Human Genome news

National Center for Human Genome Research
National Institutes of Health

A Forum For Human Genome Information Exchange

Vol. 2, No. 1, May 1990

NIH Joins DOE in Newsletter Sponsorship

Bimonthly Publication Schedule Announced

With this first issue of *Human Genome News* (published previously under the title of *Human Genome Quarterly*), two important changes are being made to keep the genome community informed of current issues and events.

First, the DOE Human Genome Program welcomes the NIH National Center for Human Genome Research (NCHGR) as copublisher and contributor. Issues of *Human Genome News* will contain information from both agencies so that readers may have a consolidated source of information about the genome project.

Second, in order to provide more complete and timely updates, the newsletter will be published six times a year. Features such as the calendar of genome events, meeting highlights, international news, and grant announcements will be continued and expanded.

NCHGR Administers NIH Genome Research Program

The U.S. government's lead biomedical research agency, NIH has long been a key player in genetics and molecular biology research through financial support of research projects in laboratories across the country and through biomedical research conducted in its in-house laboratories. NCHGR, formerly called the Office of Human Genome Research and one of the newest components of NIH, was established last fall to administer the role of NIH in the U.S. Human Genome Project and to bring to the genome effort the experience of NIH in researching biomedical problems.

As the focus for NIH-supported research on the human genome and the genomes of other animals, NCHGR:

- plans and coordinates genome project research goals,
- reviews and funds research proposals,
- develops training programs,

In This Issue. . .

Page

Genome Project News

1 NIH Joins DOE in Newsletter Sponsorship
3 1988 Memorandum Sets Foundation for Interagency Cooperation
4 NIH PAC and NIH-DOE Joint Subcommittee Discuss Mapping and 5-Year Plan
4 Five-Year Plan Goes to Capitol Hill

Ethics

5 NIH-DOE Joint Working Group on Ethical, Legal, and Social Issues Established
7 Joint Ethics Working Group Hosts Workshop
9 Juengst To Head NCHGR Ethics Program

Informatics

9 Automated DNA Sequence Analysis Software Available
10 JITF To Coordinate Development, Access to Genome Information and Analysis Tools
10 Newsgroup and Information Database Services Offered

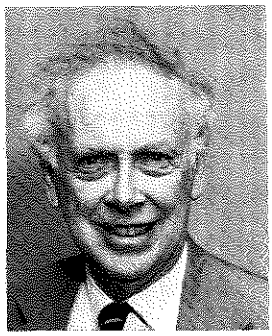
Technical Feature

12 National Laboratory Gene Library Project: Construction of DNA Libraries from Flow-Sorted Chromosomes

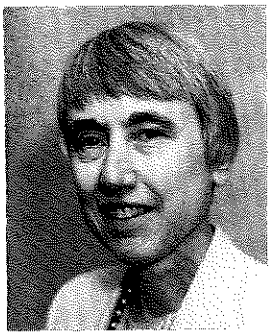
For Your Information

14 Calendar of Genome Events
15 Training Calendar
16 Acronym List, Subscription/Document Request

Genome Project News



James D. Watson
Director
National Center for
Human Genome Research



Elke Jordan
Deputy Director
National Center for
Human Genome Research

- helps coordinate international genome research, and
- communicates advances in genome science to the public.

NCHGR has research interests not only in genetic and physical mapping of the human genome and the genomes of model organisms, but also in technology development, computer management systems for biological information, research training, technology transfer, and the ethical and social impact of the availability of genetic information.

In the fall of 1987, NIH became formally involved in the Human Genome Project when Congress earmarked new funds for FY 1988 for the support of research related to the human genome. This appropriation, to be distributed through NIH's National Institute of General Medical Sciences, came after much discussion in the scientific community about the feasibility and merit of the Human Genome Project.

Early in 1988, at a meeting of the NIH Ad Hoc Program Advisory Committee on the Human Genome, James B. Wyngaarden, the NIH director at that time, announced plans for an NIH human genome office. This office was to oversee the planning and conduct of NIH-supported genome research and to coordinate NIH activities with those of other agencies, both domestic and international.

Later that year, NIH appointed James D. Watson Associate Director for Human Genome Research and established the Office of Human Genome Research as part of the NIH Director's office. Elke Jordan was appointed Director of the new office, with responsibility for managing and overseeing the genome program's daily activities.

NIH Establishes NCHGR in October 1989

In October 1989, NIH established NCHGR, with Watson as Director and Jordan as Deputy Director, in place of the Director's Office of Human Genome Research. NCHGR is equivalent to other NIH institutes in its authority to award grants and to plan and direct scientific research.

Located on the NIH campus in Bethesda, Maryland, the new NCHGR is currently staffed by about 30 scientific, administrative, and clerical employees. NCHGR expects to raise the number of employees to about 40. With a 1990 budget of nearly $60 million, NCHGR program activities include over 140 grants for individual research projects and 16 other research-related grants for genome projects on mapping and sequencing, technology development, computer technology for handling genome research data, and biomedical ethics. Funds will be allocated to support about 135 pre- and postdoctoral training positions. NCHGR plans to fund 3 multidisciplinary genome research centers this year and to increase that number to about 14 in the next few years.

NCHGR research planning and administration is divided into several main program areas. Mark S. Guyer, Assistant Director for Program Coordination, ensures that the programs are integrated effectively.

Chief of the Research Centers Branch, Jane L. Peterson oversees funding and operation of multidisciplinary research centers. These centers are designed to combine the talents of biologists, computer scientists, chemists, and scientists from other fields to tackle key genome project research problems and will serve as technical resources for other genome researchers.

Centers will occupy the core of NCHGR's research mission, but individual projects in other laboratories will also play an integral role. Bettie J. Graham is Chief of the Research Grants Branch, which supports research of individual investigators who are mapping and sequencing human DNA and the DNA of model organisms.

