Human Genome news

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STS – New Strategy May Provide Common Link for Mapping

Achievement of some of the 5-year goals of the U.S. Human Genome Project relies heavily on the use of the new sequence tagged site (STS) strategy for mapping. The following specific goals make use of this strategy:

- Completion of a fully connected genetic linkage map of human chromosomes with markers, each identified by an STS and spaced an average of 2 centiMorgans (cM) apart with gaps no greater than 5 cM.
- Compilation of STS physical maps of all human chromosomes with markers spaced at approximately 100,000-bp intervals.

What are STSs and Why Are They So Important to the Project?

An STS is a short DNA sequence that uniquely identifies a mapped gene or other marker. The order and spacing of these sequences compose an STS map. A year ago, a new mapping strategy using STSs was enthusiastically received by the scientific community because it promised to solve some of mapping's thorniest problems by providing mappers with a common language and a system of landmarks. The STS approach was made possible by development of the polymerase chain reaction (PCR), which allows rapid production of multiple copies of a specific DNA fragment, for example, an STS fragment.

STSs Will Aid Integration of Diverse Mapping Data

A major challenge in generating a complete physical map has been the difficulty in comparing directly the results obtained by different mapping methods and in combining maps constructed by different techniques into a consistent whole. Cosmids, yeast artificial chromosomes and other recombinant DNAs are being used to produce physical maps as libraries of ordered clones. STSs are expected to be invaluable in solving the problem of combining data from different kinds of recombinant DNAs. For more information on mapping, see sidebar on p. 2.

In This Issue...

Mapping and Sequencing

STSs Should Save Money, Effort, Time

How will STSs Facilitate Mapping?

If physical mapping of human chromosomes is to be achieved within 5 years, continuity of physical mapping data over long stretches of DNA is necessary. With STSs, laboratories would use whatever mapping techniques they choose; however, results would always be reported in terms of the STS markers (i.e., in the same language). Therefore, each mapped element (individual clone, contig, or sequenced region) would be defined by a unique STS – a short DNA sequence that has been shown to occur only once in the genome. A crude map of the entire genome, showing the order and spacing of STSs, could then be constructed.

Because almost all mapping methods use cloned DNA segments as landmarks, establishing an STS would require the investigator to determine a short sequence of DNA that defines the landmark. These sequences can be used to synthesize two PCR primers. The primers can then be combined with genomic DNA and DNA polymerase to produce millions of copies of the STS target DNA sequence in a few hours. The PCR-amplified DNA is thus available in sufficient quantity to be characterized further by hybridization, electrophoresis, or sequencing.

Sequence information generated in this way could be recalled easily and, once reported to a database, would be available to other investigators. With the STS sequence stored electronically, there would be no need to obtain a probe or any other reagents from the original investigator. No longer would it be necessary to exchange and store hundreds of thousands of clones for full-scale sequencing of the human genome – a significant saving of money, effort, and time. By providing a common language and common landmarks for mapping, STSs will allow genetic and physical maps to be cross-referenced.

Additional benefits include the following:

- STSs are expected to reduce labor costs, to confirm overlap between clones, and to provide one means of quality control for DNA sequencing efforts.
- The use of radioisotopes for mapping experiments should be reduced by the substitution of PCR reactions for hybridization experiments.
- STS-based techniques will be affordable for small laboratories as well as large ones; all could contribute to the data and draw from it.

Joint Mapping Working Group

An established standard for reporting data will be necessary to make the STS concept usable. Toward this end, the Joint Mapping Working Group met in March at Los Alamos National Laboratory (LANL) to develop a working standard of STSs for the Human Genome Project. They tentatively agreed that STSs would be reported as pairs of oligonucleotide primers that have been tested and shown to produce a PCR product that identifies a single band in a Southern

(see STS, p. 16)

How Will the STS Strategy Be Used in Mapping?

Mapping is the process of determining the relative position and spacing of genes or other landmarks on chromosomes. The two types of maps, genetic and physical, differ both in the methods used to construct them and in the way distance between landmarks is measured. Mapping human genes began early in the twentieth century but has been intensively pursued for only 2 decades. Recent improvements in technology have led to more extensive mapping; even so, less than 2000 of the 50,000 to 100,000 human genes have been mapped.

Genetic Map 5-Year Goal: 600–1500 Index Markers

The genetic map, or genetic linkage map, displays the relative positions of genetic markers (such as an identifiable DNA sequence or genes associated with a physical trait or disease) on a chromosome; distance is measured in centiMorgans (cM). Genetic maps have many uses, including identification of loci associated with genetic diseases, and they form an essential backbone needed to guide physical mapping efforts. Because genes that lie close together on a chromosome have a much higher chance of being inherited together than genes that are farther apart, genetic maps are often produced by studying families to determine how frequently two traits are inherited together.

Advances in genetic mapping tools have helped to make the goals of the Human Genome Project possible. The number of useful DNA index markers (such as restriction fragment length polymorphisms) has increased dramatically in the past 2 years, but about 3000 well-spaced (1 cM apart) and informative markers will be needed to achieve a completely linked framework map. The project's 5-year goal is to create a 2- to 5-cM map, which will require

Neurofibromatosis Gene Discovered

Researchers affiliated with the Howard Hughes Medical Institute (HHMI) – one group at the University of Utah School of Medicine and another at the University of Michigan Medical School – have identified the gene believed to be responsible for von Recklinghausen neurofibromatosis (NF1), the most common nervous system disease caused by a single gene defect. These investigators also uncovered a rare biological feature that emphasizes the complexity of human genetics.

The findings were reported in the July 13 issues of two journals: *Cell* [**62**: 187–192, 193–201 (1990)] by Raymond White, leader of the research team at Utah, and *Science* [**249**: 181–186 (1990)] by Francis Collins, who directs the Michigan group. White and his team earlier identified mutations that lead to colon cancer and retinoblastoma (see related articles, p. 12). In 1989 Collins and a group of collaborators in Canada identified the gene for cystic fibrosis, the most common fatal genetic disorder among Caucasians.

The NF1 form of neurofibromatosis affects more than 1 in 4000 newborns, with symptoms ranging from skin discoloration and learning disabilities to debilitating and sometimes fatal tumors of the peripheral nervous system. As many as 100,000 Americans have the disease. Children with one parent having a defective NF1 gene have a 50% chance of developing the disease. Nearly half of all cases of NF1 are not inherited, however, but are caused by new genetic mutations that occur early in development. NF1 often escapes detection until age 4 or 5, but if the gene discovery aids in early diagnosis, effective intervention may someday be possible.

Neurofibromatosis was mistakenly believed to be the cause of the deformities of Joseph Merrick, a nineteenth century Englishman who became known as "the Elephant Man" and was the subject of a popular movie and play. Health experts have since concluded that Merrick suffered from a different disorder – Proteus syndrome.

Since the protein product of the defective NF1 gene had not been isolated, investigators used the relatively new approach sometimes referred to as reverse genetics or positional cloning. This method of locating disease genes has succeeded with six others, including those for cystic fibrosis, muscular dystrophy, retinoblastoma, and Wilms' tumor.

