Human Genome news

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NIH Consortium Reviews CF Testing, Counseling

Cost, Time Major Factors in Low Demand for Tests

The NIH Cystic Fibrosis Studies Consortium (CFSC) met September 8–9, 1993, in Washington, D.C., to review results of initial studies on testing and counseling for CF mutations. Four NIH components—National Center for Human Genome Research (NCHGR), National Institute of Child Health and Human Development, National Institute of Diabetes and Digestive and Kidney Diseases, and National Center for Nursing Research—are sponsoring the 3-year research project to examine complex issues surrounding possible widespread testing for CF mutations [see *HGN* **3**(5), 1–2 (January 1992)]. The project is coordinated by NCHGR.

Meeting participants concluded that, although study results are not definitive, a number of themes are emerging that have implications for professional and public policies on CF. Highlights of the discussions follow.

Knowledge and Understanding

Public knowledge about CF is generally poor and varies according to such factors as the individual's education, socioeconomic status, ethnicity, and gender. Various education strategies have been shown to increase knowledge, at least temporarily, and to reduce the influence of these factors. A number of barriers to education were identified, including provider reluctance to discuss test implications and lack of access to educational electronic media such as VCR tapes and machines.

Interest and Demand

Interest in carrier testing is mixed in families with a history of CF and correlates with the psychodynamics surrounding individual experiences. Family attitudes range from avoiding all discussions about possible testing to having all members tested.

In the general population, demand for CF carrier testing is low. All three studies offering preconception testing experienced difficulty in recruiting subjects unless solicitations were conducted in person by health personnel. Cost was a major factor in willingness to be tested. Interest was substantially lower when special visits were required for educational interventions or for obtaining the DNA specimen. Interest in CF testing was highest among individuals seeking prenatal testing or genetic counseling for other reasons.

Informed Consent

Studies were designed to ascertain what information was viewed as most important to the decision to be tested. Identified factors included the prognoses and therapeutic prospects for people with CF, the impact

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NIH CF Studies

CFSC, which was formed in 1991, consists of 9 NIH investigative teams across the country who are conducting 10 projects:

Prescriptive Decision Modeling for Cystic Fibrosis Screening and a complementary clinical study, *How Much Information Do Couples Want?* **DAVID ASCH** *(University of Pennsylvania, Philadelphia)*

Genetic Testing in the Ashkenazic Jewish Population, **ROBERT DESNICK** *(Mount Sinai School of Medicine, New York, New York)*

Perception of Carrier Status by Cystic Fibrosis Siblings, **JOANNA FANOS** *(Children's Hospital Oakland Research Institute, Oakland, California)*

Cystic Fibrosis Mutation Screening and Counseling, **WAYNE GRODY** *(University of California School of Medicine, Los Angeles)*

Ethical and Policy Issues in Cystic Fibrosis Screening, **NEIL A. HOLTZMAN** *(Johns Hopkins University, Baltimore)*

Cystic Fibrosis Carrier Screening Educational Materials, **TRISH MAGYARI** (Macro International, Inc., Silver Spring, Maryland)

Cystic Fibrosis Screening: An Alternative Paradigm, **JOHN PHILLIPS** *(Vanderbilt University, Nashville, Tennessee)*

Testing and Counseling for Cystic Fibrosis Mutations, **PETER ROWLEY** *(University of Rochester, Rochester, New York)*

An Evaluation of Testing and Counseling for CF Carriers, **JAMES SORENSON** *(University of North Carolina, Chapel Hill)*

on a family having a child with CF, social and economic risks of testing (including risks to insurability), test uncertainty, and reproductive implications (including abortion). Consortium investigators disagreed about the level of knowledge required for informed consent. Some individuals desired testing even when their posteducation questionnaire indicated a lack of knowledge about the test and its uncertainties.

Impact and Outcome

The consortium has continued to test for the most common six CF mutations, which account for 85 to 90% of CF cases. Of 2821 individuals tested, 64 were found to be carriers. Of four couples with a risk of 1 in 4, three offspring were diagnosed with the trait. One was found to be affected.

Only short-term follow-up for psychosocial-impact assessment has been possible, and much of this data has not been analyzed. Couples consisting of one carrier and one noncarrier displayed no obvious distress in spite of their statistically increased risk of having children with CF. Complex reactions to test results were shown in family studies, including carrier self-stigmatization and guilt among survivor siblings.

Preliminary cost analyses estimate that education, testing, and follow-up services for about 3500 individuals (in which 1 fetus affected with CF will be identified) will cost about $400,000. *[Elizabeth Thomson and Eric Juengst, ELSI Program, NIH NCHGR]*◊

CRADA Signed to Speed DNA Sequencing

Lawrence Livermore National Laboratory (LLNL) and the Perkin-Elmer Corporation signed a cooperative research and development agreement (CRADA) in November 1993 to develop analytical instrumentation for faster DNA sequencing via electrophoresis. The agreement will combine the microfabrication expertise of LLNL with that of the Applied Biosystems Division (ABD) of Perkin-Elmer, a key patent holder of specific sequencing techniques and a pioneer in the development of automated DNA sequencers.

ABD will contribute $3.8 million in cash and $964,000 in equipment and effort. DOE is funding 30% of expenses at $2 million. Tony Carrano (Associate Director for Biology and Biotechnology Research at LLNL and DOE Human Genome Center Director), noted that Lawrence Livermore has initiated more than 100 cooperative research and development agreements since 1992. He said this CRADA is the largest cash contribution by an industrial partner and the first of several CRADAs expected to emanate from the LLNL genome program.

The immediate goal of the CRADA is to increase sequencing rates 10-fold in the next 2 years and 100-fold in the longer term. With current sequencing rates at about 1250 bases/h, more than 1600 person years would be required to achieve the sequencing objectives of the Human Genome Project. Future technology is expected to produce sequencing rates of more than 100,000 bases/h, enabling researchers to complete the project within 10 years. Faster DNA sequencing will also accelerate the identification of genes that cause some 4000 known genetic diseases.◊

Faster Linkage Analysis

The LINKAGE software package, which uses statistical analysis of pedigree data for locating genes, has been modified by Robert Cottingham (Baylor College of Medicine), Rama Idury (University of Southern California), and Alejandro Schaffer (Rice University) to speed up long linkage-analysis computations by roughly 10 times. Improvements were made in the combinatorial part of the code only. A paper describing the modifications appeared in the *American Journal of Human Genetics* [**53**(1) (July 1993)]. A PostScript version of this paper and the improved code can be retrieved via ftp from a computer at BCM as decribed below (a PostScript printer is needed).

FTP Instructions
(Italics indicate what to type)

ftp *gc.bcm.tmc.edu*
kiwi.imgen.bcm.tmc.edu *user*
foreign username:
anonymous
password:
userid@mailaddress
kiwi.imgen.bcm.tmc.edu
cd linkage
kiwi.imgen.bcm.tmc.edu
cd fastlink.51
kiwi.imgen.bcm.tmc.edu
get paper.ps
transfer complete.
kiwi.imgen.bcm.tmc.edu *exit*

For help, contact Cottingham at *bwc@bcm.tmc.edu.*

Information on compiling modified versions of the LINKAGE 5.1 general pedigree programs, which are written in C, is given in the *README* file (*get Readme*). Release of a future version with more improvements is expected. Monitor the *bionet.molbio.gene-linkage* newsgroup for updates.◊

Genome News

New Mutation Revealed in Cancer Gene

Discovery Will Lead to Presymptomatic Tests for Colon, Uterine Cancer

An international team of investigators has identified a gene whose alteration leads to colon cancer in about 1 in 200 people in the western world. The discovery not only revealed a new type of cancer-causing mutation but promises to shed light on the origin of other cancers. The gene, called *MSH2*, when mutated appears to be responsible for hereditary nonpolyposis colorectal cancer (HNPCC), one of the most common inherited diseases in humans. HNPCC causes as many as 1 in 6 colon cancers as well as an increased risk of uterine cancer. Isolation of the gene is expected to lead quickly to presymptomatic testing to identify people at very high risk of developing colon or uterine cancer.