NCHGR Plans Additions to Management Staff

On May 1, Eric T. Juengst will join the NCHGR staff to run its program on ethical, legal, and social implications of human genome research. He will oversee the administration of grants to researchers in ethics and social policy; coordinate NCHGR research activities with recommendations of

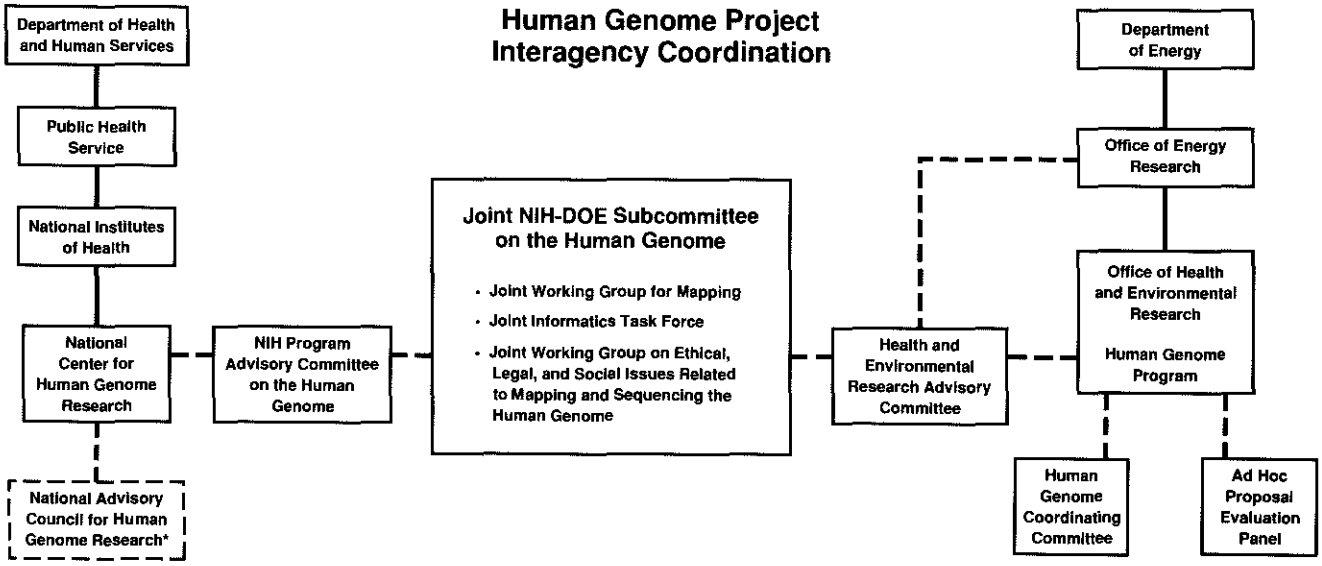
(continued on p. 3)

1988 Memorandum Sets Foundation for Interagency Cooperation

Because both DOE and NIH have major research interests in the Human Genome Project and because of the need for centralized planning and coordination of the 15-year project, NIH and DOE signed a formal Memorandum of Understanding in the fall of 1988 "to foster interagency cooperation that will enhance the human genome research capabilities of both agencies."

The document, which provides the foundation for NIH-DOE collaboration to achieve the goals of the U.S. Human Genome Project, calls for regular meetings of the Joint NIH-DOE Subcommittee on the Human Genome. The subcommittee is made up of members of the NIH Program Advisory Committee on the Human Genome and the DOE Health and Environmental Research Advisory Committee.

In addition, the joint subcommittee has established joint working groups on mapping, on informatics, and on the ethical, legal, and social issues stemming from the genome project. ◊



NCHGR *(continued from p. 2)*

the NIH-DOE Working Group on Ethical, Legal, and Social Issues (ELSI); and serve as liaison between NCHGR and the human genome programs of other countries (see related articles, pp. 5, 7, and 9).

NCHGR has announced plans to add staff to manage other areas of its genome program.

- Staff will be added to direct programs for developing computer systems to store, manage, and analyze map and sequence information.
- A position will be devoted to ensuring efficient transfer of genome project technology to the private sector for development, marketing, and use.

For a description of the DOE Human Genome Program and more information on Human Genome Project administration, see article on p. 1 of the *Human Genome Quarterly*, Vol. 1, No. 1. ◊

Reported by Leslie Fink, Chief
Office of Human Genome Communication
NCHGR

Genome Project News

NIH PAC and NIH-DOE Joint Subcommittee Discuss Mapping and 5-Year Plan

Committees See Need for Long-Range Continuity in Mapping Projects

At the third meeting of the NIH Program Advisory Committee on the Human Genome (PACHG), held on December 4, 1989, members reviewed and approved the draft of a 5-year plan for the Human Genome Project. The plan had been requested from NIH by Congress and was developed jointly by NIH and DOE staff and advisors during the late summer and autumn of 1989.

The draft plan established quantitative goals for the development of a human genetic linkage map, physical maps of human chromosomes and some mouse chromosomes, and technology for large-scale DNA sequencing. Other program topics outlined in the plan included informatics; ethics, legal, and social implications; training; technology development; and technology transfer.

Linkage and physical mapping goals engendered the most discussion. With respect to linkage maps of each human chromosome, advisors agreed that for the next 5-year period, a 2- to 5-centimorgan (cM) map is an appropriate goal that would set the average distance between markers at 2 cM with no gap greater than 5 cM. [On average, 1 cM is believed to be roughly equivalent to 1 million base pairs (bp).] The committee also agreed to establish a working group to address a number of issues:

- adequacy of resources being devoted to the linkage mapping component of the NIH program,
- support mechanisms needed to achieve the 5-year goals, and
- possible requirements of new strategies for constructing the map.

This working group was also charged with developing a detailed plan for implementing the sequence-tagged site (STS) system of reporting mapping data. The group met at the end of March and will report to the PACHG in June. The meeting report will be in a future issue of *Human Genome News*.

