetic research.
[Contact: George B. Kutukdjian; UNESCO; Place de Fontenoy, 7; 75007 Paris Cedex (+33/1-4568-3814; Fax: -4506-0772).]◊

Moyzis Wins DOE Lawrence Award

Robert Moyzis, Director of the Center for Human Genome Studies at Los Alamos National Laboratory, is one of seven winners of the 1993 E. O. Lawrence Award, presented by DOE. The award, which is named for the inventor of the cyclotron, carries with it a gold medal, citation, and $10,000.

Identifying and Cloning the Telomere

Moyzis received the Lawrence Award in life sciences for distinguished contributions to the field of molecular genetics. Often using unorthodox methods, he and colleagues constructed and searched human DNA sequence libraries, finally identifying and cloning (with yeast artificial chromosome vectors) the telomere, a repeated sequence of nucleotides at the end of a DNA strand on the chromosome. After identifying the terminal repeat sequence $(TTAGGG)_n$ and finding it to be present in the telomeres of over 100 vertebrate species tested, investigators concluded that the sequence has been conserved over the last 400 million years of evolution. Such conservation of a DNA sequence suggests an important role for this "molecular fossil." In the human telomere, this sequence is repeated 250 to 1500 times, depending on cell type, with sperm chromosomes having the most repeats. Another type of repeated telomeric DNA, found adjacent to the terminal repeat, is species specific.

Although it carries no genes, telomeric DNA is critical to chromosomal replication and stability. Scientists speculate that the ability of repetitive sequences to form novel structures may be responsible for maintaining each chromosome as a separate entity and preventing shortening during replication. Telomere shortening is thought to play a role in the aging process and the onset of cancer.

Important findings from studies of repetitive telomeric sequences support the idea that sequencing the whole genome, introns (noncoding regions) as well as exons, is crucial to understanding basic biology. For example, the unusual DNA structures formed by repeated sequences (or other DNA patterns) in telomeres represent a new type of sequence-encoded information (i.e., structural) different from that of conventional base pairing elucidated 30 years ago. Sequencing the entire genome has been the ultimate goal of the genome project from its inception, although this objective has sparked criticism from those who consider the sequencing of introns unproductive.

Centromere Research

Moyzis was also cited for his ongoing explorations in identifying the functional human centromere, a region of the chromosome that plays a key role during cell division. The discovery of human chromosome–specific repetitive sequences located in or near the centromere led to immediate scientific and clinical applications, including diagnosis of some types of human genetic abnormalities and rapid identification of abnormal numbers of chromosomes in human cells.

Moyzis, who was also recognized for his contributions to the successful initiation of the Human Genome Project, has served on numerous committees, including the DOE Human Genome Coordinating Committee and the NIH-DOE Joint Human Genome Program Advisory Committee. Moyzis earned his bachelor's degree from Northeastern Illinois University in 1971 and his doctorate in molecular biology from Johns Hopkins University in 1978; he assumed his current position in 1989. The LANL genome center is one of 19 U.S. centers whose goals are to map the estimated 100,000 genes residing along the human chromosomes and determine the sequence of the 3 billion bases contained in the human genome. *[Denise K. Casey, HGMIS]* ◊

Contributions to Molecular Genetics, Human Genome Project Cited

☛ Resource: New Panels Available for Mapping Loci in the Mouse

The Jackson Laboratory is making available a new genetic-mapping resource of interspecific backcross DNA for mapping loci in the mouse. To facilitate the collective approach to generating a comprehensive map for the worldwide genome project, two DNA panels were established in microtiter format, one containing DNA from 94 N2 animals from the cross [C57BL/6J x *M. spretus* F1 females x C57BL/6J males (BSB Panel 1)] and another from 94 N2 animals from the reciprocal backcross [(C57BL/6J x SPRET/Ei) F1 females x SPRET/Ei males (BSS Panel 2)]. These DNA panels give wide access to mapping data and allow more research groups to participate simultaneously in mapping many types of loci. With a single microtiter plate for each panel set, complete data can be obtained readily for any polymorphism, and all new data result in map positions with highly significant linkage at a 1- to 5-cM resolution.

Large quantities (24 to 50 mg) of DNA were prepared from most tissues of each backcross animal. Initial characterization of the genetic maps of both panels has been completed. Massachusetts Institute of Technology single sequence length polymorphism (SSLP) markers [Dietrich et al., *Genetics* **131**, 423–47 (1992)]; proviral loci [Frankel et al., *J. Virol.* **63**, 1762–74 and 3810–21 (1989) and *Genetics* **124**, 221–36 (1990)]; and several other sequence-defined genes [Takahashi and Ko, *Genomics* **16**, 161–68 (1993)] were used to anchor these maps to other published maps. The BSB panel map (from the backcross to C57BL/6J) now contains 255 loci and is anchored by 50 SSLP and 32 gene sequence loci. The BSS panel map (from the backcross to SPRET/Ei) contains 666 loci and is anchored by 59 SSLP loci, 43 proviral loci, and 60 gene sequence loci. To obtain a high density of markers, motif-primed polymerase chain reaction (PCR) was used to "fingerprint" the panel DNAs [Birkenmeier et al., *Mammalian Genome* **3**, 537–45 (1992)]. Since many loci are typed on only one of the panel sets, maps were constructed to represent each of the two panels. DNAs have been distributed to 38 laboratories around the world, and 23 investigators have contributed data to the maps. The Jackson Laboratory BC Panel Map Service is continuing to type additional anchor loci, and many other groups are adding new data to the map database. A complete preliminary report by Rowe et al. describing these results is in press at *Mammalian Genome*.