The *MSH2* gene discovery involved a partnership among members of the Laboratory of Cancer Genetics of the National Center for Human Genome Research (NCHGR) and investigators supported by the National Cancer Institute and the National Institute of General Medical Sciences. NCHGR Director Francis Collins called the collaboration an "ideal convergence of clinical research, basic research, and investment in the gene-finding tools of the Human Genome Project."

One team, led by Albert de la Chapelle (University of Helsinki) and Bert Vogelstein and Kenneth Kinzler (Johns Hopkins Oncology Center), published its findings in the December 17 issue of *Cell*. Among the 35 authors who contributed to various aspects of the cancer and genomics research were 2 DOE-funded investigators. David Chen (Los Alamos National Laboratory) generated somatic chromosome 2 hybrids, and Fa-Ten Kao (Eleanor Roosevelt Institute for Cancer Research) microdissected G-banded metaphase chromosomes.

The December 17 report complements an article in the December 3 issue of *Cell*, in which Richard Kolodner (Dana-Farber Institute) and Richard Fishel (University of Vermont) extended their studies of the "mismatch repair" process regulated by bacteria and yeast genes similar to *MSH2*. They used genetic similarities in these genes to find a counterpart in human DNA and link the human *MSH2* gene to HNPCC.

In 1991 Vogelstein, Kinzler, and other scientists including Ray White (University of Utah) and Yusuke Nakamura (Tokyo Cancer Institute) identified the gene associated with familial adenomatous polyposis [see article below and *HGN* 3(3), 15 (September 1993)]. Since then, an active search has been conducted for genes related to more common forms of colon cancer, including HNPCC. Last spring, the Hopkins team collaborated with de la Chapelle's group to identify a chromosome 2 region that contained the HNPCC gene. That work hinged on the use of microsatellite markers.◊

***MSH2* Mutation Affects 1 in 200 People in Western World**

Investigators Localize Mouse Colon Cancer Modifier Gene

Investigators from Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, and University of Wisconsin (UW) have localized *Mom1*, a modifying gene that affects development of colon tumors in mice carrying the cancer-promoting gene *Min1*. *Min1* causes multiple intestinal neoplasia (Min) syndrome, which is equivalent to familial adenomatous polyposis coli (FAP) in humans and thus presents a useful model for studying FAP and other colon cancers. *Mom1* (for modifier of *Min1*) maps between the markers D4MIT12 and D4MIT13 on distal chromosome 4.

FAP is an inherited human disease associated with hundreds to thousands of colon polyps and a high incidence of colon cancer, a common malignancy in industrialized countries. As with many other human diseases, colon cancer is polygenic—caused by the interaction of several genes that may modify each other's expression. The severity of FAP varies among individuals who inherit identical mutations in their FAP genes; one person may have only a few colon polyps while another may develop numerous polyps as well as tumors elsewhere in the body. Possible explanations for such variations are the presence of a modifying gene, environmental considerations such as diet, or a combination of factors.

Researchers used the Whitehead mouse genetic maps—then consisting of more than 2000 different genetic markers—to compare the inheritance patterns of disease severity (colon tumor number) with those of the markers. The dense genetic maps also offer a powerful new way to explore genetic origins of other diseases that exhibit much natural variation; these diseases include hypertension, diabetes, and atherosclerosis.

Mouse model systems offer a powerful research tool for studying complex interactions related to cancer development. Investigators in this study used mice carrying a small mutation in their homolog (gene counterpart) of the FAP-causing human gene; they found tumor reduction or even total suppression in mice that also carried the *Mom1* modifier gene, thus proving that a modifier gene affects the expression of an inherited cancer. Modifier genes are far more difficult than other types of genes to locate in mammals.

The next steps will be to sequence the *Mom1* gene and identify its human homolog, events which could have important diagnostic implications for human families. Understanding how modifying genes exert their effects on cancer-promoting genes may one day lead researchers to develop new forms of cancer therapy.◊

Genome News

"Startle Disease" Mutation Directly Affects Neurotransmitter Receptor

Neurologic Disorder Gene Identified

International teams reported in the December 1 issue of *Nature Genetics* the discovery of the defective gene and exact mutations responsible for the dominant neurologic disorder hyperekplexia. The teams were led by John Wasmuth (University of California, Irvine); Stephen Ryan and Peter O'Connell (University of Texas Health Science Center, San Antonio); and Angelica Hahn (University of Western Ontario).

The defective gene, located on chromosome 5, encodes one subunit of the inhibitory glycine receptor. Individuals with this condition, also called "stiff baby syndrome" or "startle disease," respond to loud noises or unexpected touching with sometimes life-threatening spasms and muscle rigidity. The research on hyperekplexia was supported by grants from the National Center for Human Genome Research (NCHGR), the Hereditary Disease Foundation, the Morrison Trust, and the National Institute for Neurologic Disease and Stroke.

Hyperekplexia affects about 1 in 40,000 people. Although the condition is not life threatening in adults, the spasms and muscle ridigity can cause serious injuries from falls. Infants with the condition often die from apnea (cessation of breathing), also believed to cause death in many cases of Sudden Infant Death Syndrome.

Because hyperekplexia can be treated effectively with the benzodiazepine drug clorazepam, the gene's discovery is more important to the basic understanding of neurological disorders than for any immediate clinical benefit. "Understanding how and why the mutations we've identified in this gene result in a neurologic disorder will help scientists better understand the normal role of this important neurotransmitter pathway," Wasmuth said.

Hyperekplexia is the first inherited neurologic disorder found to be caused by a mutation directly affecting a neurotransmitter receptor in the central nervous system. "It really is the ultimate of finding a needle in a haystack—one base pair change in three billion," Wasmuth said. He attributed the success to several factors, including outstanding cooperation and open exchange of information and resources among the collaborating groups; the work of Rita Shiang, the postdoctoral investigator in his laboratory who actually discovered the mutation; and accurate, pre-existing maps of chromosome 5.

Discovery of the hyperekplexia gene marks the third time in 2 years that Wasmuth's laboratory has played a role in identifying the gene responsible for a genetic disorder. His laboratory, part of the collaborative research group that discovered the Huntington's Disease gene, also cooperated with Ray White's laboratory at the University of Utah in isolating the familial polyposis gene, which causes a predisposition for developing colon cancer.

Wasmuth's laboratory was designated by NCHGR as the 16th National Center for Human Genome Science and Technology and given the specific mission of making a detailed physical map of chromosome 5. The center will also work toward identifying other chromosome 5 disease genes, including those that cause Treacher Collins syndrome (a common developmental disorder) and two types of muscular dystrophy.◊

DOE Human Genome Program Activities

Contractor-Grantee Workshop Planned

The fourth DOE contractor-grantee workshop will be held November 13–17 in Santa Fe, New Mexico. At least one person from each funded group is expected to attend. Investigators should soon receive more details, including a request for abstracts for oral presentations and posters, from Sylvia Spengler [Lawrence Berkeley Laboratory (510/486-4879, Fax: -5717, Internet: *sylviaj@violet.berkeley.edu*)].

DOE FY 1994 Human Genome Program Report Under Way

Human Genome Management Information System (HGMIS) has begun requesting figures, photographs, and updated project abstracts from grantees and contractors for the fourth DOE Human Genome Program Report, to be published early in 1995. A timely response from investigators will greatly facilitate preparation of this document, which will be similar in scope and content to the red-covered 1991–92 report. Items should be sent to the HGMIS address on page 16. [Contacts for more information: Betty Mansfield (615/576-6669, Fax: -9888, Internet: *bkq@ornl.gov*) or Anne Adamson (615/574-9851, Fax: -9888, Internet: *ae1@ornl.gov*).]