Joint NIH-DOE Subcommittee Meets

The physical mapping discussion was taken up again on December 5 at the first meeting of the Joint NIH-DOE Subcommittee on the Human Genome established under the 1988 Memorandum of Understanding between NIH and DOE. A major focus of this discussion was the need for long-range continuity in mapping and sequencing projects. A number of committee members maintained that technological efforts in mapping and sequencing should be focused toward significantly increasing the distance over which map or sequence continuity can be established. ◇

Reported by Mark Guyer
Assistant Director for Program Coordination
NCHGR

Joint Working Group on Mapping Formed

Five-Year Plan Goes to Capitol Hill

A 5-year plan (FY 1991–1995) detailing the goals of the U.S. Human Genome Project was presented to members of congressional appropriations committees in mid-February. This document, coauthored by DOE and NIH and titled *Understanding Our Genetic Inheritance, The U.S. Human Genome Project: The First Five Years (FY 1991–1995)*, examines the current state of genome science. The plan also sets forth complementary approaches of the two agencies for attaining scientific goals and presents plans for administering research agendas; it describes collaboration among U.S. and international agencies and presents budget projections for the project.

According to the document, "a centrally coordinated project, focused on specific objectives, is believed to be the most efficient and least expensive way" to obtain the 3-billion-bp map of the human genome. In the course of the project, especially in the early years, the plan states that "much new technology will be developed that will facilitate biomedical and a broad range of biological research, bring down the cost of

(continued on p. 5)

Ethics

NIH-DOE Joint Working Group on Ethical, Legal, and Social Issues Established

NIH and DOE Accepting Grant Applications

Human Genome Project research will inevitably give biomedical researchers new and powerful tools for identifying defective genes that cause diseases and for developing better treatments for the health problems these genes cause. Concerns about the applications of information and materials resulting from the Human Genome Project and from other research in human genetics have resulted in the establishment of the Joint Working Group on the Ethical, Legal, and Social Issues (ELSI) Related to Mapping and Sequencing the Human Genome. Formed by the National Center for Human Genome Research (NCHGR) and the DOE Human Genome Program, this working group will identify and address the ethical, legal, social, and economic issues that may arise with genome technology development (see related articles on pp. 7 and 9).

The working group has several goals:

- to stimulate bioethics research and assist DOE and NIH in refining their respective research activities;
- to identify issues likely to arise as human genetics research progresses, promote public discussion of those issues, and develop policy options to deal with them;
- to reach out to groups likely to be affected by genome research, such as those organized around specific diseases or disabilities;
- to promote education of professional and lay groups; and
- to collaborate with international groups such as the Human Genome Organisation (HUGO); United Nations Educational, Scientific, and Cultural Organization (UNESCO); and the European Economic Community (EEC).

Members of the working group represent various disciplines, and each has a long-standing interest in the ethical, legal, and social issues arising from the availability of data acquired in genetic research.

(continued on p. 6)

Nancy S. Wexler
Chair
ELSI Working Group

Five-Year Plan *(continued from p. 4)*

many [mapping and sequencing] experiments, and find application in numerous other fields."

The plan builds upon the 1988 reports of the Office of Technology Assessment (OTA) and the National Research Council (NRC) on mapping and sequencing the human genome. "In the intervening two years," the document says, "improvements in technology for almost every aspect of genomics research have taken place. As a result, more specific goals can now be set for the project."

The document describes objectives in the following areas:

- mapping and sequencing the human genome and the genomes of model organisms;
- data collection and distribution;
- ethical, legal, and social considerations;
- research training;
- technology development; and
- technology transfer.

These goals will be reviewed each year and updated as further advances occur in the underlying technologies.

The overall budget needs for the project are "still anticipated to be the same as those identified by OTA and NRC, namely about $200 million per year for approximately 15 years," the document says.

A copy of the 5-year plan will be distributed to everyone on the mailing list of this newsletter and also will be available to anyone requesting a copy. ◊

Reported by Leslie Fink, Chief
Office of Human Genome Communication
NCHGR

Five-Year Plan Objectives To Be Reviewed Yearly

Ethics

Working Group Identifies Relevant Topics

Joint NIH-DOE ELSI Working Group *(continued from p. 5)*

Nancy S. Wexler, chair of the working group, also serves on the NIH Program Advisory Committee on the Human Genome. Wexler is a clinical psychologist in the Department of Neurology and Psychiatry at the College of Physicians and Surgeons of Columbia University and is President of the Hereditary Disease Foundation. In the 1970s she was a member of the Huntington's Disease Commission and conducted research at the National Institute of Neurological and Communicative Disorders and Stroke.

Jonathan R. Beckwith is a bacterial geneticist in the Department of Microbiology and Molecular Genetics at Harvard Medical School. Interested in genetic screening for over a decade, he has raised concerns regarding research proposals to mount longitudinal behavioral studies of individuals with an XYY karyotype and has continued to participate in public discussions about behavioral genetics.

Patricia King of Georgetown University Law Center has served on both the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and on the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. During her career, she has worked in the areas of civil rights law and reproductive law and is interested in the impact of genetic studies on minority groups.

Victor A. McKusick has been involved in the study of human genetics for over 40 years at Johns Hopkins University. During that time he compiled the accumulated research data on human genetics into a book and an on-line computer database, both called *Mendelian Inheritance in Man*. The founding president of HUGO, McKusick now chairs its ethics committee.

Robert F. Murray, a physician in the Department of Pediatrics, Medicine, Oncology, and Genetics at the Howard University College of Medicine, has been involved in genetic testing and screening for more than two decades. He has worked on sickle cell and thalassemia testing programs and continues to offer genetic counseling to patients.

Thomas H. Murray, a social psychologist who has written extensively about the ethical impact of genetic testing and screening in the workplace, is the Director of the Center for Biomedical Ethics at Case Western Reserve University Medical School. He was recently elected a Fellow of the Hastings Center, where he worked for several years in the 1970s.