The backcross panel DNAs are available either as Southern blot filter sets (limited in 1994), aliquots of DNA for Southern blot analysis, or as aliquots of DNA to be diluted for use as PCR templates. Each backcross panel is in microtiter plate format with parental control DNAs in wells 1A and 1B and backcross N2 progeny DNAs in the remaining 94 wells. All data are catalogued by microtiter plate well position (e.g., 12H).

The Map Service is committed to providing technical support and genetic-mapping assistance as necessary to promote successful and efficient use of this DNA resource. A modest per-shipment charge is made for the use of the panels. [Contact: Lucy Rowe; The Jackson Laboratory; 600 Main Street; Bar Harbor, ME 04609 (207/288-3371, ext. 1687; Fax: -5079; Internet: *lbr@aretha.jax.org*). Return addresses should be included.] *[Lucy B. Rowe, Joseph H. Nadeau, Janan T. Eppig, and Edward H. Birkenmeier, The Jackson Laboratory]* ◊

Genome News

The Spring issue of *Risk: Health, Safety, & Environment* will be devoted to this conference. Copies of *Risk* can be ordered, but only before May 1, from Carol Ruh, Managing Editor; *Risk*; Franklin Pierce Law Center; 2 White Street; Concord, NH 03301 (603/228-1541, Fax: -0388). The set of papers prepared before the conference can be obtained from the same address.

OTA Study

The Human Genome Project and Patenting Human DNA Sequences, a study by the Office of Technology Assessment of the U.S. Congress, is scheduled for publication this summer [contact: Robyn Nishimi (202/228-6920, Internet: *rnishimi@ota.gov*)].

Conference Examines DNA Patenting, Tech Transfer Issues

The following article was written by Robert Cook-Deegan (Institute of Medicine, National Academy of Sciences) and Rebecca Eisenberg (University of Michigan Law School). The authors use topics discussed at the conference to illustrate issues relating to patenting of genome discoveries, government patenting policies, and technology transfer. Some basic information on patents is given in the shaded box below the article.

A conference on Maximizing the Return from Genome Research was convened by the Franklin Pierce Law Center (FPLC) in Manchester, New Hampshire, on July 23–24, 1993. The meeting was organized by Thomas Field and Gianna Julian-Arnold (FPLC) and funded in part by the Ethical, Legal, and Social Issues component of the DOE Human Genome Program.

Presentation topics included the genesis of the genome project; relevant intellectual property protections; technology transfer law; practical considerations in technology transfer, especially from national laboratories to the private sector; and policies governing research administration and technology transfer at NIH and DOE. Discussion was facilitated by the relatively small size of the group and the expertise of participants.

The conference addressed questions about which genome discoveries can and should be patented and who should own and control patent rights to federally funded research. These are crucial questions not only for genome research but for all biomedical research. Congress has expressed interest in technology transfer law; patent law; and operation of technology transfer offices at universities, government laboratories, and private firms (see OTA Study sidebar at left).

The controversy surrounding large-scale patenting of expressed sequence tags (ESTs) has brought intense scrutiny to the relationship between genome research and intellectual property. Although this attention has not always been welcome to those involved, it has nonetheless generated interest in the way technology transfer works, particularly in biotechnology. The debate has also highlighted contradictory federal policies that promote commercial applications of research on one hand and prompt disclosure of all map and sequence data on the other.

Data sharing, a major concern in the Human Genome Project since its inception, has been a topic at each annual sequencing meeting and on many other occasions. Because maps and databases are more useful when they are comprehensive, immediate and complete sharing of data seems desirable. Some investigators are eager to publish new data as soon as possible, particularly if multiple research groups are competing for scientific priority. Others may wish to protect data until they file a patent application and satisfy the legal requirements of novelty and nonobviousness. Once an application is filed, the applicant can release data without compromising patent rights. The U.S. Patent and Trademark Office (PTO) will keep the information confidential until a patent is issued and invention information is publicly disclosed, but some foreign patent offices disclose patent applications 6 months after they receive them. Because inventors may take up to 1 year to file foreign patent applications, the period of nondis-

Staking a Claim on Biotechnology

Patents have been called the lifeblood of the biotechnology industry for good reason—protection of investment is crucial in an industry where product research is expensive, imitation is fairly easy, and the potential value of particular genes and their protein products is high. Patents traditionally have provided companies with incentives to risk time and money in research and development. Life forms such as genes, cells, and even some animals have been held patentable since 1980, when a divided Supreme Court affirmed (by a 5-to-4 vote) the granting of a patent for an oil-dissolving bioengineered microbe. This decision stimulated the burgeoning biotechnology industry, whose annual revenues now approach $6 billion and are projected to reach $50 billion by the year 2000.

Human genes and their products can be extremely valuable. A case in point is the huge success of Epogen, a genetically engineered version of the kidney hormone erythropoietin that stimulates the production of red blood cells in the body. Synthesized by the biotechnology company Amgen, Inc., Epogen is used by thousands of people who are on dialysis because of kidney failure and thus unable to make sufficient erythropoietin. Epogen has generated over $400 million in domestic sales for Amgen, and the potential for foreign sales has been estimated at $500 million to $1.2 billion. Amgen isolated the protein and determined the sequence for the gene while trying to produce a product having the properties of erythropoietin. The company has owned the rights to the erythropoietin gene since 1987.