In 1987 a group of medical statisticians led by Mark Skolnick (University of Utah) collaborated with White's group to use genetic linkage studies to establish the NF1 locus on chromosome 17. Linkage studies further narrowed the area to which the NF1 gene could be located, and the Michigan and Utah researchers employed novel techniques such as chromosome jumping (developed by Collins' group) and yeast artificial chromosomes.

(see NF Gene, p. 4)

Research Update:

White's laboratory at the University of Utah has predicted a function for the NF1 protein, raising hope that neurofibromatosis may one day be treatable. See August 10 issue of *Cell* [62: 599–608 (1990)]

600 to 1500 index markers, each identified by an STS.

Physical Map: Technology Improvements Making Construction Easier

Physical maps can be constructed in a variety of ways; distance is measured in units of physical length, such as numbers of nucleotide pairs. These maps are used as the basis for isolation and characterization of individual genes or other DNA regions of interest, as well as to provide the starting point for DNA sequencing.

Physical maps can be categorized into two general types. The cytogenetic physical map, which is based on light microscopy, indicates the location of genes or markers relative to visible chromosome bands. Another type of cytogenetic physical map (i.e., the long-range restriction map) records the order of and distance between restriction sites on chromosomes. The second type of physical map consists of cloned DNA pieces that represent a complete chromosome or chromosomal segment, together with information about the order of the cloned pieces.

Technology for the construction of overlapping clone sets (contigs) is continually improving, and the new STS strategy is being developed to decrease the need for cloning but still allow the investigator access to the DNA to be sequenced. Initial stages in constructing physical maps of large genomes are becoming easier and faster because of improvements in pulsed-field gel electrophoresis, yeast artificial chromosome cloning, the polymerase chain reaction, fluorescent in situ hybridization, and radiation hybrid analysis. [For more information, see "Physical Mapping of Human DNA: An Overview of the DOE Program," *Human Genome Quarterly*, 1(2): 1–6 (Summer 1989).] ◇

Mapping and Sequencing

NF1 Gene Research Sponsors:

- HHMI
- National Neurofibromatosis Foundation
- NIH National Institute of Neurological and Communicative Disorders and Stroke

NF Gene *(from p. 3)*

The Utah scientists recognized that a well-studied region of mouse DNA suspected to be involved in murine leukemia was similar to DNA sequences that mapped to the 50 kb of DNA between the NF1 translocations; they characterized three small genes in this region, but none of the three showed NF1-specific point mutations. In intensive comparative studies of normal and NF1 individuals, both research groups identified and sequenced complementary DNA clones from a region showing rearrangements of genetic material in NF1 patients and predicted that the fourth gene in the translocation region would be likely to cause neurofibromatosis. The Utah researchers found NF1-specific point mutations in the gene's coding region, proving that this gene causes NF1.

Less than a month after publication of the NF1 gene's partial DNA sequence, White's group published findings that extended the sequence and examined the predicted NF1 peptide for similarities with known proteins [*Cell* **62**: 599–608 (1990)]. These studies suggested a functional homology of the NF1 peptide and the catalytic domain of the mammalian GTPase-activating proteins and their yeast counterparts, IRA1 and IRA2. The genes coding for these proteins are known to be involved in the mechanisms controlling cell growth and differentiation.

Taken together, these studies suggest that the NF1 gene controls cell growth; when the gene malfunctions, cells grow out of control and cause tumors. Collins noted that NF1 patients have a slightly higher risk for brain tumors and various other cancers, so studies of the NF1 gene may also yield new insights into various malignancies.

Identification of the NF1 gene also disclosed a rare biological feature that may have far-reaching implications: the three smaller genes are embedded in the NF1 gene and are oriented in the opposite direction; this is only the second time genes located within other human genes have been reported. Jane Gitschier at the University of California, San Francisco, recently reported finding a separate gene of unknown function embedded within the gene responsible for classic hemophilia (the factor VIII gene). This embedded gene was also in reverse orientation [*Genomics* 7(1): 1–11 (1990)].

Commenting on this unusual finding, Collins remarked that genes may be much more complex than previously thought. The embedded genes may have some function in the regulation of gene expression and may have implications for researchers looking for disease genes. These genetic challenges underscore the timeliness of the Human Genome Project, which seeks to identify all 50,000 to 100,000 genes. ◊

Researchers shown below are among those who participated in the discovery of the NF1 gene.

Francis Collins' group at the University of Michigan (upper photograph): (1st row, l. to r.) Susan Wilson-Gunn, Lone Andersen, Collins, Roxanne Letcher, and Bernice Sandri; (2nd row) David Gutmann, Douglas Marchuk, Jane Nicholson, Margaret Wallace, Ann Saulino, and Steve Hayes.

Ray White's group at the University of Utah (lower photograph): (seated) Peter O'Connell, White, and Dave Viskochil, (standing) Melanie Culver, Robert Weiss, Margaret Robertson, Gang Feng Xu, Richard Cawthon, and Diane Dunn.

Genome Project Can Benefit Search for Disease Genes

An Investigator's Perspective by Francis Collins

Francis S. Collins

Francis S. Collins is Chief of Medical Genetics at the University of Michigan Medical Center and an investigator with the Howard Hughes Medical Institute. Both a researcher and a practicing medical doctor, Collins is one of the most successful of the gene hunters. His group identified the genes that cause cystic fibrosis and neurofibromatosis and are now searching for the Huntington's disease gene. Next on their hit list is the gene that regulates production of hemoglobin. In this article, Collins gives his perspective on the importance and relevance of the Human Genome Project in the search for clues to genetically caused diseases.

The Human Genome Project, whose goal is the mapping and sequencing of all the DNA in human chromosomes, is widely believed to be an idea whose time has come. Extensively debated in the scientific community and reviewed by numerous scientific and lay advisory panels during the past 5 years, the genome project promises to open the way to true understanding of the basis for human health and disease.

One year ago, the gene related to cystic fibrosis (CF) was identified as a result of an international collaborative effort between my research group and that of Lap-Chee Tsui and Jack Riordan of Toronto's Hospital for Sick Children. When one considers all the work performed by the more than 2 dozen laboratories involved in this effort over 10 years, the cost of finding the CF gene is probably in the vicinity of $50 million to $100 million. Yet locating the gene responsible for cystic fibrosis was regarded as one of the more straightforward and solvable genetic problems because CF occurs with high frequency in the population and is caused by a single gene.

If the sets of overlapping clones and panels of genetic markers now being developed in the nascent Human Genome Project had been available for use in our quest for the CF gene, identification of that gene would have occurred considerably earlier. Similarly, the search for the neurofibromatosis (NF1) gene – a search that recently led to the almost simultaneous cloning of the gene by my group and by Ray White's group in Utah – would have greatly benefited by the prior existence of a robust genetic map and a set of overlapping clones.

Over 3000 genetic markers are known today; genome project investigators are locating additional markers at increasingly rapid rates for use by genome project researchers and gene hunters alike. Through this effort and the construction of overlapping sets of ordered clones, the genome project is developing the tools to identify more of the genes responsible for different diseases.