At its first meeting in September 1989, the ELSI working group identified nine topics of relevance to the genome project:

- fair use of genetic test information in areas such as insurance, employment, criminal justice, education, adoption, and the military;
- impact of genetic information on individuals;
- personal privacy and confidentiality of genetic information;
- impact that the dramatic increase in human genetic information will have on genetic counseling and the delivery of genetic services;
- influence of genetic information and new technologies on reproductive decisions;
- issues raised by the introduction of new genetic information and technologies into mainstream medical practice;
- historical analysis of the use and misuse of genetic information and technologies;
- issues raised regarding the commercialization of research results; and
- conceptual and philosophical questions related to human genetics.

At the recommendation of the ELSI working group, NIH issued a program announcement in the January 26, 1990, issue of the *NIH Guide to Grants and Contracts* (Vol. 19, No. 4) requesting research proposals . The DOE Human Genome Program, whose request for grant applications was published in the March 21, 1990, *Federal Register* (p. 10486), is accepting applications for research in the areas of ethical, legal, and social issues.

Many social scientists, humanities scholars, and legal analysts are interested in the issues raised by human genetics research, and the availability of grant support from DOE and NIH should attract even more researchers. ◊

Reported by Robert M. Cook-Deegan NCHGR

Joint Ethics Working Group Hosts Workshop

Nine Invited Specialists Participate in First ELSI Workshop

The Joint Working Group on the Ethical, Legal, and Social Issues (ELSI) Related to Mapping and Sequencing the Human Genome held its first workshop on February 5–6, 1990, at Williamsburg, Virginia. (See related articles, pp. 5 and 9.) Chaired by Nancy S. Wexler of the Hereditary Disease Foundation and Columbia University, the ELSI working group hosted nine specialists in the fields of sociology, history, ethics, genetic counseling, law, labor, insurance, and journalism. The invited specialists are listed in the box below.

The meeting opened with a general discussion of the following issues:

- Education: how to facilitate informed public discussion on the issues arising from potential applications of genome research data.
- History: how to use an awareness of past abuses of genetics to avoid such pitfalls in the future.
- Privacy: how to protect the confidentiality of genetic information.
- Medical insurance: how to assess the effect of genetic predisposition information on a person's ability to obtain affordable insurance from a private carrier.
- Clinical services: how to determine the impact that detailed genetic information will have on the practice of medicine.
- Commercialization of genome technologies: how to transfer technology from research laboratories to the private sector.

Participants Develop Priority Areas

After consideration and discussion of these topics, workshop participants developed the four priority areas that are highlighted below.

Cystic Fibrosis Experience

The recent identification of the gene responsible for cystic fibrosis has paved the way for development and commercialization of methods to determine a person's carrier status and to identify affected fetuses.

Tracking and examining in detail the cystic fibrosis experience promises to provide an instructive model of issues relevant to the Human Genome Project. These issues include:

- transfer of technology from research laboratories to private industry for development and marketing;
- accuracy and quality control of test kits;
- impact of genetic test information on genetic counseling options;
- role of insurance companies in covering medical costs of affected patients identified by prenatal tests;
- liability of clinicians who fail to perform genetic testing;
- confidentiality of information obtained from genetic testing; and
- psychological impact of medical prognoses on patients and family members.

Insurance Coverage

The use of genetic tests by private insurance companies to predict future health problems and thereby to determine an applicant's insurability has become an important issue. Increased availability of genetic test information may identify new, large groups of people who are predisposed to common ailments such as heart disease, cancers, diabetes mellitus, and immune disorders. The concern is how private insurers will use this information to

Important Issue Is Potential Use of Genetic Tests by Insurance Companies

Invited Specialists Attending the Ethics Workshop

February 5–6, 1990, Williamsburg, Virginia

Clinical Medicine
Elena Gates
Obstetrics & Gynecology
University of California Medical Center

Ethics
Adrienne Asch
Social Sciences and Policy
New Jersey Bioethics Commission

Journalism
Thomas Goldstein
School of Journalism
University of California at Berkeley

Law
Steven P. Goldberg
Georgetown University Law Center

Insurance
Robert J. Pokorski
Lincoln National Life Insurance

Sociology
Dorothy Nelkin
Department of Sociology
School of Law
New York University

Eugenics
Robert Proctor
The New School for Social Research

Labor
Robert Nussbaum
Department of Human Genetics
University of Pennsylvania School of Medicine

Sheldon W. Samuels
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Ethics

Human Genome news

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

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calculate the financial risk of insuring individuals who carry these genes. Studies are needed to identify how and which genetic information would be used to determine a certain group's insurance risk and to define its insurability.

Currently, insurance premium reductions are given for health-promoting behavior such as exercising, limiting alcohol intake, and not smoking. The workshop participants questioned whether insurers would give similar rewards to people who carry tumor-suppressor genes, toxin-resistance genes, or genetically hearty immune systems.

While most private insurers do not use genetic tests to determine whom they will insure, insurance companies do feel they should have access to such information if their policy holders do. Because private insurance companies operate as for-profit businesses and may withhold coverage from individuals who carry disease genes, the working group suggested that alternative systems of health insurance for these people need to be researched.

Education, Outreach

Clinicians, journalists, and other workshop participants who frequently deal with the general public observed that the public at large seems either to be uninformed or to hold strong misconceptions about medical genetics and the role of genes in biology, disease, and behavior. After the public's understanding is assessed, education and outreach programs need to be developed so that informed debate and discussion about the social implications of the Human Genome Project can take place.

Public seems to be uninformed about medical genetics.

Workshop participants also felt that, in addition to underscoring science and medical benefits likely to stem from genome project research, education should demystify genetics and genome science. Special precautions should be taken to point out that determining the complete sequence of human DNA will not necessarily produce immediate cures or knowledge of how gene functions determine human characteristics. Also, the opportunity to examine genetic material of large numbers of people is likely to force a redefinition of the concepts of "normal," "health," and "disease"; value-neutral language should be adopted when referring to the wide variations in human genetic composition.