- **How do patents protect rights to an invention, and who grants them?**

Patents encourage the investment of resources by providing a monopoly to the inventor and prohibiting competitors from making, using, or selling the invention without a license. This monopoly is limited to 17 years in the United States, subject to extension in the case of patented drugs and medical devices. By granting exclusive rights, patents allow inventors to disclose their information safely, give information on technical advances to competitors and the general public, and avoid duplication of efforts.

closure is typically 18 months. Thus patent considerations may lead to interim delays, but they should not prevent full disclosure in the long run.

Indeed, two purposes of the patent system are to (1) promote disclosure by offering exclusive rights to inventors and (2) encourage new inventions by conferring profitable exclusive rights that will foster private investment in research and development. During the 1980s, Congress passed several statutes aimed at furthering technology transfer, including the Bayh-Dole Act (1980), the Stephenson-Wydler Act (1980), and the Federal Technology Transfer Act (1986). These and other related statutes and executive orders assumed that patenting the results of government-sponsored research and vesting patent rights in research institutions would accelerate commercial applications, produce more jobs, and strengthen the competitive position of U.S. firms in the global economy.

While this is generally true, some patent rights held by research institutions performing government-funded basic research could interfere with, rather than encourage, private-sector product development. Instead of providing industry with otherwise unavailable exclusive rights, government- and university-held patents might burden firms with obligations toward institutions whose product-development contributions seem remote and inconsequential. How much control should a partial gene sequence's discoverer, who may not know its biological function or other uses, have over subsequent systematic investigations of that gene and its products?

Another conference topic was whether or not patents should be allowed on discoveries that are useful mainly as research tools, even if they have commercial value. Such patents could present obstacles to commercial product development by increasing costs and slowing research progress. Grantees might be forced to build licensing fees and transaction costs into grant applications, and commercial firms might have to negotiate a complex network of licenses to avoid the threat of infringement liability. As the number of patents and the complexity of relationships among patent holders increase, "patent clutter" could defeat the very goals that patent law is intended to promote.

Some potential harm might be mitigated by what Marilyn Hartig (Warner-Lambert) characterized as a de facto period of research exemption arising from the delay between application filing and patent issuance. Patent rights are not enforceable during this interim period, thus creating an opportunity to use a research tool without risking infringement liability. The lengthy process of issuing biotechnology patents, coupled with rapid progress in the field, may allow time for researchers and firms to learn all they need to know from a research tool before a patent is granted. Users incur no obligations to the eventual patent holder before the patent is granted, but a license is required thereafter.

Views differ about whether EST patent applications, now abandoned by NIH and the British Medical Research Council but still being pursued by other entities, would help future commercial interests or hinder them. Some say that patenting such discoveries is inappropriate because the effort to find any given EST is small compared with the work of isolating and characterizing a gene and gene product, finding out what it does, and developing a commercial product. They feel that allowing holders of such "gatekeeper" patents to exercise undue control over the commercial fruits of genome research would be unfair. Others say that patents on ESTs preserve the commercial options of future inventors whose discoveries may be

(see Patenting, p. 12)

IOM Project

The Institute of Medicine and the Commission on Life Sciences, both units of the National Academy of Sciences, are collaborating on a project that will address patenting, technology transfer, and conflict of interest in molecular biology [contact: Richard Rettig (202/334-1734, Internet: *rrettig@nas.edu*)].◊

- **What criteria are used to determine the patentability of an invention?**

The patentability of inventions under U.S. law is first determined by the Patent and Trademark Office (PTO) in the Department of Commerce. A patent application is judged on four criteria. It must be "useful" in a practical sense (the inventor must identify some useful purpose for the invention); "novel" (i.e., not known or used before the filing); and "nonobvious" (i.e., not an improvement easily made by someone trained in the relevant area). The invention must also be described in sufficient detail to enable one skilled in the field to use it for the stated purpose (sometimes called the "enablement" criterion).

- **To whom is a patent granted?**

In the United States, patent priority is based on the "first to invent" principle: whoever made the invention first (and can prove it) is awarded property rights for the 17-year period. Inventors have a 1-year grace period to file after they publish. All other countries except the Philippines, however, follow a "first inventor to file" rule in establishing priority when granting patents.

- **Since it is common to patent genes, why were the EST patenting applications questioned?**

While previous patents were granted for genes whose full sequences and functions were known, new methodology now enables researchers to partially characterize genes where no function is known. Beginning in the summer of 1991 NIH filed for patents on over 6000 gene fragments. Questions arose over the issue of when, from discovery to development into useful products, exclusive rights to genes could be claimed. The 300- to 500-base gene fragments, called expressed sequence tags (ESTs), represented only 10 to 30% of the average cDNA, and the genomic genes are often 10 to 20 times larger than the cDNA. In addition, the original chromosomal locations and biological functions of the full genes identified by ESTs were unknown in most cases.

In 1992 and 1993, some of the NIH EST patent applications were rejected by PTO for not meeting the requirements outlined above. Although NIH announced recently that it would not appeal the rejections, questions concerning gene patenting continue to generate much debate in the scientific and biotechnology communities. *[Denise Casey, HGMIS]*

Genome News

Human Genome news

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

Human Genome Management Information System

Managing Editor
Betty K. Mansfield

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

Production Manager/Editor
Judy M. Wyrick

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

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

Sponsor Contacts

Daniel W. Drell
DOE Program Office
Germantown, MD 20545
301/903-6488, Fax: -8521
Internet: *daniel.drell@mailgw.er.doe.gov*

Leslie Fink
NIH National Center for Human Genome Research
Bethesda, MD 20892
301/402-0911, Fax: -4570
Internet: *lsf@cu.nih.gov*

National Center for Human Genome Research

Third Transcribed Sequences Workshop

The Third International Workshop on the Identification of Transcribed Sequences, held in New Orleans October 2–4, 1993, was sponsored by DOE, NIH, and Amgen, Inc. Some 60 scientists from 9 countries discussed new approaches for identifying genes in genomic material, experiences and challenges in applying these methods, and preliminary data on assembling transcriptional maps.