Carried out in a traditional manner, the search for the myriad genes responsible for more complex diseases such as Alzheimer's, cancer, or schizophrenia would be unnecessarily costly and wasteful of scientists' time. The Human Genome Project is not just a convenient alternative; it is organized to achieve the specific goals of systematically mapping and sequencing human genes, and it is likely to be the only viable approach for identifying major genetic influences that affect the health of everyone. Without the data arising from the project, progress in identifying genes for common multigenic disorders would be unacceptably slow.

The project will stimulate more investigator-initiated research because generated data will spin off thousands of research projects over the course of the next few decades. Individual investigators will be able to use information generated by the genome project to pursue their own creative ideas.

A large number of highly talented individuals have recognized the promise of this effort and have shifted their own research priorities to help in attaining the goals of the Human Genome Project. It is critical to continue the planned funding program to get the project under way in an effective manner and to retain the creative people involved. ◇

Human Genome news

NATIONAL INSTITUTES OF HEALTH

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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Genome News

Program Advisory Committee on the Human Genome

Next PACHG Meeting:
December 3

The NIH Program Advisory Committee on the Human Genome (PACHG) convened in Bethesda, Maryland, on June 18 to hear scientific presentations on genomic research, review reports from the National Center for Human Genome Research (NCHGR) and the joint working groups, and discuss administrative and other issues and events related to the Human Genome Project.

After welcoming the committee members (see table on p. 7 for members and their affiliations) and guests, Chairman Norton Zinder remarked that antipathy toward the project was evident in the scientific community. This antipathy, he said, seems to stem in part from the erroneous perception that the genome project has caused a decrease in NIH funding for other research. He encouraged participants to promote the program and to dispel misperceptions through communication with their colleagues.

NCHGR Presents Ideas for New Initiatives

NCHGR Deputy Director Elke Jordan compared funding estimates for FY 1991 with those of the FY 1991 President's budget, which includes increases for research centers and training. She also discussed the NCHGR award rate, professional seniority and geographic distribution of grantees, and distribution of awards among the areas of mapping, sequencing, and technology development.

The meeting continued with scientific presentations on advances in genomic research. Robert Waterston (Washington University) described a project being conducted in collaboration with Cambridge University scientists to map and sequence the genome of the roundworm *Caenorhabditis elegans*. Thomas Brennan (Genomyx, Inc.) reported on efforts to develop new sequencing technology, and David Housman (Massachusetts Institute of Technology) discussed progress in mapping chromosome 11, specifically in isolating the Wilms' tumor gene.

PACHG members adopted a resolution expressing appreciation to the Centre d'Etude du Polymorphisme Humain (CEPH) (see sidebar below).

The afternoon session began with presentations by NCHGR staff on concepts for new initiatives. Bettie Graham described a proposed program announcement designed to be more specific than the previous one and to incorporate the objectives outlined in the 5-year plan. She added that the new program announcement would emphasize technology development and collaborative research and establish research objectives in genetic and physical mapping, sequencing, and informatics. She also discussed the NCHGR new minority initiative; to enable minority students or faculty to attend meetings or courses relevant to the Human Genome Project, the program would provide travel supplements to active

(see PACHG, p. 7)

CEPH Resolution Adopted by PACHG

At its June 18 meeting, the NIH PACHG passed a resolution to express appreciation to CEPH for contributions to the genome project effort and the hope that CEPH will continue to play a role in this important initiative. Following is the text of the resolution:

"In the context of the genetic mapping effort, the Advisory Committee particularly recognizes the continuing participation of the CEPH in Paris. Their collection of mapping family resources and provision of DNA and data services to facilitate consensus map construction constitute the premier example of productive, long-term, and truly international collaboration. The committee notes with appreciation CEPH's interest in continuing their contributions using mainly internal and French government funds as well as their cooperation in making cell lines and genotypes available in a timely way. The committee appreciates CEPH's interest in furthering collaboration by expanding family resources and data services. It makes much easier and faster the large task of making a better, more generally useful genetic map."

CEPH Public Database Issued

CEPH, which intends to coordinate internationally the production of primary consortium maps for each human chromosome, recently announced the availability of the first issue of the CEPH public database, containing 799 genetic markers. The database contains genotypes for all genetic markers, mostly DNA polymorphisms, that have been tested and contributed to CEPH as of January 1, 1990, including those used in construction of the CEPH consortium map of chromosome 10 [*Genomics* 6: 393–412, 575–577 (1990)]. To receive the database, available on a 5.25-in. disk, and a book of LOD scores and recombination-frequency estimates for syntenic markers in the database, write to CEPH; 27 rue Juliette Dodu; 75010 Paris, France. ◇

Joint NIH-DOE Subcommittee

The second meeting of the Joint NIH-DOE Subcommittee on the Human Genome convened in Bethesda, Maryland, on June 19 to discuss administrative issues, reports of the joint working groups, policies for sharing data and materials, the role of the Human Genome Organisation (HUGO), and the agenda for the annual retreat. (See table for list of members and their affiliations.)

Cochair Sheldon Wolff opened a discussion of DOE and NIH draft policy statements on sharing data and materials. Elke Jordan noted that the NCHGR draft was intentionally nonspecific because working groups were still discussing issues related to sharing and because NIH was exploring sharing issues with respect to grant regulations. Until more specific guidelines can be developed, community consensus and peer pressure must serve to encourage sharing. The NIH policy has been to expect sharing at the time of publication.

Describing the DOE policy draft, Benjamin Barnhart remarked that the DOE document outlined specific requirements for areas such as cell lines, libraries, vectors, clones, probes, and mapping and sequencing data. He emphasized that the intent was to establish sharing guidelines, not to address enforcement issues.

(see Subcommittee, p. 8)

Subcommittee December 4 Meeting Topic: Communication

PACHG *(from p. 6)*

genome-related research grants. A third initiative, for pilot projects or feasibility studies for genomic analysis, would encourage high-risk proposals for which there are no preliminary data. Grants would be limited to approximately $100,000 and a maximum of 2 years.

Jane Peterson outlined the content of a proposed RFA (Request For Applications) on sequencing. This RFA would incorporate the Joint Sequencing Working Group's suggestion that large-scale pilot projects attempt to sequence about 3 Mbp of contiguous DNA segments within 3 years.

Mark Guyer briefed the committee on a proposed RFA to support development of the framework genetic linkage map consisting of index markers; the map was described by the Joint Mapping Working Group. He emphasized that NCHGR considered the availability of maps and markers developed with the support of NCHGR to be essential. Investigators will be urged to deposit index markers in a central repository.

The final discussion focused on setting an agenda for the annual NIH and DOE retreat, held to assess progress in meeting the 5-year plan goals. Zinder believed an examination of the Human Genome Project's approach to communicating with the scientific community should be among the issues addressed. David Botstein called for increased efforts to communicate the fact that the program represents "good science" and that its goals are achievable. He added that although the community's concern about restricted funding is understandable, the Human Genome Project is not the cause of the problem. ◊

Submitted by Leslie Fink, NCHGR Office of Human Genome Communication

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Genome News

NCHGR Meets With Minority Group

NCHGR, DOE, RCMI Grantees To Finalize Participation Plan at Fall Meeting

Staff of the National Center for Human Genome Research (NCHGR) met on July 20 with members of the Association of Minority Health Professional Schools (AMHPS) and researchers supported by the Research Centers in Minority Institutions (RCMI) to discuss how minority institutions can become involved in the Human Genome Project. The meeting, held in Nashville and hosted by Meharry Medical School, was sponsored by RCMI and NCHGR.