The ability to use an individual's genetic makeup to make biological predictions may intensify the notion of "genetic determinism" – the idea that genes alone direct a person's biological and, possibly, social fate. Education should emphasize the roles that environment and many other factors play in an individual's social, behavioral, and physical development.

Organizations and institutions already in place for disseminating information must be identified. They may include the mass media and school systems, health volunteer associations, organizations for medical and allied health professionals, labor groups, policy makers, and religious groups. Also, the needs of people most likely to be affected by the availability of genetic information should be addressed by open dialogue between the ELSI working group and members of genetic disease and disability support groups.

Confidentiality Guidelines

As genetic testing technology becomes more widely available, access to genetic information by the individual, family, employers, insurance companies, and other institutions will increasingly affect personal privacy and the dissemination of medical information. Workshop participants identified three current levels of confidentiality in medical information: patient, medical institution, and government.

In addition, computerized databases now exist for storing "confidential" medical information. The participants felt that guidelines establishing responsible use of such information should address consent to be tested, the patient's right to know or not to know test results, how information is used by physicians to make decisions about medical care, and how information may be used by a patient's family.

To implement the working group's recommendations, NCHGR and DOE may fund projects initiated by the research community or may invite applications from other groups with appropriate expertise. Some possibilities considered are workshops, task forces, commissioned papers, reports, and contracts. ◇

Juengst To Head NCHGR Ethics Program

Eric T. Juengst, a specialist in the ethical dilemmas that arise when medical technology interfaces with society, will join the National Center for Human Genome Research (NCHGR) on May 1 to run its program on ethical, legal, and social implications of human genome research.

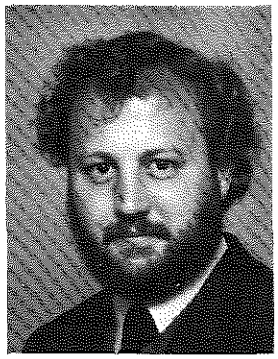
Juengst comes to NCHGR from Pennsylvania State University College of Medicine, where he was Assistant Professor of Philosophy in the Department of Humanities. A 1978 graduate in biology from the University of the South and a member of Phi Beta Kappa, Juengst received his Ph.D. degree in philosophy from Georgetown University, where he concentrated his studies in the philosophy of science and bioethics.

In 1984 he joined the Division of Medical Ethics at the Medical School of the University of California at San Francisco, where he researched ethical issues in prospective "gene therapy" of germ line cells. Juengst became the acting chief of the division in 1987.

A year later Juengst became bioethics consultant to the National Research Council during preparation of its report, *Mapping and Sequencing the Human Genome*. He now serves on the Office of Technology Assessment panel examining genetic testing in the workplace.

He has cochaired the grants review panel of the National Endowment for the Humanities (NEH)–National Science Foundation program on ethics in science and technology and has chaired the NEH interdivisional policy committee on humanities studies of science and technology.

Juengst is a member of the American Philosophical Association, the Philosophy of Science Association, and the International Society for the History, Philosophy, and Social Studies of Biology. ◇



Eric T. Juengst
Manager
NCHGR Program on Ethical, Legal, and Social Implications of Human Genome Research

Automated DNA Sequence Analysis Software Available

A complete source code distribution of version 1.0 of the **gm** automated DNA sequence analysis system software is available free of charge to nonprofit laboratories. The **gm** software identifies all sets of in-frame coding exons separated by introns that satisfy a user-specified set of criteria and translates the exons of each candidate gene to generate a predicted protein sequence. Capable of correctly identifying multiexon genes in 10-kb sequences in a few seconds on a Sun 4 workstation, **gm** has been tested successfully on sequences of up to 150 kb in length.

This software may be run from a text-only terminal and includes a graphic interface that runs under X-windows (Athena Project, MIT), version 11, release 3, for displaying identified genes and their translation products. C. A. Soderlund, P. Shanmugam, and C. A. Fields of New Mexico State University are developing the automated DNA sequence analysis software with support from the DOE Human Genome Program.

The **gm** code, written in the C programming language, has been compiled and tested on Sun, Vax, MIPS, Sequent, Silicon Graphics, and Cray computers operating under versions of the Unix operating system. The distribution includes code, documentation, sample input files, and test cases. The code can be obtained either by anonymous file-transfer protocol (ftp) to haywire.nmsu.edu, directory **gm**, file **gm**.tar.Z, or by sending a 1/4-inch cartridge tape to Chris Fields, Box 30001/3CRL, New Mexico State University, Las Cruces, NM 88003-0001. Inquiries can also be addressed to cfields@nmsu.edu (internet). ◇

Submitted by C. A. Fields
Computing Research Laboratory
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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 operated by Martin Marietta Energy Systems, Inc., for the U.S. Department of Energy, under Contract DE-AC05-84OR21400.

Informatics

JITF To Coordinate Development, Access to Genome Information and Analysis Tools

Joint Informatics Task Force Chaired by Dieter Soll

Human genome advisory committees from NIH and DOE, responding to the magnitude and complexity of mapping and sequencing data to be generated by the Human Genome Project, have established the Joint Informatics Task Force (JITF) to develop genome information and analysis tools and make them available to scientists and physicians.

This group, chaired by Dieter Soll of Yale University (see box, p. 11, for list of members), is responsible for identifying user needs, setting informatics goals, establishing research and development priorities, and enhancing the effectiveness of computational solutions to genome informatics problems. In addition, JITF will make recommendations to the Joint NIH-DOE Subcommittee on the Human Genome in both technical and policy areas relating to:

- genome database structures, management, and services;
- informatics tool development—algorithms, software, and hardware for organization and analysis of data;
- standards for data exchange;
- electronic networks for collection and distribution of genome data;
- training and education of informatics personnel; and
- coordination of genome informatics activities among laboratories, agencies, and nations.