DOE FY 1993 Supplemental Program Report Available Soon

The 1993 supplement to the 1991–92 program report will be distributed this spring.◊

CEPH MAP AVAILABLE ON E-MAIL

The first Centre d'Etude du Polymorphisme Humain (CEPH) draft map of the human genome, announced by a team led by Daniel Cohen in the December 16 issue of *Nature*, is available on the Internet. Detailed tiling path information can be requested by e-mail from *ceph-genethon-map@genethon.genethon.fr*.◊

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NIST ATP Promotes Growth, Competitiveness

Proposals are due in mid-March for the Advanced Technology Program (ATP), begun in 1990 at the National Institute of Standards and Technology (NIST) to promote economic growth and competitiveness in U.S. business and industry, including DNA sequencing and biotechnology. ATP accelerates the commercialization of promising, high-risk technologies that are unlikely to be developed in time to compete in rapidly changing world markets without such an industry-government partnership. The program funds cooperative research agreements with single businesses or industry-led joint ventures.

For guidelines and more information, contact ATP at NIST; A430 Administration Building; Gaithersburg, MD 20899-0001 (800/287-3863, Fax: 301/926-9524, Internet: *atp@micf.nist.gov*).

Proposals for Current Award Cycle Due March 15

Essential ATP Features

- Projects selected through a fair and rigorous competition. Criteria include potential for U.S. economic benefit, technical and business merit, strong industry commitment, and the opportunity for ATP funds to make a significant difference.
- Direct support to for-profit companies of all sizes.
- Broad mission to promote large economic benefits for the nation. The ATP legislative mandate, which offers tremendous scope, is to promote rapid commercialization of new scientific discoveries and refine manufacturing practices.
- Market oriented. Industry conceives, manages, and executes ATP projects in response to its analysis of market opportunities.
- ATP performance monitored and evaluated according to its comprehensive plan.

Successful applicants share the costs of ATP projects. Awards to individual companies are limited to $2 million over 3 years and can be used only for direct R&D. Awards to joint ventures, which must provide more than 50% of project resources, can be for up to 5 years. ATP will support production of laboratory prototypes and studies of technical feasibility but not product development.

Two independent studies of ATP projects funded in FY 1991 revealed substantial, early beneficial impacts on participating companies. These benefits include expanded R&D activity, cost and time savings, improved competitive standing, formation of valuable strategic business alliances, improved ability to attract investors, assistance in converting from defense to commercial applications, and acceleration of technology development. The ATP program has received broad public support from major trade associations, professional societies, and high-technology companies.◊

Investigators Win Nobel Prizes

Laureates' Work Has Great Impact on Human Genome Project Research

Phillip Sharp (Massachusetts Institute of Technology) and Richard Roberts (formerly Cold Spring Harbor Laboratory, now New England Biolabs) were jointly awarded the 1993 Nobel Prize in Medicine and Physiology for their 1977 work on gene splicing. Sharp served on the Program Advisory Committee of the NIH National Center for Human Genome Research from 1988 to 1991.

Working independently, Sharp and Roberts discovered that genes in eukaryotic cells are distributed among widely spaced segments separated by introns (DNA segments that have no apparent protein message); about 99% of human genes are believed to share this structure. In a dramatic change from commonly accepted theories, human genes were thus shown to differ markedly from often-studied bacterial genes, which run continuously along the DNA strand. Research indicates that some introns have persisted for a billion years, and even though they do not carry translatable code, they may provide an evolutionary advantage. Interruptions in the code may facilitate the creation of new combinations and allow species to evolve.

The investigators also showed that after DNA is copied into a primary RNA transcript, introns are deleted and the remaining genetic material is spliced together in the correct order. The edited message then leaves the cell nucleus and travels to the ribosomes, where it is translated for protein assembly. Mistakes in RNA processing are related to a number of disorders including thalassemia, and recent results suggest these editing mishaps may also play a role in cancer.

The Nobel chemistry prize was awarded to two investigators for techniques that have become standard in research and clinical laboratories throughout the world. Kary B. Mullis, who is now an independent consultant in molecular biology, was employed by Cetus, Inc., in 1984, when he conceived the polymerase chain reaction (PCR). PCR allows investigators to make millions of copies of any specific region of a DNA sample in a very short time. Because the reaction can amplify minute amounts of sample, PCR has had an especially profound impact in clinical medicine, genetic disease diagnostics, forensic science, and evolutionary biology. PCR has become an essential tool for genome researchers, who use it to detect the presence of unique landmarks (e.g., sequence tagged sites) in a much larger DNA sample (such as pools of clones) and amplifying them for use as probes or starting material for sequencing.

Mullis shared the chemistry prize with Michael Smith (University of British Columbia, Vancouver) who formulated a method that enables scientists to induce specific mutations in normal genes and then examine their altered protein products. This site-directed mutagenesis technique is used by researchers involved in molecular biology and protein engineering to investigate gene function and create new and potentially useful proteins for medicine and industry. As the goals of the Human Genome Project are realized and the estimated 100,000 genes in the human genome are identified, gene-hunting activities will increasingly give way to studies focusing on how genes work to guide the development and function of all organisms.◊

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NIH Identifying Research Areas for Testing, Counseling for Heritable Cancer Risk

The RFA resulting from these discussions was released February 4 by NCHGR. Contact:

Elizabeth Thomson or Eric Juengst
301/402-4997
Fax: /480-2770
Internet:
exx@cu.nih.gov

The NIH National Center for Human Genome Research (NCHGR) held a workshop on October 28, 1993, to gather information and advice on the delivery of genetic testing and counseling for heritable cancer risks. Attendees were asked for their views on research questions that need to be addressed, studies for answering these questions, and evaluation of alternative testing and counseling protocols. Participants included representatives from the genome science and social and behavioral sciences communities, as well as service providers and consumers.

Research Needs and Recommendations

Genetic tests are now becoming available to identify members of families with heritable cancers who have an increased risk of developing cancer. Participants agreed that as this testing becomes feasible for a much wider population, well-designed clinical protocols are urgently needed to ensure that the tests are responsibly integrated into clinical practice. To guide protocol development, better information should be gathered about different approaches to pre-test and post-test education and counseling; management of test results; and the psychosocial, behavioral, and clinical impact of genetic testing in high-risk families.

Attendees agreed that the optimal approach would be to focus on genetic linkage or direct DNA-mutation testing for alleles associated with heritable breast, ovarian, and colon cancers. They also recommended that NIH develop a consortium of studies, each addressing a subset of the overall research agenda in cooperation with the others. This approach would allow for the possible standardization of evaluation tools, laboratory quality control, and protection of human subjects, as well as more-reliable comparisons between studies. Participants felt that initiatives should be interdisciplinary and that qualitative, ethnographic approaches should be encouraged to assess family dynamics and psychosocial impact. Surveys and a policy analysis of provider and public attitudes about genetic testing for cancer risk should be conducted.

Applicants will need to detail plans for protecting the rights and interests of individuals and families involved in clinical testing.

High-Priority Research Questions

The goal of these studies would be to identify clinical practices that best increase individual and provider understanding of genetic testing, the meaning and implications of test results, and strategies for promoting health and preventing the development of cancer. Equally important is reducing the risk for test-related psychological harm, stigmatization, and discrimination in tested individuals and families.

Workshop participants identified important research areas, including the following:

- Identification and readiness assessment of individuals most likely to benefit from testing.
- Optimum strategies for educating the individual and the public.
- Informed consent issues.
- Examination of diverse models for delivering testing and counseling services.
- Identification and evaluation of post-test counseling and follow-up.
- Psychological impact of test results on individuals.
- Effect of test results on relationships with health professionals and insurance companies.
- Health behavior of family members who decide against testing.
- Attitudes, levels of understanding, and interest in genetic testing among providers and individuals and families of diverse ethnocultural backgrounds.
- Economic impact of testing strategies, including health-care costs related to early detection and intervention.◊

ELSI Bibliography Published

The second print edition of *ELSI Bibliography: Ethical Legal and Social Implications of the Human Genome Project* is available for distribution. Compiled by Michael Yesley and staff at Los Alamos National Laboratory (LANL), the 265-page document lists publications drawn from an underlying database on major topics related to ethical, legal, and social implications (ELSI) of the Human Genome Project. [Contact for DOE and DOE contractors: Office of Scientific and Technical Information; P.O. Box 62; Oak Ridge, TN 37831 (615/576-8401). Contact for public: National Technical Information Service; U.S. Department of Commerce; 5285 Port Royal Rd.; Springfield, VA 22161.] ◊

NIH Genome Council Updated on Programs, Centers

The ninth meeting of the National Advisory Council for Human Genome Research was convened on September 20, 1993, with Francis Collins, Director of the National Center for Human Genome Research (NCHGR), presiding. Collins announced that Harold Varmus, an enthusiastic supporter of the Human Genome Project, had been nominated for the post of NIH director. (Note: Varmus was confirmed shortly after this meeting.)