RCMI, comprising 17 institutions, is a grant program supported by the NIH National Center for Research Resources (NCRR). The primary goal of RCMI is to enable predominantly minority institutions offering doctoral degrees in health and science professions to compete more effectively for research grants in the biomedical and behavioral research mission of the Public Health Service. The FY 1990 operating budget for the RCMI program is $19 million: $17.5 million appropriated by Congress and $1.5 million provided through cofunding from the National Institute of Allergy and Infectious Diseases. The RCMI program is directed by Sidney A. McNairy, Jr. (NCRR).

The opening address of the 2-day meeting was given by David Satcher (Meharry Medical College). Robert A. Whitney (NCRR Director) gave an overview of NCRR programs, and Elke Jordan (NCHGR Deputy Director) reviewed and discussed the 5-year goals of the Human Genome Project. Seven scientific presentations by NCHGR and RCMI grantees followed.

Mark Guyer (NCHGR Assistant Director for Program Coordination) described NCHGR programs and resources, and RCMI representatives gave brief presentations about their respective university's interests and capabilities for taking part in the Human Genome Project. A panel discussion on obstacles and opportunities for participation by scientists in minority institutions was coordinated by Bettie Graham (Chief, Research Grants Branch, NCHGR). Panel members were Georgia Dunston (Howard University), Terrance Lyttle (University of Hawaii), George Hill (Meharry Medical College), Mary-Claire King (University of California, Berkeley), Stephen Warren (Emory University School of Medicine), Bruce Roe (University of Oklahoma), and Jordan.

A session primarily for RCMI and AMHPS participants included information sharing and demonstrations of software. RCMI representatives discussed development of a plan by which member institutions could share in the Human Genome Project. ◇

Reported by Bettie J. Graham, Chief
Research Grants Branch
NIH NCHGR

NCHGR Invites Grant Applications

NCHGR invites applications for funding of research related to the Human Genome Project in the following categories:

1. Use of the National Research Service Award to support predoctoral students and postdoctoral fellows interested in genome research (receipt dates are September 10, January 10, and May 10);
2. Pilot projects or feasibility studies to support creative and novel high-risk/high-payoff research in human genomics;
3. Support for research that will significantly advance progress toward achieving the scientific goals of the Human Genome Project; and
4. Assistance awards for research into the isolation of highly polymorphic genetic linkage markers and their use for the development of a framework linkage map of the human genome.

For information on the first three items above, contact:
Bettie J. Graham; NIH NCHGR; Building 38A, Room 610; Bethesda, MD 20892;
(301) 496-7531; Internet: B2G@CU.NIH.Gov.; Bitnet: B2G@NIHCU.
For the fourth item, contact:
Mark S. Guyer; NIH NCHGR; Building 38A, Room 605; Bethesda, MD 20892;
(301) 496-0844; Internet: GY4@CU.NIH.Gov.; Bitnet: GY4@NIHCU. ◇

Subcommittee *(from p. 7)*

Charles Cantor presented an update of HUGO activities. HUGO has recently received private funding and anticipates additional support from foreign governments. The organization is expanding this year by over 100 members to broaden both the subject and geographic areas represented. Former NIH Director James Wyngaarden will serve as HUGO's corporate executive officer, effective July 1, 1990.

HUGO's short-term focus will be to form committees to help coordinate genetic and physical mapping of each human chromosome; some committees will evolve from existing ones, while others will be created as needed. Cantor added that HUGO has established a seven-member committee charged with advising on physical and genetic mapping.

Established in 1988, the subcommittee coordinates activities of the joint working groups and facilitates coordination between the NIH and DOE human genome programs. ◇

Submitted by Leslie Fink, NCHGR
Office of Human Genome Communication

Joint Sequencing Working Group To Serve Agencies in Technology Awareness

The NIH-DOE Joint Sequencing Working Group met for the first time on May 10 in Herndon, Virginia. The Sequencing Working Group will report to the Joint DOE-NIH Subcommittee on the Human Genome about all aspects of sequencing so the agencies can make well-informed decisions and formulate programs to accomplish the goals of the genome project.

Discussion Topics

1. Role of the Joint Sequencing Working Group.

Sequencing programs are multidisciplinary, so this working group's objectives will necessarily overlap those of the mapping and informatics working groups. Because technology for mapping and sequencing is evolving so rapidly, the working groups and the agencies' staffs must inform the scientific community about changing technology in the field.

2. Federal Sequencing Program Support.

NIH currently funds about $1 million a year for sequencing and $1.5 million for developing sequencing technology. DOE spends about $5.7 million annually on sequencing technology development and is considering a program to sequence cDNAs in support of physical mapping activities.

3. Current Large Sequencing Projects.

Sequencing bacterial DNA has taken longer than expected because of problems in managing the large amount of data and in reading autoradiographs. Two efforts to sequence *Escherichia coli* have each resulted in nearly 100 kbp of finished sequence and are expected to generate data considerably faster in the future.

Automated sequencers can produce 7000 to 8000 bp of raw DNA sequence per day for each machine, with greater than 99% accuracy. Several laboratories have recently completed 100 kbp in several months and expect to complete I Mbp in the next year. Automation of sample preparation and data handling will cut labor costs, which account for the largest part of the sequencing expense.

Working Group Conclusions

- New technology and innovative projects should be supported to meet the goal of reducing the cost of sequencing. Reasonable goals are to use large contiguous segments of DNA to sequence an aggregate of 10 Mbp and to lower the cost to $.50 or less per base pair. Careful attention must be paid to error rates, and the sequenced regions of DNA should be those of most interest to the scientific community.
- Sequencing limited regions of genomic DNA should not be funded at this time. Even with NIH and DOE subsidizing the effort, the total cost of sequencing small regions of DNA would be very high, and current investment should go into technology development.
- Sequencing at the mid range (< 500 kbp) should be supported only when the region is extremely interesting biologically.
- Data generated from sequencing should usually be available to the community within 3 to 6 months, and in no case should sequence data be held longer than a year. An aggressive policy is needed to ensure timely release of information.

For a list of members, see *HGN* **2**(2): 4 (July 1990). ◇

NIH Genome Research Review Committee Established

NIH Acting Director William F. Raub recently announced the establishment of the Genome Research Review Committee to achieve greater consistency of review and more efficient evaluation of applications and proposals.

The committee will provide a primary review of applications for research and training grants related to the NIH Human Genome Program, a function previously carried out by ad hoc review groups.