The two major ways of assembling transcriptional maps of the human genome are to (1) isolate and sequence all expressed mRNAs as cDNA clones and place them on the physical and genetic maps or (2) identify all transcribed sequences in cloned mapped genomic DNA. Three different approaches can be used for the latter method: interpret genomic sequence with the help of computer programs, assay genomic sequences functionally for their ability to splice out exons in exon-trap protocols, and hybridize genomic DNA to cDNA. Although all hybridization methods are conceptually based on the same process, a number of technical variations exist. For example, the genomic partner can be yeast artificial chromosome (YAC) clones, cosmids, or parts of chromosomes; both partners in the hybridization reaction can be in solution or one can be fixed on a solid support; and the cDNA can be eluted and cloned or used to score signals on genomic clones.

Methods and Technical Developments

Three new variations on hybrid selection were presented: a coincidence-cloning protocol involving a selective ligation step (Anthony Brookes, Medical Research Council Human Genetics Unit); a hybrid-selection protocol based on the polymerase chain reaction (PCR) and involving a genomic-cDNA chimera (Pudur Jagadeeswaran, University of Texas); and a selection through genomic RNA and single-stranded cDNA (Anand Swaroop, University of Michigan). John Hozier (Applied Genetics Laboratories, Inc.) described pilot experiments on hybrid selection using metaphase chromosome spreads as the genomic partner and cloning cDNAs eluted from microdissected parts of chromosomes. Bento Soares (Columbia University) combined the hybrid-selection method with the direct cDNA-screening approach by hybridizing cDNAs to filters carrying genomic clones from entire chromosomes, making cDNA-genomic hybrids visible through a sandwich technique, and eluting the cDNAs from positive genomic clones.

A new version of the pSPL-1 exon-trap vector, pSPL-3, was described by Paul Nisson (Gibco BRL/Life Technologies, Inc.). Nicole Datson (Leiden University) reported progress in using the pETV-SD2 exon-trapping vector.

Advances in three neural network approaches for gene identification in genomic sequences were presented for GeneParser (Eric Snyder, University of Colorado), GeneID (Roderic Guigo, Los Alamos National Laboratory), and GRAIL (Richard Mural, Oak Ridge National Laboratory). GRAIL now recognizes smaller exons, and the Gene Assembly Program assembles full-length coding sequence from genomic sequence with high reliability.

Techniques to identify and sequence cDNAs were presented. James Eberwine (University of Pennsylvania), Mark Erlander (Scripps Research Institute), and Wai-Choi Leung (Tulane University) discussed identifying cDNAs by differential display techniques in single cells, different areas of the brain, and different tissues, respectively. Radoje Drmanac (Argonne National Laboratory) and Joachim Rothe [Imperial Cancer Research Fund (ICRF)] reported on sequencing by hybridization. James Sikela (University of Colorado) addressed sequencing full-length cDNA clones by using *Nco*I sites in 5′ ends of cDNA clones.

Applications and Experiences

A number of groups presented different versions of the hybrid-selection approach. Although use of whole-cell DNA from YAC-containing yeast as the genomic partner is possible (Sherman Weissman, Yale University), other investigators have used purified YACs or cosmids as the genomic partner. After exclusion of ribosomal and repeat-sequence contaminants, 60 to 90% of cDNAs map to the genomic region.

Improvements were reported in direct cDNA screening of arrayed genomic libraries. Sensitivity was increased by using a subtracted cDNA probe (Jeffrey Falk, Scripps Research Institute), and GRAIL allowed investigators to proceed quickly from identified genomic clones to coding sequences (Wolfgang Schwabe, National Institute of Mental Health).

Results on exon trapping with the pSPL vector system were reported for three different genomic regions (Ken Abel, University of Michigan; Michael North, ICRF; Marie-Laure Yaspo, ICRF). Although exon trapping on YACs is possible, individual or pools of cosmids seem to be the preferred unit for exon trapping because of skewing in the PCR step. A difficulty is verifying that a trapped product is an exon. Their generally small size frequently makes trapped products ineffective probes for zoo blots or cDNA library screenings.

In addition to these newer methods for gene identification, successes were reported with more-standard procedures: cloning CpG islands (Daniela Toniolo, Consiglio Nazionale delle Ricerche), identifying evolutionarily conserved sequences (Jerome Gorski, University of Michigan), and screening cDNA libraries with cosmid probes (Sue Rider, ICRF).

The use of PCR on pools of YACs was discussed for mapping random end-sequenced cDNA clones to the physical map (Sikela).

The Fourth International Transcribed Sequences Workshop is planned for October 16–18 in Montreal, Canada. [Contact: Nan Matthews; Eleanor Roosevelt Institute; 1899 Gaylord St.; Denver, CO 80206 (303/333-4515, Fax: -8423).]

William Nierman (American *Type Culture* Collection) reported that 59% of PCR primers from end sequences were usable for mapping. Donald Moir (Collaborative Research, Inc.) presented the hybridization of cDNAs to gridded arrays of mega-YAC clones as an alternative to commonly used PCR-based cDNA mapping. David Beier (Harvard Medical School) demonstrated mapping mouse cDNAs by single-stranded conformation polymorphisms in inbred mouse strains.