Collins reported on the requested FY 1994 NCHGR appropriation. He also updated the council on the status of the new intramural program, which focuses on the many applications of genome research to medical genetics. The extramural program continues to pursue long-range Human Genome Project goals. He asked members to help clarify the distinct missions of each program to their colleagues.

Council members asked about the possibility of researchers visiting NIH for 3 to 6 months to use the intramural program's genomic tools and resources. Collins explained that laboratory space is limited and the NCHGR facility is not designed to replace outreach programs in the extramural community. However, fair selection criteria and request prioritization will be used to make these resources available to as many researchers as possible.

Collins gave an overview of the meeting on cystic fibrosis (CF) held by the genome project's Ethical, Legal, and Social Implications (ELSI) program on September 8–9 in Washington, D.C. (see article, page 1). Council members agreed that the CF study offered valuable data for understanding issues such as screening and presymptomatic testing for other diseases. Because each disease has its own set of quantitative and qualitative issues, members stressed that the results should not be overgeneralized.

Because of tremendous achievements and progress in genome science, the original 5-year goals of the U.S. Human Genome Project have been revised and extended [see the October 1, 1993, issue of *Science* and *HGN* 5(4), 1–3, 5 (November 1993)]. The draft document was circulated among council members for their comments and editorial changes. After discussing several points, the council recommended that the new goals be published and disseminated.

Schedule for NIH-DOE Meetings

Elke Jordan (NCHGR) pointed out that NIH and DOE have a Memorandum of Understanding that provides for three annual joint advisory meetings in addition to numerous ongoing collaborations between the two agencies. Because of the merger of the NIH Program Advisory Committee and the council, a new schedule was proposed for joint meetings between the council and the DOE Human Genome Coordinating Committee. One meeting would be held after the January council meeting and another at a national conference such as the May genome mapping and sequencing meeting at Cold Spring Harbor. The third date would be left open for possible fall events such as a retreat or the American Society of Human Genetics meeting. Members agreed with the schedule and expressed the need to have small groups with well-defined purposes and agendas. They also suggested that different subsets of council members might attend meetings according to the topic being discussed. Jordan stated that the ELSI working group, the only one remaining from the Program Advisory Committee, would report at the joint DOE-NIH advisory meeting.

Report on Centers Management

Jane Peterson, Chief of the NCHGR Mammalian Genomics Branch, summarized current practices for managing large grants and listed a number of discussion items for the council's consideration. She described how NCHGR manages centers, from application to award, and monitors progress toward achieving the centers' goals.

Peterson explained that she and Jeffery Schloss visited and surveyed many other NIH institutes about management practices for centers programs. Peterson stated that staff are closely involved with NCHGR genome centers, an advantage that builds in some flexibility and encourages rapid progress. Annual written reports and staff site visits are extremely

(see Council, p. 8)

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Varmus Confirmed as NIH Director

New Schedule Proposed for Joint DOE-NIH Meetings

Whitehead/MIT Mouse Genetic Map Available

Release Five of the Whitehead Institute/ Massachusetts Institute of Technology Genome Center Genetic Map of the Mouse, containing 3011 markers (1000 more than Release Four), is now available. For access information and a description of the map, see *HGN* 5(4), 7 (November 1993). [Contact: Ert Dredge (619/252-1922, Fax: /252-1902, Internet: *ert@genome.wi.mit.edu*).] ◊

Genome News

Sequence Analysis Tools Facilitate DNA, Protein Comparisons

ORNL Announces genQuest and X-GRAIL

The Informatics Group at Oak Ridge National Laboratory (ORNL) is making available several new sequence-analysis tools that operate within the distributed environment of genome resources. A major addition is genQuest ("Q" server), which uses such methods as Smith-Waterman, FastA, and BLAST to facilitate rapid and sensitive comparisons of DNA sequence and proteins in a number of databases. These databases include the Genome Sequence Database (GSDB) at Los Alamos National Laboratory (LANL), SWISS-PROT protein sequence database, PROSITE protein motif library, a human repetitive library provided by Jerzy Jurka (Linus Pauling Institute), Steve Henikoff's BLOCKS/BLIMPS resource, dbEST, IBM dFLASH server, and sequences in PDB protein/nucleic acid structure database. Future genQuest features will include capabilities for Smith-Waterman comparison of very long DNA sequences, multiple sequence alignment of DNA and proteins, methods for graphical visualization of sequence similarity, and a Macintosh client version. The genQuest server is accessible via e-mail and X-based client server.

The diagram (p. 9) shows the graphical client-server version of the main genQuest menu and use of the Smith-Waterman method to search for a partial protein sequence against SWISS-PROT and Prosite. The menu provides "point and click" options to specify sequence type, methods, and target databases. The client code runs on any Sun Sparc workstation having Internet access and communicates with the ORNL server system running on workstations and a parallel computer.

Significant improvements have also been made to GRAIL (Gene Recognition and Analysis Internet Link), a suite of tools that provides annotation of DNA sequences both interactively and through automated computation. GRAIL I and GRAIL II are available by several methods, including a

(continued next page)

Next Advisory Council Meeting Set for May 9–10

Council *(from p. 7)*

useful to NCHGR in discussing progress and other important issues for each center. The policy of requiring data- and material-release statements as an award condition is unique.

Several members stated that specific program areas such as sequencing may need more recruitment, but this should be done through new requests for applications, not necessarily new centers. Peterson explained that cost sharing by applicant institutions varies widely and that NCHGR requires much less institutional commitment than do most NIH institutes. Members agreed that cost-sharing issues should be examined carefully with each applicant but that institutions differ markedly in the financial resources they can contribute.

The council did not set a maximum on NCHGR funding for laboratory alterations but agreed that many renovations are costly and too time consuming. Members strongly recommended that applicants use the space they have and make only modest changes.

In general, members agreed that budget reductions due to changes in plans or poor performance should be approached cautiously so that high-risk projects would not be discouraged. David Botstein (Stanford University School of Medicine) suggested that in some cases the council could make conditional awards in which funds could be removed or restored based on a center's progress. Shirley Tilghman (Princeton University) proposed that such decisions should be made in conjunction with the council to maintain consistency.

Several members stated that convening formal meetings among centers is not necessarily the responsibility of NCHGR. Rather, center directors are obligated to be aware of what others in the field are doing and to use a wide variety of sources for keeping abreast of current scientific progress.