About 100 applications are expected to be assigned to the committee each year, including grant applications, cooperative agreements, contracts, proposals for program projects and centers, institutional training fellowships, conference proposals, and special developmental award programs. The 18 committee members will be outstanding authorities in the scientific fields that fall within the committee's jurisdiction. ◇

Genome News

Anthony V. Carrano
Director
Center for Human Genome Research
Lawrence Livermore National Laboratory

DOE Establishes Center for Human Genome Research at LLNL

Secretary of Energy James D. Watkins has directed the department's Lawrence Livermore National Laboratory (LLNL) in Livermore, California, to establish a center to study the human genome. The Human Genome Center will be directed by Anthony V. Carrano, Genetics Section Leader in the Biomedical Sciences Division and member of HUGO, the DOE Human Genome Coordinating Committee, and the Joint DOE-NIH Subcommittee on the Human Genome. The Livermore Center becomes the third DOE center for human genome research. The other two are at Lawrence Berkeley Laboratory (LBL) in Berkeley, California, and at Los Alamos National Laboratory (LANL) in Los Alamos, New Mexico.

"I am excited about the work that Livermore will now do as a center," said Admiral Watkins. "The quality of their current work in the area justifies the creation of the center. The stature of DOE's genome program is growing, and it is appropriate that the stature of the work in our laboratories grows as well. The center is another example of the advantage of using the multidisciplinary resources of our national laboratories to contribute to an important national project."

Livermore is already participating in the Human Genome Project; research at the Livermore center includes the following:

- continued physical mapping of chromosome 19 [*Human Genome 1989–90 Program Report*, DOE (1990)], which contains several genes important to the repair of damaged DNA;
- investigation of new approaches to physical mapping of chromosomes [*Genomics* **4**: 129–136 (1989)];
- continued participation with LANL in the National Laboratory Gene Library Project (NLGLP) [*HGN* **2**(1): 12–13 (May 1990)]; and
- development of new computer software to analyze physical maps and graphically display resulting data (*Genomics*, 1990, in press).

Other activities will involve instrument development, including an image-analysis system used in fluorescent in situ hybridization studies; a general robotic tool to automate the handling of DNA and relieve researchers of highly repetitive tasks; and scanning tunneling microscopy/spectroscopy for cost-effective, high-volume DNA sequencing.

The LLNL Biomedical Sciences Division has been involved in genetics research for 20 years, and its human genome work is building on expertise and research in molecular biology, cytogenetics, mutagenesis, computational sciences, and instrumentation, as well as its participation in the NLGLP. Livermore researchers have already mapped about 60% of chromosome 19 and have identified 3 genes that code for DNA repair.

The short-term goal of the department's Human Genome Program is to provide computational, engineering, and biological research capabilities needed to reduce the cost and increase the speed of DNA analysis. The long-term goal is to construct high-resolution physical maps of human chromosomes – the ultimate map being the DNA sequence. As part of the DOE mission to evaluate health effects of energy production and by-products, the agency is spending $26 million on the Human Genome Program this fiscal year and is requesting $46 million for the program in FY 1991. ◇

Shown below are LLNL Human Genome Center researchers Jesse Combs (pipetter in hand) and Nancy Allen assessing chromosome 19 clones for viability in fingerprinting.

Postdoctoral Fellowships Offered by DOE

The DOE Office of Health and Environmental Research (OHER) has recently established the Human Genome Distinguished Postdoctoral Research Program. It will provide recent doctoral-degree recipients with funding to conduct genome-specific research at approved DOE and university laboratories.

The program developed from a 1988 recommendation of the DOE Energy Research Advisory Board to "increase support through expansion of the targeted [science and engineering] graduate and postgraduate research fellowship programs with emphasis given to energy-related areas of greatest projected human resource shortages."

The genome postdoctoral program is modeled on the successful Alexander Hollaender Distinguished Postdoctoral Fellowship Program, initiated in 1986 by DOE OHER. The Hollaender Fellowships provide support in all areas of OHER-sponsored research; several fellows have been involved in research related to the genome project. Both postdoctoral programs are administered by Oak Ridge Associated Universities (ORAU), which is a university consortium and DOE contractor.

Applicants must be either U.S. citizens or permanent resident aliens and must have recently completed an internship or residency or received a research doctoral degree within 2 years of the desired starting date. The first-year stipend will be $35,000. A total of ten postdoctorates will be sponsored annually when the program is fully operational, with up to five new awards announced each year.

Program literature and application packets will be available in October; the application deadline is January 15, 1991. ◇

Application Deadline:

January 15, 1991

For additional information, contact:

Human Genome (or Hollaender) Distinguished Postdoctoral Research Program
Science/Engineering Education Division
ORAU
P. O. Box 117
Oak Ridge, TN 37831-0117
(615) 576-4805

UNESCO/TWAS Fellowships Announced

The United Nations Educational, Scientific and Cultural Organization (UNESCO) and the Third World Academy of Sciences (TWAS) recently announced the establishment of the UNESCO/TWAS Fellowship Programme in the Human Genome. Designed to promote international cooperation in the human genome community by stimulating and facilitating research and training, the program will enable scientists from developing countries to carry out research in well-established scientific centers and to learn new research techniques.

To be eligible for a UNESCO/TWAS human genome fellowship, candidates must already be engaged in genome research. They must agree to return to the country in which they were living at the time of application and must show that the theoretical and practical knowledge or training to be acquired will benefit their scientific development.

The fellowships, lasting from 1 to 3 months, will partly or fully fund transportation, a modest subsistence allowance, or both. The institute of origin or the host institute would be expected to defray part of the fellow's expenses. ◇

Program Offers Opportunities To Learn New Research Techniques

For application information, contact:

Svetlana Matsui
UNESCO/TWAS Human Genome Fellowship Committee
Division of Scientific Research and Higher Education
1 rue Miollis, No. 7
Place de Fontenoy
75700 Paris, France
(331) 456-83887
Fax: (331) 456-72639

Genome News

Raymond L. White
University of Utah School of Medicine

Webster K. Cavenee
Montreal Branch of the Ludwig Institute for Cancer Research at McGill University

White and Cavenee Share Mott Prize

Raymond L. White and Webster V. Cavenee are the 1990 winners of the Charles S. Mott prize for outstanding contributions to the understanding or prevention of cancer. White is cochairman of the Department of Human Genetics at the University of Utah School of Medicine and an investigator at the Howard Hughes Medical Institute (HHMI); Cavenee is director of the Montreal Branch of the Ludwig Institute for Cancer Research at McGill University.

Using restriction fragment length polymorphism (RFLP) analysis, White and Cavenee demonstrated the first proof that loss of a protective suppressor gene, one that prevents cells from becoming malignant, can trigger cancer [*Nature* **305**: 779–784 (1983)]. Their discovery is "one of the most important in human cancer genetics," says Margaret Kripke of the University of Texas, M. D. Anderson Cancer Center.

Reading the Genes

RFLP analysis takes advantage of subtle DNA variations among individuals and between the genes that individuals inherit from each parent. These variations, called polymorphisms, can be detected by exposing DNA, obtained from an individual's white blood cells, to restriction enzymes that cut the DNA into many fragments. Variations in the lengths of corresponding fragments (RFLPs) from different individuals are used as markers along the DNA. If a disease gene is near the marker, both were probably inherited together. This approach is used to locate genetic alleles that cause various diseases or make one susceptible to them. White and Cavenee used it to study the genes of families with retinoblastoma, a rare hereditary eye cancer. To streamline the search, they also used RFLPs to compare the genes of both normal and cancerous cells within the same individual. A combination of the two approaches allows scientists to specify which genetic elements associated with the disease are inherited and which occur later, during the disease process.