In addition to NIH and DOE, other agencies with responsibilities and activities in

(continued on p. 11)

Newsgroup and Information Database Services Offered

The NIH and DOE human genome programs are implementing two new services to distribute information about the Human Genome Project.

The Human Genome Program Newsgroup began operating through the GenBank® BioSci electronic bulletin board network. The newsgroup will give the agencies another way to distribute information about their genome programs, including requests for grant applications, reports from recent scientific and advisory meetings, and announcements of future events. The program staffs of both agencies regularly monitor the newsgroup and respond to postings when appropriate. Operating in an E-mail format, the newsgroup is intended to be a forum for issues pertaining to genome research; the public is encouraged to use this mechanism to discuss genome issues with the scientific community and with the funding agencies. For details on accessing the system, see inset.

To subscribe to the Human Genome Program Newsgroup, send a message to the internet address (which also serves BITNET users):
biosci@genbank.bio.net

To post messages to the newsgroup, send messages to:

Internet : human-genome-program@genbank.bio.net
BITNET: gnome-pr@genbank.bio.net

Please refer questions about the newsgroup to Jane L. Peterson, NCHGR, NIH: (301) 496-7531 or jp2@nihcu.bitnet.

The Human Genome Information Database is being developed as a text management and user-conferencing mechanism by the Human Genome Management Information System at Oak Ridge National Laboratory. Referred to as an electronic bulletin board in past issues of the *Human Genome Quarterly*, the facility will support investigators and managers in the Human Genome Project.

The database will be accessible via modem or mainframe network systems and will provide users with a fully searchable database containing text from meeting reports, newsletters, program and technical reports, archived announcements from the BioSci Human Genome Program Newsgroup, and calendars. Bibliographic and abstract information related to the Human Genome Project will be extracted from both scientific and popular literature. Over 250 requests have been made for access to this database, which is in an advanced stage of development using Information Dimensions, Inc., BASISplus™ software. To subscribe to this facility, see the Subscription/Document request form on page 16. ◇

the area of genome informatics – the National Science Foundation, the U.S. Department of Agriculture, and the privately funded Howard Hughes Medical Institute – send representatives to the JITF meetings as liaison members. As necessary, JITF will convene ad hoc advisory panels to address specific technical and policy issues. JITF will also interact with international informatics groups in organizations such as the Human Genome Organisation (HUGO).

While most of the initial near-term efforts of JITF will focus on the development of mapping and sequencing software tools and the rapid and convenient dissemination of genetic map and DNA sequence data, the longer-term goals are more ambitious. These goals include the following:

Long-term goals include standardization, coordination, and interaction.

- establishing standards to allow simple connectivity among the many databases currently being developed in individual laboratories;
- coordinating data collection, software tool development, and networking within the human genome research community; and
- promoting more creative interactions among computer scientists, mathematicians, and biologists through courses, meetings, and workshops.

As it begins its activities, JITF will consider development in the following areas:

- bulletin board systems like BioNet to enhance electronic communications within the genome community;
- interaction among individuals in research institutions, medical practice, and the private sector;
- database access and data quality assessment;and
- cooperation and coordination with the informatics communities of other countries.

The intent of JITF is to promote an ongoing dialogue with all persons interested in genome informatics. Comments or suggestions for improving the effectiveness of genome informatics should be directed to any of the JITF members. The first meeting of the JITF was held March 8-9 in Washington, D.C. ◇

Submitted by Mark L. Pearson
Central Research & Development Department
E. I. du Pont de Nemours & Co., Inc.

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Technical Feature

National Laboratory Gene Library Project: Construction of DNA Libraries from Flow-Sorted Chromosomes

Larry L. Deaven, *Life Sciences Division, Los Alamos National Laboratory*
Marvin A. Van Dilla, *Biomedical Sciences Division, Lawrence Livermore National Laboratory*

LLNL, LANL Conduct Coordinated Genome Research Effort

The National Laboratory Gene Library Project (NLGLP), a coordinated research effort between Lawrence Livermore National Laboratory (LLNL) and Los Alamos National Laboratory (LANL), was formed in 1983 as a result of the development of flow cytogenetic analysis and chromosome sorting at the two laboratories. The purpose of NLGLP is to construct libraries to be used in mapping projects. Libraries are unordered DNA fragments for each human chromosome; they are created by digesting the chromosome with a given restriction enzyme.

NLGLP announced in the December issues of *Science* and *Nature* that its first group of partial digest libraries is available for testing. Laboratories to receive the libraries for chromosomes 11, 21, 22, and Y (LLNL) and 4, 5, 8, and 17 (LANL) will be selected on the basis of short proposals (proposal forms available from the authors). Proposals will be accepted in late 1990 for initial distribution of the eight additional chromosomes that make up the second group of partial digest libraries; initial distribution of the third group will take place in 1991. The availability of these libraries will be announced in future issues of this newsletter.

At first, libraries were constructed from Chinese hamster chromosomes, but as flow-sorting technology became more refined, highly purified human chromosomes could be obtained in quantities sufficient for library construction. Scientists at LANL and LLNL, believing that a set of libraries would provide useful tools for the restriction fragment length polymorphism (RFLP) approach to gene mapping and for locating human disease loci, requested that a joint project be initiated between the two national laboratories. DOE staff concurred, and NLGLP was formed.

The aim of NLGLP is to construct libraries (covering each human chromosome) useful to a broad segment of the scientific community in the study of the molecular biology of genes, gene mapping, and the diagnosis of genetic diseases.

Options for constructing restriction fragment digest libraries include partial and complete digest. Partial digest libraries are made using restriction enzymes at low concentrations on purified chromosomes, so that not all enzyme recognition sites are cleaved. Complete chromosomal digest libraries result when the restriction enzyme is present at sufficiently high concentrations to cleave virtually all recognition sites.