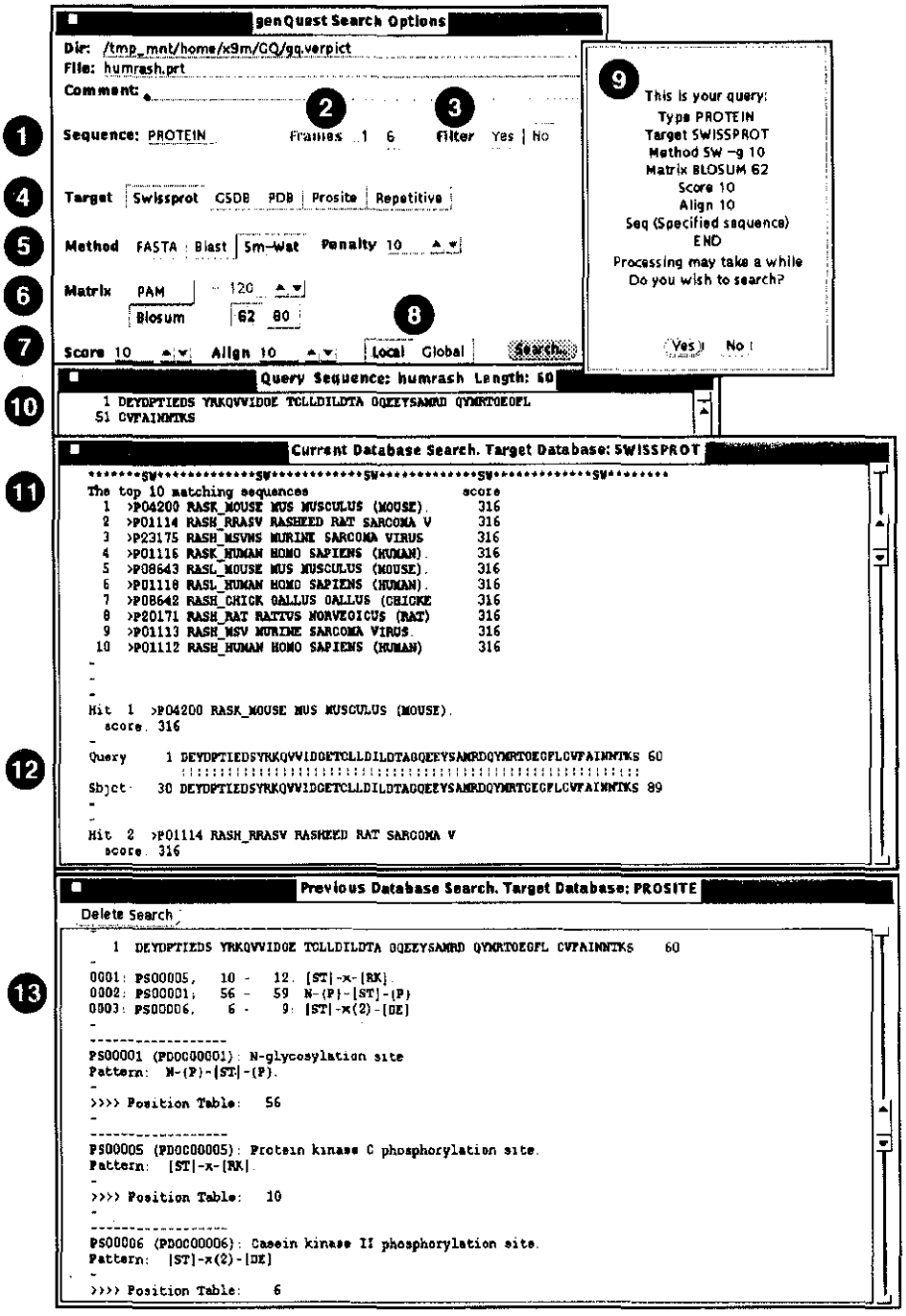
During the closed portion of the meeting, the council reviewed 89 applications requesting $25,805,530 and recommended for approval a total of 69 applications requesting $12,522,748. Future meetings were set for January 24–25 and May 9–10.◊

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.◊

Genome News

simple e-mail interface that analyzes and characterizes coding regions in DNA sequences and returns results automatically by e-mail in a few minutes. New capabilities include comparison of discovered exons with the SWISS-PROT protein sequence database, Prosite, and the repetitive library. X-GRAIL, an interactive graphical X-based client-server system, is now capable of such functions as gene model construction, pol II promoter recognition, and repetitive element annotation. X-GRAIL also transparently accesses genQuest, furnishing additional capability for querying a multitude of databases for sequence comparison.

The Informatics Group plans to incorporate several tools that will provide sequence feature and map information for searches and databases as well as an easy-to-use menu-driven "glossary" for queries to a number of relational database systems. ORNL is also working with Richard Douthart (Pacific Northwest Laboratory) on a client-server version of GnomeView. Manesh Shah of the Informatics Group says, "Our goal is to provide an interoperable environment that allows users to ask a wide variety of questions about their sequence, ranging from sequence analysis to sequence comparison, and to access a variety of databases and other resources in a user-friendly manner. Our tools are designed to allow users without expert computer knowledge to interact with complex databases and analysis systems."
[Ed Uberbacher, ORNL] ◊



The graphical client-server version of the main genQuest menu is displayed. The Smith-Waterman method was used to search for a partial protein sequence against SWISS-PROT and Prosite.

For instructions on using these resources, send an e-mail message with the word *help* in the subject line or first text line to

- *q@ornl.gov* (e-mail genQuest or client-server version downloading).
- *grail@ornl.gov* (e-mail GRAIL and X-GRAIL).

Contact: Edward Uberbacher, Manesh Shah, Sergey Petrov, Xiaojun Guan, or Richard Mural; ORNL *(grailmail@ornl.gov)*.

genQuest Window Key

(Main menu and query results from the genQuest server)

The menu allows the user to select options related to sequence comparison and specify target databases.

Main Menu

(1) DNA or protein sequence can be searched.
(2) Six-frame DNA searches are possible.
(3) Human repetitive elements can be removed from DNA query sequence.
(4) Multiple databases can be searched (not all are shown).
(5) A full range of search methods, including Smith-Waterman, is available.
(6) PAM and BLOSUM matrices are selectable.
(7) Number of scores and alignments can be specified.
(8) Local or global alignment can be selected.

Query and Sequence

(9) Query synopsis.
(10) Query sequence.

Search Result

(11) Top scores.
(12) Alignments.
(13) Prosite motifs found with query.

GDB Forum

SURVEY OF COMPUTER USAGE

The development of computer software to support the Human Genome Project—from analytical tools for the individual investigator to public databases such as GDB, GenBank®, and SWISS-PROT—is hampered by the lack of reliable statistics on computer usage by geneticists, molecular biologists, physicians, and other data users.

This survey is a modest attempt to collect this information, *NOT ONLY FOR GDB's USE* but for sharing with all groups who are working to develop better tools for gathering and analyzing biological data. The development of more useful software to aid research will be greatly facilitated by users who fill out this form and return it to GDB by fax, direct mail, or e-mail. Each response will be very much appreciated.

Survey Return Information
GDB User Support
Johns Hopkins University
2024 E. Monument Street
Baltimore, MD 21205
410/955-7058, Fax: /614-0434
Internet: *help@gdb.org*
Electronic survey form: *survey.txt* is available via ftp from *ftp.gdb.org* and via Gopher (*gopher.gdb.org*) in the Genome Project/GDB section.

1. How would you classify your organization? (circle one)
   A. University B. Genome Center C. Industry D. Hospital/Patient care E. Other _____
2. What is your major responsibility in your organization? (circle one)
   A. Genetics research B. Administrative/Management C. Computer/Systems D. Education E. Patient care F. Other _____
3. What kind of computers do you use? (rank usage with 1 = most frequent; specify model)
   A. __ Mac ( ) B. __ PC ( ) C. __ Sun ( ) D. __ DEC Alpha ( ) E. __ Other UNIX workstation ( )
   F. __ ASCII terminal ( ) G. ___ Other ( )
4. Which computers do you use to access GDB/OMIM? (circle all that apply)
   A. Mac B. PC C. Sun D. DEC Alpha E. Other Unix workstation F. ASCII terminal G. Other _____
5. Which of your computers has Internet access? (circle all that apply)
   A. Mac B. PC C. Sun D. DEC Alpha E. Other Unix workstation F. Other _____
6. Which of your computers has a CD-ROM? (circle all that apply)
   A. Mac B. PC C. Sun D. DEC Alpha E. Other Unix workstation F. Other _____
7. Which of your computers has a modem? (circle all that apply; specify speed)
   A. Mac ( ) B. PC ( ) C. Sun ( ) D. DEC Alpha ( ) E. Other Unix workstation ( ) F. Other _____ ( )
8. Which Internet services do you use? (circle all that apply)
   A. E-mail B. FTP C. Gopher D. WAIS E. USENET news F. World Wide Web G. Other _____
9. If you have problems using hardware/software, where do you go most often for help? (circle one)
   A. Local technical support B. Knowledgeable coworker C. Manufacturer/Distributor D. Manual
10. Which biological databases do you use? (circle all that apply)
    A. GDB B. OMIM C. GenBank D. Medline E. PIR (Protein Identification Resource)
    F. SWISS-PROT G. PDB (Protein Data Bank) H. Entrez I. Other _____
11. Which methods do you use to access GDB data? (circle all that apply)
    A. GDB application (APT forms) B. GDB/Accessor C. WAIS D. Gopher E. FTP F. HGM book (HGM11, CCM92)
12. Which methods do you use to access OMIM data? (circle all that apply)
    A. OMIM application (IRX) B. GDB/Accessor C. WAIS D. Gopher E. FTP F. MIM book
13. Do you presently have data to submit to GDB? (circle one)
    A. No B. Yes, waiting for complete data C. Yes, waiting to find out how to submit it
14. Would a software package analogous to GenBank's Authorin increase your willingness to submit data to GDB?
    A. Yes B. No
15. Please add any comments you feel would help improve GDB services.