A Defective Gene Revealed

When White and Cavenee began their award-winning work, funded by HHMI, there were two theories explaining how loss of a gene might trigger cancer. First, the loss could mean that once-separated genes were now neighbors, a circumstance that could trigger changes in gene expression. The other possibility – proved correct by White and Cavenee – was that loss of one copy of a gene would leave

(see Mott Award, p. 13)

Recent Studies by Mott Awardees

Since the prize-winning retinoblastoma discovery mentioned above, White and Cavenee have made other genetic research contributions. White's group has located genes for several other hereditary diseases, including von Recklinghausen neurofibromatosis; familial polyposis, a condition that predisposes an individual to colon cancer; and cystic fibrosis.

He is now conducting molecular studies aimed at characterizing products of these disease genes, and his work in developing markers is supported by the Human Genome Project. "Cancer is very close to being described on a genetic level," he said. "In just a few years, we'll know which genes are involved, their types, and how they become damaged. Then the work moves over to protein chemists and X-ray structure specialists."

White's group is now beginning to study the molecular genetics of behavioral and psychiatric diseases. White believes those studies can provide a "real insight" into psychiatric illnesses. "Genes play a role, and understanding how even a few function could clarify which biological systems are affected," he said.

Follow-up work by Cavenee's group showed that the retinoblastoma gene plays a role in bone cancers of children and several major tumors of adults. His study explains the puzzling observation that individuals who surive the eye cancer sometimes develop bone tumors later in life.

Cavenee has also located genes whose loss interrupts normal muscle cell development and leads to muscle tumors in children. His recent studies show that as tumor cells become more aggressive and more resistant to treatment, they lose additional suppressor genes. "We can now begin to consider selecting therapies according to how aggressive the tumors really are," Dr. Cavenee said, "basing treatment on number and type of genetic changes." Such an approach is now being used to treat pediatric muscle cancers and other tumors. ◇

NSF Announces Interagency Agreement To Map Plant Genome

The National Science Foundation (NSF) has concluded an agreement with three other federal agencies to coordinate research efforts in the area of basic plant genetics using *Arabidopsis thaliana* as a model system. NSF will work with the NIH National Center for Human Genome Research (NCHGR); the Office of the Assistant Secretary for Science and Education, U.S. Department of Agriculture; and the DOE Office of Basic Energy Sciences.

Many researchers have adopted the simple weed, *Arabidopsis*, as a model in the study of plant biochemistry, genetics, and physiology. NSF will now lead efforts to map and sequence the genes of this plant, which can be genetically engineered to incorporate genes from economically important plants.

Arabidopsis is popular as a model because it undergoes the same processes of growth, development, flowering, and reproduction as higher plants, yet its genome has about 30 times less DNA than a corn or human genome and very little repetitive DNA. The smaller genome makes *Arabidopsis* easier to study, as does its prolific seed production and 5- to 6-week generation cycle.

A Long-Range Plan for the Multinational Coordinated Arabidopsis thaliana *Genome Research Project* was published in August and is available through NSF. ◇

Small Genome Makes *Arabidopsis* Popular Plant Model

For more information on the *Arabidopsis* genome project, contact:

Machi Dilworth
NSF Division of Instrumentation and Resources
1800 G Street, N.W.
Room 312
Washington, DC 20550
(202) 357-7652

Mott Award *(from p. 12)*

only one version of the gene to be expressed. If the unmasked gene were defective, cancer would develop.

"We knew members of this family were missing a chunk of DNA from chromosome 13, but only some [members] got retinoblastoma," White explained. In those who escaped it, the missing DNA was found to be "stuck in the middle of another chromosome," said White. This discovery argued against the first explanation in the case of retinoblastoma and suggested that loss of a normal gene function was allowing a defective version of the gene to take over, an occurrence not seen before in studies of human cancer.

The researchers then applied the RFLP technique to show that retinoblastoma is caused by loss of a particular gene on chromosome 13—a gene that can prevent malignant transformation. This landmark study provided the first proof of the theory put forward by Alfred Knudson, winner of the Mott Prize in 1988, that development of retinoblastoma and other hereditary cancers requires two genetic events, each affecting one of the two copies of a particular gene. White and Cavenee extended Knudson's theory to show how the gene loss can be one of those events. They began their work just as other geneticists were discovering oncogenes, normal genes that can trigger cancer when damaged or inappropriately activated. White and Cavenee proved that there are also genes that protect against malignancy.

The award, sponsored by the General Motors Cancer Research Foundation, is supported by grants totaling $14.2 million. It originated in 1979 and is named for Charles S. Mott, philanthropist and long-time General Motors Corporation officer. ◇

French Journal on Bioethics Begins Publication

The *International Journal of Bioethics*, edited by Christian Byk, began publication in March. This quarterly journal is presented by the science, ethics, and law association known as the Milazzo Group, an international and multidisciplinary network for bioethics created in 1989.

The aim of the Milazzo Group, which takes its name from the Sicilian city in which it meets, is to promote international exchange of information and to foster multidisciplinary debate in the field of bioethics.

The group plans a conference in July 1991 to be devoted to the legal, ethical, and social consequences of mapping the human genome. Forthcoming issues of the journal will deal with topics related to the 1991 conference.

The journal, written in French and English, is available by subscription. Contact:

Editions Alexandre Lacassagne
162 Avenue Lacassagne
69003 Lyon, France ◇

Latin American Symposium on Molecular Genetics and the Human Genome Project

Presentations Centered on Population Genetics

The Latin American Symposium on Molecular Genetics and the Human Genome Project was held June 28–30 at the University of Chile, Santiago. Meeting organizer Jorge Allende developed the symposium to be as inclusive as possible; many countries not traditionally having strong research programs, such as Honduras and Bolivia, sent delegates. Representatives from Latin American countries described their human genome research and began preparation of a consensus document outlining their approach to the Human Genome Project.

Edwin W. Southern (University of Oxford, U.K.) described the European Community's human genome analysis program and the Human Genome Organisation (HUGO). Discussion showed that many Latin American scientists are reaching out to other countries, such as France and Germany, for assistance in research and training; international cooperation and exchange of information can be fostered by HUGO and by U.S. agencies sponsoring the Human Genome Project. Southern asked participants to suggest ways HUGO could be useful to them.

Information on the U.S. Human Genome Project, presented by Bettie Graham (National Center for Human Genome Research), was well received. She indicated that workshops, communication through bitnet/internet, and the DOE- and NIH-sponsored *Human Genome News* provide excellent avenues for exchange of information between Latin American scientists and Human Genome Project participants. A few countries, such as Chile and Brazil, have access to bitnet/internet through the cooperation of the National Aeronautics and Space Administration. Conference attendees expressed hope that access could be extended to all interested Latin American countries.

Cassandra Smith [Lawrence Berkeley Laboratory (LBL)] described LBL efforts to construct a physical map of human chromosome 21. Southern discussed his work on the human Y chromosome and the isolation of telomeres to produce a cloning vector.