Transcriptional Maps

Several groups are assembling transcriptional maps of whole chromosomes or chromosome regions: 21 (Katheleen Gardiner, Eleanor Roosevelt Institute; Yaspo; Andrew Peterson, University of California at San Francisco); Xq28 (Bernhard Korn, German Cancer Research Center; Toniolo; Hubert Smeets, University of Nijmegen); Xp21 (Francoise Muscatelli, ICRF); Xp11.21 (Gorski); Xq13.3 (Jozef Gecz, Slovak Academy of Science); and 7q22 (Johanna Rommens, Hospital for Sick Children). Different methods were applied singly or in combination. More data are needed to determine how effective the various methods will be over large regions and before gene distributions within chromosomal regions emerge.

Problems and Perspectives

One problem common to different methods of gene identification was how to define a gene. When can a hybrid-selected cDNA, an exon-trapped product, or a GRAIL-positive genomic fragment be identified positively as a coding sequence of a gene? Parameters suggested by workshop participants were reverse transcription PCR across an intron-exon boundary, signal on a Northern blot, and isolation of a poly A–containing cDNA clone.

Another problem specific to candidate exons retrieved through exon trapping or hybrid selection is to avoid redundant analyses of multiple short fragments from the same gene. One possibility discussed is to isolate full-length cDNA clones with the first probe available and use this to rescreen the pool of other isolates (e.g., exon-trap products or hybrid-selected clones). This would identify other small cDNA clones in the selected library that are parts of the same gene.

Although each of these methods has advantages, no method is perfect. Future experiments will show which is best suited for a particular application, from cloning disease genes within a relatively small, defined region to assembling large-range transcriptional chromosome maps. *[Ute Hochgeschwender, National Institute of Mental Health, and Katheleen Gardiner, Eleanor Roosevelt Institute]* ◊

GDB USER SUPPORT, REGISTRATION

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

The new telephone number for GDB user support in Baltimore is 410/955-9705.

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

GDB, OMIM Training Schedule

Contact U.S. GDB User Support Office (below). General User Classes will be held in Baltimore on April 18–19 and June 13–14.

User Support Offices

UNITED STATES
GDB User Support
Genome Data Base
Johns Hopkins University
2024 E. Monument Street
Baltimore, MD 21205-2100
410/955-9705
Fax: /614-0434
Internet: *help@gdb.org*

GERMANY
Otto Ritter
Molecular Biophysics Dept.
German Cancer
Research Center
Im Neuenheimer Feld 280
D-6900 Heidelberg
Germany
+ 49/6221-42-2372
Fax: -2333
Internet: *dok261@*
cvx12.dkfz-heidelberg.de

UNITED KINGDOM
Christine Bates
Human Gene Mapping
Program Resource Center
CRC, Watford Road
Harrow, Middx HA1, 3UJ
United Kingdom
+ 44/81-869-3446
Fax: -3807
Internet: *cbates@uk.ac.crc*

NETHERLANDS
GDB User Support
CAOS/CAMM Center
Faculty of Science
University of Nijmegen
P.O. Box 9010
6500 GL NIJMEGEN
Netherlands
+ 31/80-653391
Fax: -652977
Internet:
post@caos.caos.kun.nl

AUSTRALIA
Alex Reisner
ANGIS
Electrical Eng. Bldg. J03
University of Sydney
Sydney, N.S.W. 2006
Australia
+ 61/2-692-2948
Fax: -3847
Internet: *reisner@*
angis.su.oz.au

SWEDEN
GDB User Support
Biomedical Center
Box 570
S-751 23 Uppsala
Sweden
+ 46/18-174057
Fax: -524869
Internet:
help@gdb.embnet.se

GDB Contains New Genethon YAC Data

Genome Data Base (GDB) is making available the data presented in the paper by Cohen et al. on mega–yeast artificial chromosome (YAC) maps of all the human chromosomes [*Nature* **366**, 698–701 (1993)]. In conjunction with the paper's publication, data on YAC clones became accessible December 16, 1993, on the Genethon ftp and Gopher servers. GDB staff downloaded these data and formatted them for electronic loading into GDB.

From this data set, 7484 D-segment assignments have been made. A total of 34,495 clone records and nearly 100,000 links to already defined Genethon sequence tagged sites and between overlapping YACs are available in GDB.

Since GDB will contain records of all publicly available Genethon YAC information, Genethon markers included in future maps need not be resubmitted to GDB. Research groups having clone information should contact GDB for assistance in the data-submission process.◊

Calendar of Genome-Related Events* (acronyms, p. 12)

April

27–30. 2nd Carolina Conf. on Chromosome Structure and Dynamics: Biological Consequences of Genomic Instability; Chapel Hill, NC [J. McPherson, 919/966-6800, Fax: -6821]

May

2–4. Workshop on Information Retrieval and Genomics; Bethesda, MD [J. Guldi, 207/288-3371, ext. 1391, Fax: -5079, Internet: *jng@jax.org*]

4–7. AMIA 94 Spring Cong.: Medical Info. and Record Systems—Integration at the Enterprise and Individual Levels; San Francisco [AMIA, 301/657-1291, Fax: -1296, Internet: *amia@camis.stanford.edu*]

5–6. Ethical Implications of New Genetics; Boston (reg. deadline: April 21) [PRIM&R, 617/423-4112, Fax: -1185]

7–9. **3rd Intl. Workshop on Human Chromosome 16; Pittsburgh, PA [N. Doggett, 505/665-4007, Fax: -3024, Internet: *doggett@gnome.lanl.gov* or D. Callen, +61-8/204-7342, Fax: -7333]