(Optional) Name_____ Organization_____

Search GDB and OMIM via E-mail

GDB and OMIM can be searched via e-mail by sending a query to *mailserv@gdb.org.* No subject line is necessary when querying mailserv. The e-mail server uses the Wide Area Information Server (WAIS) for all searches. WAIS locates and ranks documents according to frequency of use of query terms and their appearance in the title.

Databases Available

gdb-citation	Articles and abstracts
gdb-contact	Scientist contact information
gdb-locus	Genetic loci
gdb-map	Genetic maps
gdb-mutation	Genetic mutations
gdb-polym	Genetic polymorphisms
gdb-probe	Genetic probes
gdb	Superset of the above (searches all the gdb-* databases)
omim	Online *Mendelian Inheritance in Man*

Valid Commands

A single e-mail message can contain an unlimited number of commands. The results of all commands, except *help*, will be sent in a single message. Valid commands include the following:

- *HELP:* Requests the mailserv helpfile document, which is mailed separately if *help* is alone on a line within the body of the message. The help document lists all valid commands and search strategies.
- *SEARCH [database] [keywords]:* Searches the specified database for the occurrence of one or more keywords. Only one database can be specified per e-mail line. Examples: *search omim marfan; search gdb-citation marfan.*
- *GET [GDB or OMIM Accession number]:* Retrieves a specific document from GDB or OMIM. Accession numbers are returned when a keyword search is performed so the exact document may be retrieved. Database need not be specified because GDB and OMIM have different accession numbers. The first example retrieves a GDB document and the second an OMIM document: (1) *get G00-000-123*; (2) *get 193005.*
- *DONE:* Instructs the mailserv program to ignore all lines following.◊

Example Query

The following example query will return one message with the help file and a second message with all the search results.

To: *mailserv@gdb.org*
Subject:
help
search gdb-citation marfan
search omim marfan
done

GDB Enters New Genethon Data

Polymerase chain reaction (PCR) and microsatellite data have been loaded into GDB from the latest set of highly informative Genethon markers. Records in this set consist of over 1200 new cloned probes, PCR probes, polymorphisms, and loci complete with PCR conditions and allele-frequency information.

To access this data in GDB, first retrieve the GDB ID# G00-230-332, then call the Locus, Probe, or Polymorphism Manager.◊

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 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
410/955-7058
Fax: /614-0434
Internet: *help@gdb.org*

GERMANY
Otto Ritter
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German Cancer Research Center
Im Neuenheimer Feld 280
D-6900 Heidelberg
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+ 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
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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*

New Version of GDB/Accessor Available

The new version of GDB/Accessor, called 5.2 to match the GDB version, includes the following enhancements:

- Faster startup and searching,
- Capability for specifying default servers for GDB and other databases,
- Command key shortcuts for printing (**Cmd-P**), using Probe Query Screen (**Cmd-R**), and canceling queries or reports in progress (**Cmd-.**),
- Meeting abstracts available as type of citation, and
- Progress information display when generating reports.

Current GDB/Accessor users can get the new 5.2 version by following the directions below.

1. Start up current version. Notice will appear that new version is available.
2. Choose *Update* from the *Special* menu. New program will be automatically downloaded from Gopher.
3. UnBinHex new 5.2 application.
4. Quit old version and start up new version.

GDB/Accessor is available via ftp (*ftp.gdb.org*) in *pub/mac/accessor directory.* For more information, contact GDB User Support.◊

Genome News

Human Genome news

National Center for Human Genome Research

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

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Workshop on Sequencing by Hybridization

The Second International Workshop on Sequencing by Hybridization (SBH) was held at the Houston Advanced Research Center (HARC) in The Woodlands, Texas, on October 28–30, 1993. The workshop was organized by Kenneth Beattie (HARC) and supported by DOE; the Human Genome Organization; The Wellcome Trust; HARC; Beckman Instruments, Inc.; Affymetrix, Inc.; and Genosys Biotechnologies, Inc. Some 75 scientists from 8 countries attended the meeting, which reported significant progress in the SBH field since the inaugural workshop held 2 years ago in Moscow. Some highlights are summarized below.

Chemistry and Analogs

In a session chaired by Daniel Brown (Medical Research Council, Cambridge, U.K.), recent advances were reviewed in chemical synthesis, modification, and surface attachment of hybridization probes. Gerald Hurst (Genosys Biotechnologies) opened the conference with a discussion of high-throughput oligonucleotide synthesis. Robert Matson and Peter Coassin (Beckman Instruments) reported the hybridization properties of oligonucleotide arrays synthesized directly on polypropylene sheets. Philip Andrews (University of Michigan) discussed the chemical synthesis and hybridization properties of improved universal base analogs, which potentially can be incorporated into gapped probes to extend the length of DNA sequence that can be reconstructed from SBH data. Stephen Case-Green (Oxford University) presented data on the positional effects of mispairing. The analog inosine (and probably canonical nucleosides), for example, tends to base pair with reduced specificity during hybridization when present at the ends of a duplex, especially the 3′ end. Andrei Mirzabekov (Engelhardt Institute of Molecular Biology, Moscow) reviewed the significant progress of his laboratory in constructing hybridization matrices within thin films of polyacrylamide. Roger Giese (Northeastern University) ended the session with a description of electrophore DNA labels, which could be coupled with electron-capture mass spectrometry to enable a vast multiplexing of hybridization reactions.

Engineering and Automation

Progress in the production of hybridization arrays was summarized in the session chaired by Mirzabekov. Stephen Fodor (Affymetrix, Inc.) reviewed the impressive progress made in the use of photolithography to synthesize gene-targeted oligonucleotide arrays directly onto silicon dioxide substrates and described the use of these arrays to analyze mutations in cystic fibrosis and p53 exons. Several speakers described microfabricated genosensors for use in SBH. Dennis Rathman [Massachusetts Institute of Technology (MIT)] reported recent progress in developing an electronic permittivity device for direct detection of hybridization within a genosensor array; Robert Reich (MIT) described a charge-coupled device genosensor for direct-contact imaging of hybridization; and Beattie introduced the concept of a flow-through genosensor designed for improved detection sensitivity and the ability to analyze dilute nucleic acid solutions. David Wallace (Microfab Technologies, Inc.) described a microfluidic jet system being developed for precision dispensing of DNA solutions to individual test sites within hybridization arrays.

Victor Barsky and Gennady Yershov (Engelhardt Institute) described engineering aspects of preparing gel matrix sequencing microchips. Edwin Southern (Oxford University) presented a discussion of RNA analysis by hybridization to a novel oligonucleotide array synthesized directly onto glass. Hybridization data were not predicted entirely from the higher-order structure of target RNA nor from using energy calculations. Southern suggested that scanning arrays could be useful for optimizing primer selection for polymerase chain reactions as well as for antisense oligonucleotide design and mutation detection.