Complete Digest Libraries Constructed (1984-1986)

The most urgent need for chromosome-specific libraries in 1983 was for isolating probes to locate genes responsible for human genetic diseases. Because complete digest libraries maximize the probability of finding unique sequence probes, the NLGLP Advisory Committee (see box at left for membership) agreed that the first priority for the project should be the construction of a set of small-insert libraries. The construction of larger-insert, partial digest libraries was to be reconsidered when the small insert libraries were completed.

To maximize chromosomal coverage, two libraries were made for each chromosome, one cut with *Eco* RI (LANL) and one cut with *Hind* III (LLNL). Both types of libraries were cloned into Charon 21A (size acceptance range from 0 to 9 kb). The complete digest libraries for the human karyotype were constructed between 1984 and 1986. Initially, these libraries were distributed directly from LANL and LLNL; however, in February 1986 a library repository was established by NIH at the American Type Culture Collection (ATCC) in Rockville, Maryland.

Before the repository was established, approximately 1200 libraries were distributed from the two national laboratories. Since 1986, the number of yearly requests

NLGLP Advisory Committee

(Project strategy planners)

Paul Berg	Stanford University School of Medicine
Fred Blattner	University of Wisconsin
Thomas Caskey	Baylor College of Medicine
Marshall Edgell	University of North Carolina
Richard Gelinas	University of Washington
Samuel Latt (deceased)	Harvard Medical School
Thomas Manlatis	Harvard University
Arno Motulsky	University of Washington School of Medicine
William Rutter	University of California at San Francisco
Carl Schmid	University of California at Davis
Thomas Shows	Roswell Park Memorial Institute

for the libraries has grown from 167 to 816, and more than 2250 complete digest libraries have been distributed.

Partial Digest Library Construction (1987 to Present)

The establishment of the Human Genome Project made the construction of partial digest libraries even more valuable than originally envisioned, since the larger inserts (up to 40 kb of human DNA in phage or cosmid vectors) provided by these libraries are more useful in physical mapping studies. NLGLP scientists began

Partial digest libraries valuable in mapping studies.

developing the necessary techniques in 1987, and the first partial digest phage library was completed that year. In 1988 the first cosmid libraries were constructed and put to use in the physical mapping projects at LANL (chromosome 16) and LLNL (chromosome 19). These libraries are useful sources of fragments for assembly of ordered clone maps by DNA fragment fingerprinting methods (Anthony Carrano, *Human Genome Quarterly*, Vol. 1, No. 2).

Compared to the work on complete digest libraries, the NLGLP strategy for the construction of partial digest libraries has changed in several ways. The karyotype has been divided between the two laboratories: LANL is constructing phage and cosmid libraries for chromosomes 4, 5, 6, 8, 10, 13, 14, 15, 16, 17, 20, and X; LLNL is doing the same for chromosomes 1, 2, 3, 7, 9, 11, 12, 18, 19, 21, 22, and Y.

To construct libraries from single homologs, all chromosomes are being sorted from rodent-human hybrid cells. Both laboratories are currently using the same phage vector (Charon 40); the cosmid libraries from LANL will be cloned into sCos1, and those from LLNL will be cloned into Lawrist 5. If new vectors or host strains with substantially improved properties are developed during the project, attempts will be made to use them for the remaining libraries.

Each library will be examined for purity by plaque or by colony hybridization to total rodent and total human DNA. This information will be compared with purity data derived during chromosome sorting and library construction. If results are consistent and the library appears to be of high quality, it will be distributed to several (six to ten) selected laboratories for further characterization. Phage libraries will be available as aliquots of a single amplification and cosmid libraries as aliquots of a plate amplification or as fivefold coverage arrays in microtiter plates. When data are available from the test laboratories, a decision will be made to determine whether a library should be reconstructed or go into general distribution. In parallel with this work, the laboratories are examining the feasibility of using flow-sorted chromosomes to construct yeast artificial chromosomes (YAC) libraries. Preliminary results suggest that construction of the first YAC libraries may be completed in late 1990.

Scientists in the NLGLP are attempting to construct libraries of the highest possible purity. To a large extent, purity depends on how well a human chromosome is resolved from the rodent background on a flow karyotype. This level of resolution varies considerably from one hybrid cell line to another. There has been excellent cooperation from a number of laboratories in sharing hybrid lines for library construction, and there is now a collection of cell lines that includes all the human chromosomes. However, the search is continuing for more suitable lines for chromosomes 1, 14, 15, 20, and X.

Any reader who has a hybrid containing one or more of these chromosomes and is willing to share it for library construction should contact the authors (see side column for contact information). ◇

The NLGLP is searching for suitable hybrid lines containing human chromosomes 1, 14, 15, 20, and X.

Anyone willing to share these lines should contact:

Larry Deaven:
(505) 665-3024

Marvin Van Dilla:
(415) 422-5662

Calendar of Genome Events*

April	30–May 2	**National Research Council, Computer Science and Technology Board, Computing and Molecular Biology Workshop**; Washington, DC
May	2–6	**Genome Mapping and Sequencing Conference**; Cold Spring Harbor, NY
	24–25	**Workshop on Computational Issues in the Life Sciences and Medicine**; Austin, TX [*M. Witten, (512) 471-2457, Fax: (512) 250-9034*]
	25	**"Panel on Database Issues of the Human Genome Project"** at the **1990 International Conference on Management of Data**; Atlantic City, NJ [*R. Pecherer, (505) 665-1970*]
June	10–13	**Development of Physical Methods for Mapping the Human Genome (Meeting and Workshop)**; Mt. McKinley Park, AK
	18	**NIH Program Advisory Committee on the Human Genome**; Bethesda, MD [*C. Mohan, (301) 496-0844*]
	19	**Joint NIH-DOE Subcommittee on the Human Genome**; Bethesda, MD
	19	**DOE Human Genome Coordinating Committee**; Bethesda, MD
July	9–11	**International Meeting: Bioinformatics, Integration of Organismic and Molecular Data Bases, and Use of Expert Systems in Biology**; Fairfax, VA [*H. Morowitz, (703) 323-2262, Fax: (703) 764-4725*]
	18–21	**Genetics Societies of America and Canada Joint Meeting**; San Francisco, CA; [*J. Francese, (301) 571-1825, Fax: (301) 530-7079*]
	22–27	**CIOMS 24th Conference – Genetics, Ethics, and Human Values: Human Genome Mapping, Genetic Screening, and Genetic Therapy**; Tokyo
	23	**5th International Conference on Scanning Tunneling Microscopy/ Spectroscopy** and **1st International Conference on Nanometer-Scale Science and Technology**; Baltimore, MD [*J. Murday, Code 6100, Naval Research Laboratory, Washington, DC 20375-5000*]
August	27–30	**"Symposium on Mapping and Sequencing"** at the **1990 National American Chemical Society Meeting – Analytical Division**; Washington, DC [*L. Smith, (608) 263-2594*]
September	6–11	**International Workshop on Human Gene Mapping (HGM 10.5)**; Oxford, U.K.
	30–Oct. 3	**Genome Sequencing Conference II**; Hilton Head, SC; abstract deadline: July 15 [*S. Wallace, (301) 480-0634, Fax: (301) 480-8588*]
October	1–3	**First International Conference on DNA Fingerprinting**; Berne, Switzerland [*G. Dolf, Fax: (Int.) 031-24-7021*]
	16–20	**American Society of Human Genetics Annual Meeting**; Cincinnati, OH [*J. Francese, (301) 571-1825, Fax: (301) 530-7079*]
	22–24	**Human Genome II: An International Conference on the Status and Future of Human Genome Research**; San Diego, CA; abstract deadline: August 15 [*Scherago Assoc., Inc., (212) 730-1050, Fax: (212) 382-1921*]

*Attendance at meetings listed without contact information is by invitation only.

Calendar of Genome Events*

November	12–14	**Mapping and Sequencing the Genome: New Opportunities/New Dilemmas – The Ethical Issues**; Monte Picayo, Spain
	14–16	**Conference on the Impact of Biotechnology on Health Care**; Barcelona, Spain [*P. Moon, Oxford, U.K., (Int.) 44-865-512242, Fax: (Int.) 44-865-310981*]
January 1991	8–11	**"Biotechnology Minitrack"** at the **Hawaii International Conference on System Sciences–24**; Kailua-Kona, HI [*L. Hunter, (301) 496-9300, Fax: (301) 496-0673*] ◇

*Attendance at meetings listed without contact information is by invitation only.

Training Calendar: Workshops and Coursework

May	14–18 & 21–25	**Course on Recombinant DNA Methodology**; Washington, DC [*Center for Advanced Training in Cell and Molecular Biology, The Catholic University of America, (202) 635-6161*]
	22–25	**Recombinant DNA Workshop**; Doylestown, PA [*BRL Technical Services, (800) 638-4045*]
	28–June 1	**Course on Expression of Recombinant DNA in Mammalian Cells**; Washington, DC [*See contact: May 14–18*]
June	11–15 & 18–22	**"Recombinant DNA Techniques" Workshop**; Rochester, NY [*The Rochester Institute of Technology, (716) 475-6600*]
	26–29	**Recombinant DNA Workshop**; Buffalo, NY [*See contact: May 22–25*]
July	16–27	**31st Annual Short Course in Medical and Experimental Mammalian Genetics**; Bar Harbor, ME [*T. Roderick, Training and Education Office, The Jackson Laboratory, 600 Main Street, Bar Harbor, ME 04609*]
	20–21	**Polymerase Chain Reaction in Molecular Biology**; Washington, DC [*See contact: May14–18*]
	23–24	**DNA Sequencing**; Washington, DC [*See contact: May14–18*]
	23–27	**Gordon Research Conference on Molecular Genetics**; Newport, RI [*A. Cruickshank, (401) 783-4011/3372*]
August	6–8	**Pittsburgh Supercomputing Center Nucleic Acid and Protein Sequence Analysis Workshop for Biomedical Researchers**; Pittsburgh, PA; application deadline: June 4 [*N. Kiser, (800) 222-9310 (PA), (800) 221-1641 (outside PA)*]
	12–17	**Meetings on "Techniques: Physical Manipulation of the Human Genome" and "Human Genetics" at the Research Conference on Cellular and Molecular Genetics**; Copper Mountain, CO [*M. Marsh, (301) 530-7093*] ◇

Acronym List

Acronyms listed were chosen because they were either used in the text or 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.

ANL*	Argonne National Laboratory, Argonne, Ill.
ATCC	American Type Culture Collection
BISP	Biological information signal processor
BNL*	Brookhaven National Laboratory, Upton, N.Y.
CIOMS	Council for International Organizations of Medical Sciences
DHHS	Department of Health and Human Services (U.S)
DNA	Deoxyribonucleic acid
DOE	Department of Energy (U.S.)
EEC	European Economic Community
ELSI*†	Working on the Ethical, Legal, and Social Issues
HERAC*	Health and Environmental Research Advisory Committee
HGCC*	Human Genome Coordinating Committee
HGMIS*	Human Genome Management Information System (ORNL)
HHMI	Howard Hughes Medical Institute
HUGO	Human Genome Organisation [international]
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.
NCHGR†	National Center for Human Genome Research (NIH)
NEH	National Endowment for the Humanities
NIH†	National Institutes of Health
NLGLP*	National Laboratory Gene Library Project (LANL, LLNL)
NRC	National Research Council (NAS)
ORNL*	Oak Ridge National Laboratory, Oak Ridge, Tenn.
OTA	Office of Technology Assessment (U.S. Congress)
PACHG†	Program Advisory Committee on the Human Genome (NIH)
PNL*	Pacific Northwest Laboratory, Hanford, Wash.
RFLP	Restriction fragment length polymorphism
STS	Sequence-tagged site
UNESCO	United Nations Educational, Scientific, and Cultural Organization
USDA	U.S. Department of Agriculture
YAC	Yeast artificial chromosome

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