8–9. 5th Intl. Chromosome 3 Conf.; Ann Arbor, MI [D. Smith, 313/577-6968, Fax: -5218 or B. Loder, Fax: +32-2/295-5365]

8–9. Nordic Genome Workshop; Helsinki [L. Peltonen, +35-80/474-4393, Fax: -4480]

9–10. **12th Ann. Biotechnol. Patent Conf.; Arlington, VA [ATCC, 301/231-5566, Fax: /770-1805]

9–10. **NIH Natl. Advisory Council for Human Genome Res.; Bethesda, MD [J. Ades, 301/402-2205, Fax: -2218]

11–15. Genome Mapping and Sequencing; Cold Spring Harbor, NY [CSHL, 516/367-8346]

19. Joseph Nadeau: Mouse Genome Informatics; Bethesda, MD [NCHGR Lecture Series, E. Feingold, 301/496-7531, Fax: /480-2770]

20–21. 2nd Intl. Workshop on Chromosome 13; Groningen, Netherlands [C. Buys, +31-50/63-2925, Fax: -2947 or A. Bowcock, 214/648-1675, Fax: -1666]

21–25. ASBMB; Washington, DC [G. Goodenough, 301/530-7010, Fax: -7014]

23–27. BIO Intl.; Toronto [R. Okiuye, 202/857-0244, Fax: -0237]

June

1–4. 3rd Intl. Conf. on Bioinformatics and Genome Res.; Tallahassee, FL [P. Meredith, Fax: 904/644-1010, Internet: *bio94@scri.fsu.edu*]

1–8. Symposium: Mol. Genetics of Cancer; CSHL, Cold Spring Harbor, NY [see contact: May 11–15]

3–5. Intl. Workshop on Human Chromosome 2; Aarhus, Denmark [T. Kruse, +45-86/139711, Fax: /123173 or S. Naylor, 210/567-3842, Fax: -6781]

7–11. BioWest/*BioPacifica* 94; San Diego [BioConferences Intl., 301/652-3072, Fax: -4951]

8–10. New Horizons in Gene Amplification Technologies: New Techniques and Applications; San Francisco [CHI, 617/487-7989, Fax: -7937]

14–15. Genetic Predisposition to Cancer; Bethesda, MD [GMCRF, L. Pearson, 212/418-6229, Fax: -6388]

16. Shirley Tilghman: Genetics of Neural Crest Development in Mice; Bethesda, MD [see contact: May 19]

20–22. Chromosome 12 Workshop; New Haven, CT [R. Kucherlapati, 212/430-2069, Fax: /823-6550, Internet: *kucherla@aecom.yu.edu* or I. Craig, +44-86/527-5327, Fax: -5318, Internet: *icraig@crc.ac.uk*]

July

2–5. 4th Intl. Workshop on the Mapping of Human Chromosome 22; Cambridge, U.K. [P. Scambler, +44-71/242-9789, ext. 2635, Fax: /831-0488 or K. Beutow, 215/728-2813, Fax: -3574]

3–8. 9th Intl. Workshop on the Mol. Genetics of the Mouse; Edinburgh, U.K. [I. Jackson, +44-31/332-2471, Fax: /343-2620]

6–10. SINEs, LINEs, and Retrotransposable Elements: Functional Implications; Davis, CA [M. Batzer, 510/423-3637, Fax: -3608, Internet: *batzer2@llnl.gov*]

10–24. **Open Problems in Computational Mol. Biol.: 4th Intl. Workshop; Telluride, CO [A. Konopka, 301/663-1206, Internet: *akonopka@lifsci.sdsu.edu*]

27–29. DNA Sequencing/Bioinformatics; San Francisco [IBC Conf., 508/481-6400, Fax: -4473]

28–Aug. 5. Human Genome Analysis: From YAC to Gene; London (application deadline: Mar. 31) [WLMG, P. Faik, +44-71/403-6998, Fax: /407-5281]

August

9–12. Interconnection of Mol. Biol. Databases; Stanford, CA [P. Karp, 415/859-6375, Fax: -3735, Internet: *pkarp@ai.sri.com*]

31. Chromosome 14 Associated Neurological Diseases: Antwerp, Belgium [C. van Broeckhoven, +32-3/820-2301, Fax: -2541]

31–Sept. 2. **Automation in Mapping and DNA Sequencing; Hinxton, U.K. [D. Cooper, +44-22/349-4957, Fax: -4919, Internet: *denise@sanger.ac.uk*]

31–Sept. 4. Mouse Molecular Genetics; CSHL, Cold Spring Harbor, NY [see contact: May 11–15]

September

1–3. **2nd Intl. Chromosome 14 Workshop; Oxford, U.K. [J.H. Edwards or S. Craig, Fax: +44-86/527-5318, Internet: *c14@bioch.ox.ac.uk*]

16–18. 2nd Intl. Chromosome 8 Workshop; Oxford, U.K. [N. Spurr, +44-71/269-3846, Fax: -3802 or R. Leach, 210/567-6947, Fax: -6781]

17–21. Intl. Genome Sequencing and Anal. Conf. VI; Hilton Head, SC (abs. deadline: June 29) [D. Hawkins, 301/869-9056, Fax: /977-7233, Internet: *seqconf@tigr.org*]

19–20. **NIH Natl. Advisory Council for Human Genome Res.; Washington, DC [see contact: May 9–10]

21–25. Gene Therapy; CSHL, Cold Spring Harbor, NY [see contact: May 11–15]