Detailed presentations, given principally by Latin American scientists, centered on population genetics.

Sergio D. J. Pena (Universidade Federal de Minas Gerais, Brazil) presented data on a minisatellite DNA. He isolated a probe from the parasite *Schistosoma mansoni*, which has many of the consensus sequences present in Jeffreys' human VNTR (i.e., variable number of tandem repeats) core motif; this probe is a very effective tool in investigative work involving paternity testing and criminal analysis. Pena's work was motivated by his inability to obtain the probe from researchers in other countries and by patent constraints.

Maximo E. Drets (Instituto de Investigaciones Biologicas Clemente Estable, Uruguay) discussed a new karyotyping method using computer graphics, a technique developed in collaboration with German scientists and so sensitive that even minor differences between chromatids can be seen. The approach enhances the quantitative cytogenetic analysis of banding patterns and promises to be useful in studying chromosomal breakage and organization as well as in clinical cytological tests. ◇

Reported by Bettie J. Graham, Chief
Research Grants Branch
NIH NCHGR

U.S. Legislation Calls for Inter-American Cooperation

Concern about the need to reinvigorate cooperation between the United States and Latin America in science and technology was expressed on the floor of the U.S. House of Representatives on June 12 when the House passed H.R. 2152. The bill calls for the National Science Foundation to establish an Inter-American Scientific Cooperation Program to foster innovative projects, scientist exchange, joint research, fellowships, course development, computer assistance, and other activities that would encourage scientific progress in Latin America and cooperation between the United States and Latin America. ◇

PNL Mass Spectrometry Workshop

Potential Role of Mass Spectroscopy Examined

A workshop sponsored by the DOE Office of Health and Environmental Research (OHER) was held April 4–5 at the Battelle Seattle Conference Center to examine the potential role of mass spectrometry in the Human Genome Project. Richard D. Smith and Charles G. Edmonds of Pacific Northwest Laboratory (PNL) were organizers and cochairmen. The workshop included experts in DNA sequencing technologies and conventional mass spectrometric methods, as well as researchers who are developing new mass spectrometric techniques appropriate for direct study of large biomolecules.

The relative merits, risks, and uncertainties of three mass spectrometric approaches to DNA sequencing were discussed:

1. Detection of stable, isotopically labeled DNA sequencing mixtures fractionated using gel electrophoresis;
2. Direct analysis of unfractionated sequencing mixtures using desorption ionization techniques, including electrospray ionization (ESI), where the measured mass of constituents serves to identify and order the base sequence (separation by gel electrophoresis is replaced by fluorescent or radioactivity detection); and
3. A novel approach in which a single highly charged molecular ion of a large DNA segment produced by ESI is rapidly sequenced in an ion cyclotron resonance ion trap.

Potential sequencing speeds associated with these various approaches range from 10^4 to 10^7 bases per day.

These and other recent developments in mass spectrometry provide new levels of selectivity and sensitivity and, in particular, new methods of ionization appropriate for large biopolymers. ◇

Reported by Gerald Goldstein, Acting Director
Physical and Technological Research Division
DOE

ACM–SIGMOD Panel on Database Issues of the Human Genome Project

Database Researcher Contributions Needed

The 1990 International Conference on the Management of Data, sponsored by the Association for Computing Machinery – Special Interest Group on Management of Data (ACM–SIGMOD), was held in May in Atlantic City, New Jersey. One conference activity was a panel discussion on "Database Issues of the Human Genome Project." Panelists were:

- Robert Pecherer [Los Alamos National Laboratory (LANL)],
- Richard Roberts (Cold Spring Harbor Laboratory),
- Frank Olken [Lawrence Berkeley Laboratory (LBL)], and
- Robert Robbins [National Science Foundation (NSF)].

The panel discussion was held to inform conference attendees about the goals and objectives of the Human Genome Project and about contributions that database researchers can make. As moderator, Pecherer introduced the panelists and gave some historical perspective and scientific background information. Roberts stated that access to databases for proteins and for model genome physical maps and sequences will provide clues to guide researchers in understanding human genomic structure and function.

Olken spoke of general database problems of molecular biologists and of the specific research direction taken at LBL toward developing data management systems for multilevel, integrated physical maps.

Robbins described various funding mechanisms for computer scientists interested in human genome research and applied some thought-provoking analogies from the computer science domain to the province of genome mapping and sequencing. ◇

Reported by Robert M. Pecherer
Theoretical Division
LANL

Meeting Reports, Requests

Workshop on Computational Issues in the Life Sciences and Medicine

Role of High-Performance Computer Science Explored in a Variety of Areas

About 225 research scientists from the United States and Canada attended the Workshop on Computational Issues in the Life Sciences and Medicine, held May 24–25 at the Balcones Research Center of the Center for High-Performance Computing, University of Texas System, in Austin. Participants were provided with a broad introduction to and overview of the role and use of high-performance computing. The meeting focused on the breadth and cross-disciplinary nature of the field rather than on a single topic.

Many corporate sponsors provided floor demonstrations of state-of-the-art hardware and software applicable to research in chemistry, molecular biology and genetics, cell biology, physiology, demography, dentistry, veterinary medicine, and biological database management.

Presentations covered a diversity of topics highlighting the importance of high-performance computing in the investigation and study of complex biomedical and biological systems. Each plenary speaker reviewed a particular specialized aspect of high-performance computing and its role in biological research. ◇

Plenary Speakers

John Wooley	National Science Foundation
Arthur Olson	Scripps Clinic and Research Foundation
Paul Gilna	GenBank®, Los Alamos National Laboratory
David McQueen	Courant Institute, New York University
William Samayoa	Cray Research
Richard Hart	Tulane University
Frederick Hausheer	University of Texas System, Health Science Center

Reported by Matthew Witten
Associate Director
Center for High Performance Computing
University of Texas System

For details on this and upcoming conferences on this topic, interested readers may contact Matthew Witten at:
E-mail: M.WITTEN@UTCHPC.BITNET or M.WITTEN@FRIO.CHPC.UTEXAS.EDU

E. Coli Map Data Requested

Barbara Bachmann (Department of Biology, Yale University) is revising the 1990 *Escherichia coli* linkage map, edition 8 [*Microbiol. Rev.* **54**: 130–197 (1990)]. So that the map can be revised in the shortest possible time, she asks that authors of papers containing any mapping data send her reprints from all journals other than the *Journal of Bacteriology* to the following address:.

Barbara J. Bachmann
Department of Biology, OML 355
Yale University
P.O. Box 6666
New Haven, CT 06511-7444.

Reprints of Bachmann's article and wall charts of the 1990 *E. coli* linkage map are available from the American Society for Microbiology (ASM) for $10.50 (United States and Canada) and $12.50 (foreign). Charge card orders: (202) 737-3600. Fax: (202) 737-0368. Mail orders: ASM Publication Sales; 1325 Massachusetts Avenue, N.W.; Washington, DC 20005-4171.