Hybridization Data

Uwe Maskos (NIH) opened a session chaired by Southern with a forthright discussion of the challenges of interpreting real data obtained by hybridization of target DNA with oligonucleotide arrays. Using representative data obtained in his extensive work in Southern's laboratory, Maskos stressed that the SBH community must learn to deal with hybridization patterns that are only partially predicted from a known target sequence. A vast hybridization data set should be acquired, he continued, to enable definition of hybridization rules that will be needed for valid data interpretation and for guiding the selection of appropriate probes to include in an array. Toward this end, Mitch Doktycz [Oak Ridge National Laboratory (ORNL)] gave a progress report on an extensive effort to catalog the effects of base sequence on octamer hybridization in solution. This work, to be repeated later in surface hybridization in collaboration with Robert Foote (ORNL) and Beattie, will examine mismatch discrimination as a function of sequence and position.

James Wetmur (Mount Sinai School of Medicine) emphasized the importance of the Doktycz approach and presented a theory for thermodynamic and kinetic consequences of stacking and branching in SBH. Data on tandem ligation strategies were presented by Levy Ulanovsky (Weizmann Institute, Israel), Keith Kretz (Stratagene), and Cassandra Smith (Boston University). Zhen Guo (University of Wisconsin) reported optimization of linker arm

(see Sequencing, p. 13)

MacroMolecules, Genes, and Computers

Leading-Edge Computing Demonstrated

MacroMolecules, Genes, and Computers International Symposium and Workshop: Chapter Three (MGC3) was held August 17–22, 1993, in Waterville Valley, New Hampshire. The symposium, organized by Temple Smith (Boston University), was designed and the schedule arranged to facilitate formal and informal discussion in the interdisciplinary domains of computer science, mathematics, genetics, medicine, and molecular biology. Session topics focused on fundamental properties of biological systems, enabling technologies, and anticipated computational challenges.

Software and database workshops coordinated by Wayne Rindone (Harvard University) constituted one of the most active components of the meeting. More than two dozen different computers were available, from workstation minisupercomputers to laptops displaying molecular structure in color graphics. These computers, connected via a local area network, were set up and attended by staff members from two of the meeting's sponsors, Applied Biosystems and Digital Equipment Corporation. "Within 24 hours, we converted an empty demonstration room into a leading-edge computing facility comprising up to 50 workstations, all interconnecting among themselves—and with the rest of the world," commented Joseph Modelevsky, a member of the MGC3 organizing committee.

Demonstrations were presented on all major molecular and genetic databases including GenBank®, Genetics Computer Group, Protein Information Resource, FlyBase, Protein Data Bank, and others. Emphasis was placed on intelligent front ends, relational infrastructures, network servers, multiple database integration, and cross referencing. Attendees at adjacent workstations could simultaneously search, extract, and compare information retrieved from widely dispersed international databases with analyses available on computers at their home institutions.

Lively discussions were held on sequence-data accuracy, genetic algorithms and neural nets as tools for structure analyses, in vitro selection of new ribonucleic acid catalyses, and potential linguistic representation of complex regulatory networks. A number of computer science tools, such as machine learning and advanced pattern grammars, were shown to be moving toward practical biological applications. This represents a shift from past meetings dominated by presentations on comparative sequence algorithms, evolutionary reconstruction problems, and the need for better data structures.

Debate continued on the relative importance of vast amounts of higher eukaryotic intergenic sequences or "junk" DNA. Sydney Brenner (Scripps Research Institute) suggested using a fish as a model organism because of its small, gene-rich genome. Speaking about very large regulatory regions, Carl Parker (California Institute of Technology) questioned whether information on complex higher organisms might be encoded in much of the so-called junk. In the discussions that followed, the possibility was suggested that very complex neural systems involve about the same genes as simpler systems but are regulated in more complex sets, thus requiring many more regulator elements. *[Temple Smith, Boston University]* ◊

Sequencing *(from p. 12)*

and attachment density in surface hybridization and presented results on detecting mutations in the human tyrosinase gene.

Elmar Maier and Sabastian Meier-Ewert (Imperial Cancer Research Fund, London), Jörg Hoheisel (German Cancer Research Center), and Radomir Crkvenjakov and Radoje Drmanac [Argonne National Laboratory (ANL)] summarized the use of robotics to prepare very large numbers of DNA samples and array them at high density onto membranes. Real progress was also reported by these investigators in the use of such arrays in clone mapping and partial sequencing.

Theory and Informatics

Crkvenjakov chaired a session that focused on the usefulness of reduced probe sets and additional biochemical data in SBH. William Bains (PA Consulting Group and Cambridge Laboratory) discussed the utility of a reduced-set hybridization chip containing 4096 octamers with 2 redundant sites and also pointed out that analysis of cDNAs by SBH is facilitated when a single open reading frame is known. Alexander Chetverin (Institute of Protein Research, Moscow Region) described an elaborate nested-strand hybridization strategy that may enable sequencing of complex mixtures of fragments. SBH strategies for recognizing functional gene regions in genomic DNA were discussed by Victor Solovyev (Baylor College of Medicine) and Ivan Labat (ANL).

Yuri Lysov (Engelhardt Institute) described a computer simulation with additional rounds of continuous stacking hybridization to extend the length of sequences that can be determined by SBH. Pavel Pevzner (Pennsylvania State University) described binary chips requiring 5 to 10% of the probe number. Aleksandar Milosavljevic (ANL) and Robert Lipshutz (Affymetrix) described comprehensive sets of software tools that have been developed to handle the informatics needs of large SBH projects. *[Kenneth Beattie, HARC]* ◊

Abstracts available online via Johns Hopkins University Computational Biology Gopher under Human Genome Project [see *HGN* 5(3), 8 (September 1993)].

Calendar of Genome-Related Events* (acronyms, p. 16)

February

28–Mar. 2. HGP: Commercial Implications; San Francisco [CHI, 617/487-7989, Fax: -7937]

March

3–4. Gene Transcription-Based Therapeutics; CHI, San Francisco [see contact: Feb. 28–Mar. 2]

4–10. **Mol. Basis of Cancer Therapy; Tamarron, CO (abs. deadline: Oct. 27) [Keystone Symposia, 303/262-1230, ext. 110, Fax: -1525]

6–8. 3rd Intl. Chromosome 5 Workshop; Laguna Beach, CA [J. Wasmuth, 714/856-8242, Fax: /725-3403 or M. Dixon, +44-61/275-5620, Fax: -3915]

17. †Jeffrey Trent: Genomic Applications of Chromosome Microdissection; Bethesda, MD [NCHGR Lecture Series, E. Feingold, 301/496-7531, Fax: /480-2770]

25–27. 1st Intl. Workshop on Human Chromosome 1; Bethesda, MD [N. Dracopoli, 301/402-4558, Fax: -2120, Internet: *dracopol@helix.nih.gov*]

28–29. Recent Developments in the Diagnosis & Treatment of CF; CHI, Alexandria, VA [see contact: Feb. 28–Mar. 2]

April

2–5. 1st Intl. Workshop on Human Y Chromosome; Cambridge, U.K. [N. Affara, +44-22/333-3700, Fax: -3346, Internet: *na@mbuc.bio.cam.ac.uk* or C. Lau, 415/476-8839, Fax: /502-1613, Internet: *clau@itsa.ucsf.edu*]

7–8. 2nd Intl. *Nature Genetics* Conf.: Mouse Genetics, Transgenics, and Polygenics; Toronto [D. Berger, 212/477-9699, Fax: /505-1364]

9–11. 3rd Intl. Workshop on Human Chromosome 9; Cambridge, U.K. [S. Povey, +44-713/807-410, Fax: /873-496, Internet: *mpovey@mrc-crc.ac.uk*]

10–13. 85th Ann. Mtg. of AACR; San Francisco (abs. deadline: Oct. 25) [AACR, 215/440-9300, Fax: -9313]

21. †Ronald Davis: Technol. Development for High-Throughput DNA Sequencing; Bethesda, MD [see contact: Mar. 17]

21–22. **NIH-DOE Joint Working Group Meeting: Genetic Privacy; Washington, DC [M. Yesley, 505/665-2523, Fax: -4424, Internet: *msy@lanl.gov*]

23–26. 4th European Workshop on Cytogenetics and Mol. Genetics of Human Solid Tumors; Noordwijkerhout, The Netherlands (abs. deadline: Nov. 15) [J. van Dam, +31-20/566-4801, Fax: /696-3228]