25–28. 4th Chromosome 11 Workshop; Oxford, U.K. [V. van Heyningen, Fax: +44-31/343-2620, Internet: *vervan@mrcvax.ed.ac.uk* or G. Evans, 619/453-4100, ext. 279, Fax: /558-9513, Internet: *gevans@salk-sc2.sdsc.edu*]

October

2–5. Human Genome 94: The Genes and Beyond; Washington, DC (abs. deadline: July 1) [G. Griffin, 703/671-1400, Fax: -7695]

16–18. Ident. of Transcribed Seq. Workshop; Montreal (abs. deadline: August 15) [N. Matthews, 303/333-4515, Fax: -8423]

November

13–17. **4th DOE Genome Contractor-Grantee Workshop; Santa Fe, NM [S. Spengler, 510/486-4879, Fax: -5717, Internet: *sylviaj@ux5.lbl.gov*] ◊

Training Calendar*

May

2. Intro. to PCR; Houston [BTP, S. Chance, 800/821-4861, Fax: 603/659-4708]

2–6. Recombinant DNA Techniques I; Germantown, MD [LTI, 800/952-9166, Fax: 301/258-8212]

3–4. Quantitative RNA-PCR; BTP, Houston [see contact: May 2]

5–6. Basic Cloning and Hybridization Techniques; BTP, Houston [see contact: May 2]

9–10. Clinical Applications of PCR; BTP, Houston [see contact: May 2]

9–13. Recombinant DNA Methodology; Columbia, MD [Exon-Intron, Inc., 410/730-3984, Fax: -3983]

16–20. PCR Methodology; Exon-Intron, Inc., Columbia, MD [see contact: May 9–13]

16–20. PCR Techniques; LTI, Germantown, MD [see contact: May 2–6]

➠

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

16–20. Recombinant DNA: Techniques & Applications; Rockville, MD [ATCC, 301/231-5566, Fax: /770-1805]

19–20. Metaphase and Interphase Chromosome Analysis; Gaithersburg, MD [Oncor, Inc., 800/776-6267, Fax: 301/926-6129]

22–24. PCR Techniques; Washington, DC [CATCMB/CUA, M. Miller, 202/319-6161, Fax: -4467]

23–27. Basic Cell and Tissue Culture; CATCMB/CUA, Washington, DC [see contact: May 22–24]

23–27. Biotech. for Business; Durham, NC [M. Pirrung, 919/660-1579, Fax: -1591]

24–27. DNA Sequencing; CATCMB/CUA, Washington, DC [see contact: May 22–24]

24–27. DNA Sequencing PCR Applications/Cycle; ATCC, Rockville, MD [see contact: May 16–20]

25–26. Intro. to In Situ PCR; BTP, Durham, NC [see contact: May 2]

29–June 3. **Nucleic Acid and Protein Sequence Analysis Workshop for Biomedical Researchers; Pittsburgh [PSC, N. Blankenstein, 412/268-4960, Fax: -5832]

31–June 7. Medical Informatics; Woods Hole, MA [MBL, 508/548-3705, ext. 401]

June

5–11. Intensive Bioethics Course XX; Kennedy Institute, Washington, DC [M. Favreau, 202/687-6771, Fax: -6770]

6–10. Recombinant DNA Techniques: Hands-on Course; New Brunswick, NJ [Rutgers Univ., M. Bell, 908/932-9271, Fax: -8726]

6–10. **PCR—Methods and Applications: Hands-on Course; Buffalo [R. Cunningham, 716/829-2901, Fax: -2158]

6–10. Expression of Recombinant DNA in Mammalian Cells; CATCMB/CUA, Washington, DC [see contact: May 22–24]

6–11. cDNA Library Techniques; LTI, Germantown, MD [see contact: May 2–6]

8–10. Methods and Advanced Techniques in Human Id.; Bethesda, MD [ARP/AFIP, 301/427-5231, Fax: -5001]

9–10. DNA Sequencing without Radioactivity; BTP, Seattle [see contact: May 2]

9–10. Tissue In Situ Hybridization; Oncor, Inc., Gaithersburg, MD [see contact: May 19–20]

10–30. Advanced Bacterial Genetics; Cold Spring Harbor, NY [CSHL, 516/367-8346]

12–15. **Genomic Information: Ethical Implications; Seattle [B. Brownfield, 206/543-5447, Fax: /685-7515]

13–14. GDB/OMIM Training Courses [see schedule, p. 9]

13–17. DNA Binding Proteins and Transcriptional Regulators; CATCMB/CUA, Washington, DC [see contact: May 22–24]

20–24. In Situ Hybridization Techniques; LTI, Germantown, MD [see contact: May 2–6]

20–25. Genetic Education for Middle and Secondary Sci. Teachers; Kansas City [D. Collins, 913/588-6043, Fax: -3995]

23–24. Customized Res. Assistance in FISH; Oncor, Inc., Gaithersburg, MD [see contact: May 19–20]

27–July 1. In Situ Hybridization Techniques; CATCMB/CUA, Washington, DC [see contact: May 22–24]

July

4–24. *Arabidopsis* Mol. Genetics; CSHL, Cold Spring Harbor, NY [see contact: June 10–30] ◊

For Your Information

U.S. Genome Research Funding Guidelines

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

NIH National Center for Human Genome Research (NCHGR)

(For more information, see p. 3.)

Application receipt dates:

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

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

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

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

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

DOE Human Genome Program (For more information, see p. 4.)