24–27. 5th Intl. Workshop on Human X Chromosome Mapping 1994; Heidelberg, Germany [A. Poustka, +49-6221/423-409, Fax: -454 or D. Schlessinger, 314/362-3203, Fax: -2744]

24–28. 1st World Cong. on Computational Med., Public Health, and Biotech.; Austin, TX (abs. deadline: Dec. 31) [L. Bockoven, 800/262-2472, Fax: 512/471-2445, Internet: *compmed94@chpc.utexas.edu*]

25–27. Gene Therapy: New Technologies & Applications; CHI, Bethesda, MD [see contact: Feb. 28–Mar. 2]

26–28. Natl. SBIR Conf.; Houston [Hotline, 407/791-0720, Fax: -0098]

27–May 1. Zebrafish Development and Genetics; Cold Spring Harbor, NY [CSHL, 516/367-8346]

28–29. Modulation of Signal Transduction & Gene Expression; CHI, Bethesda, MD [see contact: Feb. 28–Mar. 2]

May

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]

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; CSHL, Cold Spring Harbor, NY [see contact: Apr. 27–May 1]

19. †Joseph Nadeau: Mouse Genome Informatics; Bethesda, MD [see contact: Mar. 17]

20–22. 2nd Chromosome 13 Intl. Workshop; Groningen, The Netherlands [C. Buys, +31-50/63-29-48, Fax: -47 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, Computing, and Complex Genome Analysis; Tallahassee, FL [P. Meredith, 904/644-1010, Fax: -0098]

1–8. Symposium: Mol. Genetics of Cancer; CSHL, Cold Spring Harbor, NY [see contact: Apr. 27–May 1]

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]

7–10. BioWest 94; San Diego [BioConferences Intl., 301/652-3072, Fax: -4951]

8. PCR: Applications, Alternative Technologies & New Techniques; CHI, San Francisco [see contact: Feb. 28–Mar. 2]

16. †Shirley Tilghman: Genetics of Neural Crest Development in Mice; Bethesda, MD [see contact: Mar. 17]

August

9–12. Interconnection of Mol. Biol. Databases; Stanford, CA (abs. deadline: Mar. 11) [P. Karp, 415/859-6375, Fax: -3735, Internet: *pkarp@ai.sri.com*]

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*

February

23–May 11. Incorporation of Genetics into Clinical Practice; Wednesdays, 3–5:30 p.m., Washington, DC [L. Brown, 202/687-8635, Fax: -1954]

March

5–9. Advanced Bioethics Course V; Kennedy Institute, Washington, DC [M. Favreau, 202/687-6771, Fax: -6770]

7–11. In Situ Hybridization and rDNA Technol.; Columbia, MD [Exon-Intron, 410/730-3984, Fax: -3983]

7–11. In Situ Hybridization Techniques; Germantown, MD [LTI, 800/952-9166, Fax: 301/258-8212]

7–11. Recombinant DNA Methodology; Washington, DC [CATCMB/CUA, M. Miller, 202/319-6161, Fax: -4467]

10–11. Tissue In Situ Hybridization; San Francisco [Oncor, Inc., 800/776-6267, Fax: 301/926-6129]

11–12. Mol. Biol. and Recombinant DNA Technol.; San Diego [ACS, 800/227-5558, Fax: 202/872-6336]

11–12. Practical Capillary Electrophoresis; ACS, San Diego [see contact: Mar. 11–12]

14–18. PCR Techniques; LTI, Germantown, MD [see contact: Mar. 7–11]

20–25. Psychoneurogenetics; Ventura, CA [GRC, 401/783-4011, Fax: -7644]

*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.
†NCHGR-funded event.
‡DOE-funded event.

21–25. Recombinant DNA Methodology; Exon-Intron, Columbia, MD [see contact: Mar. 7–11]

24–25. Metaphase and Interphase Chromosome Analysis; Oncor, Inc., Gaithersburg, MD [see contact: Mar. 10–11]

April

6–19. Cloning and Analysis of Large DNA Molecules; Cold Spring Harbor, NY [CSHL, 516/367-8346]

18–19. GDB/OMIM Training Courses [see schedule, p. 11]

18–22. Baculovirus Techniques; LTI, Germantown, MD [see contact: Mar. 7–11]

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

25–29. RNA Isolation & Characterization; Exon-Intron, Columbia, MD [see contact: Mar. 7–11]

26–27. Quantitative RNA-PCR; BTP, Houston [see contact: Apr. 25]

28–29. Basic Cloning and Hybridization Techniques; BTP, Houston [see contact: Apr. 25]

May

2–6. Recombinant DNA Techniques I; LTI, Germantown, MD [see contact: Mar. 7–11]

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

22–24. PCR Techniques; CATCMB/CUA, Washington, DC [see contact: Mar. 7–11]

23–27. Basic Cell and Tissue Culture; CATCMB/CUA, Washington, DC [see contact: Mar. 7–11]

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

24–27. DNA Sequencing; CATCMB/CUA, Washington, DC [see contact: Mar. 7–11]

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

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

June

5–11. Intensive Bioethics Course XX; Kennedy Institute, Washington, DC [see contact: Mar. 5–9]

6–10. Expression of Recombinant DNA in Mammalian Cells; CATCMB/CUA, Washington, DC [see contact: Mar. 7–11]

6–11. cDNA Library Techniques; LTI, Germantown, MD [see contact: Mar. 7–11]

10–30. Advanced Bacterial Genetics; CSHL, Cold Spring Harbor, NY [see contact: Apr. 6–19]

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

13–17. DNA Binding Proteins and Transcriptional Regulators; CATCMB/CUA, Washington, DC [see contact: Mar. 7–11]

July

5–29. Summer Program on Mol. Biol.; Minneapolis (application deadline: May 6) [IMA, A. Friedman, 612/624-6066, Fax: 626-7370]

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)

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

Solicitations for proposals are announced in the *Federal Register*, *Science*, and other publications. Proposals for FY 1995 will be due in summer 1994.

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

- 301/903-6488, Fax: -8521, or Internet: *genome@oerhp01.er.doe.gov*

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 conference (407/791-0720): Houston, TX (April 26–28, 1994).

NIST Advanced Technology Program

Proposals for the current cycle are due March 15. More information is given in the article on page 5.

National Science Foundation

NSF 93-172. The Academic Research Infrastructure Program (ARI) of NSF is designed to improve the condition of U.S. research equipment and facilities in all disciplines. NSF is soliciting proposals to support instrumentation development and acquisition from institutions of higher education, independent nonprofit research institutions, research museums, and consortia of these entities. About $55 million is available for FY 1994. Cost sharing is required, with the 50% level strongly encouraged. The proposal success rate for the previous ARI competition was about 26%. Submission deadline: March 15. For further information, contact Office of Science and Technology Infrastructure; ARI; NSF; 4201 Wilson Boulevard, Room 1270; Arlington, VA 22230 (703/306-1040, Internet: *ari@nsf.gov*, BITNET: *ari@nsf*).] ◊

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4. ___ *Meeting Report: DOE Informatics Summit*—DRAFT (April 26–27, 1993, Baltimore, Maryland)

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AACR Am. Assoc. for Cancer Res.
ACS Am. Chem. Soc.
ASBMB Am. Soc. for Biochem. and Mol. Biol.
ATCC Am. *Type Culture* Coll.
CATCMB/CUA Ctr. for Advanced Training in Cell and Mol. Biology/Catholic Univ. of Am.
CF cystic fibrosis
CHI Cambridge Healthtech Inst.
CSHL Cold Spring Harbor Laboratory
DOE Dept. of Energy
GDB/OMIM Genome Data Base/Online *Mendelian Inheritance in Man*
GRC Gordon Res. Conferences
HGP Human Genome Project
IMA Inst. for Mathematics and its Applications
LTI Life Technologies, Inc.
NCHGR Natl. Ctr. for Human Genome Res.
NIH Natl. Inst. of Health
PSC Pittsburgh SuperComputing Ctr.
SBIR Small Business Innovation Res.

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