Solicitations for proposals were announced in the *Federal Register* (February 18), *Science*, and other publications. Proposals for FY 1995 are due July 14.

For funding information or general inquiries, contact the program office via

- 301/903-6488 or Internet: *genome@er.doe.gov*. Relevant documents are available by ftp to *oerhp01.er.doe.gov* in directory */genome*.

DOE Microbial Genome Initiative

Proposals due April 21. Announcement and information: Jay Grimes (301/903-4183, Fax: -8519, Internet: *darrell.grimes@mailgw.er.doe.gov*).

SBIR Grants

DOE and NIH invite small business firms to submit grant applications addressing the human genome topic of SBIR programs, which are designed to strengthen innovative firms in research and development and contribute to the growth and strength of the nation's economy. For more information on human genome SBIR grants, contact

- Kay Etzler; c/o SBIR Program Manager, ER-16; DOE; Washington, DC 20585 (301/903-5867, Fax: -5488).
- Bettie Graham; Bldg. 38A, Rm. 610; NIH; 9000 Rockville Pike; Bethesda, MD 20892 (301/496-7531, Fax: /480-2770).

National SBIR conferences: Houston, TX (April 26–28); Washington DC (October 12–14); San Jose, CA (November 14–16); Chicago, IL (April 26–28, 1995). Conference Hotline: 407/791-0720.◊

An extended list of training events is available from HGMIS. See p. 8 for contact information.

For Your Information

HUGO Offers Travel Awards

The international Human Genome Organization (HUGO) has announced that new travel awards up to $1500 are available to researchers, generally those who are under the age of 40 and actively engaged in human genome research. These awards will cover travel costs for short-term laboratory visits by investigators wishing to transfer technology or conduct collaborative research. The program, which is not for travel to meetings, will run on a continuing basis as long as financial support is available.

Application Requirements

- Declaration by a HUGO member acting as supporting sponsor of the application.
- Work plan including reasons for the choice of host laboratory, which must be in a country other than the applicant's home country.
- Declaration by the host laboratory's head, who need not be a HUGO member, stating host's willingness to accept the applicant and furnish lodging. If the host laboratory cannot furnish lodging, a portion of the travel award may be available to cover modest lodging expenses (not living or research costs), the total not to exceed $1500.
- Applicant's curriculum vitae, including a publications list.
- Travel expense details.

The HUGO Travel Award Committee will consider applications in the order in which they are received, and applicants will be notified of the committee's decision within 2 weeks of receipt.◊

Submission Address

Charles Buys, Director
HUGO Travel Award Program
c/o Department of Medical Genetics
A. Deusinglaan 4
9713A W. Groningen
Netherlands
Fax: +31-50/63-2947

For further information on travel awards, contact either the HUGO Europe or Americas office.

HUGO Europe
One Park Square West
London NW1 4LJ, U.K.
+ 44/71-935-8085, Fax: -8341

HUGO Americas
7986-D Old Georgetown Road
Bethesda, MD 20814
301/654-1477, Fax: /652-3368

Patenting *(from p. 7)*

rendered obvious (and therefore unpatentable) by prior publication of partial sequence information. In such a situation, the inventor could enjoy market exclusivity under a license from the EST patent holder. The validity of this view depends on the accuracy of the prediction that inventors will be unable to obtain their own patent rights and on the scope of patent protection available to EST discoverers. If EST patents do not cover the entire gene and gene product, for example, they may not offer effective commercial protection to firms seeking to market these products.

Patentability standards depend on the state of knowledge in the field at the time of the invention, thus limiting the precedential value of earlier cases. For example, an invention that was novel and nonobvious in 1985 might well be familiar and unpatentable in 1991. Patent attorney Kate Murashige (Morrison and Foerster) discussed one case in which a biotechnology patent application had been pending for over a decade. If litigation over infringement were to follow, many more years would be consumed. Moreover, patent laws are national in scope, so fundamental issues may be resolved differently in different countries. Decisions must be made in the face of necessarily incomplete information.

The discussions did not resolve these questions but helped clarify the complexity and interdependence among several areas of law and science.◊

CALENDAR ACRONYMS

AMIA Am. Medical Informatics Assoc.

ARP/AFIP Am. Registry of Pathol./Armed Forces Inst. of Pathol.

ASBMB Am. Soc. for Biochem. and Mol. Biol.

ATCC Am. *Type Culture* Collection

BTP Biotechnol. Training Programs

CATCMB/CUA Ctr. for Advanced Training in Cell and Mol. Biology/ Catholic Univ. of Am.

CHI Cambridge Healthtech Inst.

CIMB Ctr. for Intl. Meetings on Biol.

CSHL Cold Spring Harbor Lab.

DOE Dept. of Energy

GDB/OMIM Genome Data Base/Online *Mendelian Inheritance in Man*

GMCRF General Motors Cancer Res. Foundation

IBC Intl. Bus. Comm.

LTI Life Technologies, Inc.

MBL Marine Biological Lab.

NCHGR Natl. Ctr. for Human Genome Res.

NIH Natl. Inst. of Health

PRIM&R Pub. Respon. in Med. & Res.

PSC Pittsburgh Supercomputing Ctr.

WLMG Wellcome Lab. for Mol. Genetics

This newsletter is prepared at the request of the DOE Office of Health and Environmental Research and the NIH National Center for Human Genome Research by the Biomedical and Environmental Information Analysis Section of the Health Sciences Research Division at Oak Ridge National Laboratory, which is managed by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy, under Contract DE-AC05-84OR21400.◊

☆U. S. GOVERNMENT PRINTING OFFICE: 1994-550-220/80004