The *Journal of Bacteriology* plans to publish quarterly the physical locations of genes and loci assigned to the *E. coli* chromosome and is calling for related manuscripts. For information on submissions, see the January issue of *ASM News*, pp. 6–7. ◇

STS *(from p. 2)*

blot with total DNA from a human male. Several experimental projects are already under way to test the practicality of the proposed standard. As experience is gained in generating and using STSs, this standard may be modified, especially as technology changes.

The working group also stated that a primer pair that meets a less stringent standard (e.g., one that amplifies a single sequence but does not identify a single Southern band when tested on genomic DNA) might still be useful under some circumstances.

This article was compiled from information drawn from *Understanding Our Genetic Inheritance, the U.S. Human Genome Project: The First Five Years, FY 1991–1995*; *Science* **245**: 1434–35, 1438–40 (September 29, 1989); and *Science* **248**: 805 (May 18, 1990). HGMIS wishes to thank Maynard Olson and Eric Green (Washington University School of Medicine) for reviewing this article prior to publication. ◇

Workshop: Mapping Human Chromosome 22: Progress and Strategies

An international group of 34 participants gathered in Paris under the sponsorship of the Ministere de la Recherche et de la Technologie (France) and the NIH National Center for Human Genome Research (United States) April 27–30 for a workshop on "Mapping of Human Chromosome 22: Progress and Strategies."

The first session covered recent observations on the involvement of chromosome 22 in neoplasia. The second session was devoted to describing translocations of chromosome 22 and hybrid mapping panels. The presentations highlighted the usefulness of these cell lines for regional localization of the rapidly growing number of new DNA markers.

A new chromosome-22-only hybrid (GM10888) that appears to be free of other human chromosomes has been banked at the Human Mutant Cell Repository of Coriell Institute in Camden, New Jersey. Many investigators have been using other hybrid cell lines as starting material for chromosome-22-specific libraries, as well as radiation hybrids of those lines. Screening and mapping efforts with these lines may be complicated by additional material that originated from chromosomes other than 22.

Significant attention was devoted to physical mapping technologies and their application to mapping chromosome 22:

- yeast artificial chromosome (YAC) and cosmid approaches to chromosomal mapping; microcloning of chromosome-22-specific libraries;
- radiation hybrid and long-range mapping approaches to chromosome 22; and
- development of a new large-fragment cloning vector, the bacterial artificial chromosome (BAC), which is based on an F factor modified to contain a *cos* site, a selectable marker, polymerase initiation sites, and cloning sites.

The most recent genetic map of 22q was reported to use 17 markers and cover 102 cM from the most proximal marker (D22S24) to the most telomeric of the mapped markers on 22q (D22S45). A separate session dealt with mapping the regions of chromosome 22 that are involved in DiGeorge and Cat Eye syndromes.

Participants agreed that yearly workshops would be desirable to maximize sharing of data and materials. The group selected a set of 15 reference markers for chromosome 22, 10 of which were designated as consensus anchor markers, and identified a set of 4 nonrandom translocation breakpoints as anchors in the map. A set of standard hybrid cell lines was designated for use in mapping chromosome 22; these hybrids will be banked at the Human Mutant Cell Repository. ◊

Reported by Beverly S. Emanuel
Division of Human Genetics
and Molecular Biology
The Children's Hospital of Philadelphia

For more information, contact:

Beverly Emanuel
The Children's Hospital of Philadelphia
34th St. and Civic Blvd.
Philadelphia, PA 19104
(215) 590-3855
Fax: (215) 590-3850

Editors' Note

HGMIS Requests Articles, Comments

Subscribers Number Over 4500

Call for Articles

To further our goal of providing a forum for the exchange of information relating to the genome project, the editors of *Human Genome News* invite readers to submit relevant articles for publication. For further information or to discuss proposed topics and format, contact Betty Mansfield at (615) 576-6669, Fax: (615) 574-9888, or at the address on the masthead, p. 5.

Suggestions and Comments

We welcome suggestions and comments about format, types and style of articles, and topics covered in the newsletter.

Correction

Some copies of the July issue contained a sequencing gel photograph that was the victim of imprecise cropping, causing a frame shift that could result in an alteration of gene expression. We apologize for the mutation.

Growth in Readership

The number of subscribers, national and international, has grown from about 800 in April 1989 to over 4500 in August 1990, with more than 1/3 of that number requesting other documents as well. HGMIS welcomes this indication of interest in the Human Genome Project.

Mailing List Database

Subscribers can remove their names or add others by filling out the form on the last page of the newsletter. ◊

Calendar of Genome Events*

September	6–11	**International Workshop on Human Gene Mapping (HGM 10.5)**; Oxford, U.K.
	10–11	**ELSI Working Group**; Rockville, MD
	13–16	**Converging Approaches in Computational Biology**; Rensselaerville, NY; [*C. Keith, (518) 442-4327, Fax: (518) 442-4767*]
	18	**DOE Human Genome Coordinating Committee**; Livermore, CA
	30–Oct. 3	**Genome Sequencing Conference II**; Hilton Head, SC; [*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; [*Scherago Assoc., Inc., (212) 730-1050, Fax: (212) 382-1921*]
	25	**Session on "Developments in Genomic Mapping and Sequencing"** at the **IBEX 1990 Scientific Conference**; San Mateo, CA [*Cartlidge and Associates, Inc., (800) 882-3976, Fax: (408) 985-0660*]
November	4–8	**Fourth International Workshop on Mouse Genome Mapping**; Annapolis, MD [*Verne Chapman, (716) 845-2300*]
	7–9	**Fourth Annual AMA Conference on DNA Probes in the Practice of Medicine**; Chicago [*Mark Evans, (312) 645-4567*]
	12–14	**2nd Workshop on International Cooperation for the Human Genome Project: Ethics**; Monte Picayo, Spain
	14–16	**"Mapping the Human Genome; Genetic Screening"** at the **Conference on the Impact of Biotechnology on Health Care**; Barcelona, Spain [*P. Moon, Oxford, U.K., (Int.) 44-865-512242, Fax: 44-865-310981*]
	26	**Instrumentation Meeting**; [*Details unavailable at press time; call HGMIS*]
December	3	**NIH Program Advisory Committee on the Human Genome**; Bethesda, MD [*C. Mohan, (301) 496-0844*]
	4	**DOE-NIH Subcommittee on the Human Genome**; Bethesda, MD
	4	**DOE Human Genome Coordinating Committee**; Bethesda, MD
	10–12	**HUGO Meeting on Genome Analysis: From Sequence to Function**; Frankfurt, Germany; application deadline: September 28, 1990 [*DECHEMA Meetings Office, HUGO, Fax: (Int.) (49-69) 756-4201*]

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

Calendar of Genome Events*

January 1991	8–11	**Biotechnology Computing Minitrack** at the **Hawaii International Conference on System Sciences–24**; Kailua-Kona, HI [*L. Hunter, (301) 496-9300, Fax: (301) 496-0673*]
	27–Feb. 1	**Bio/Technology Magazine Winter Symposium – Advances in Gene Technology: The Molecular Biology of Human Genetic Disease**; Miami Beach, FL [*The Miami Bio/Technology Winter Symposia, (800) 624-4363, Fax: (305) 324-5665*]
February	24–28	**"Special Mini-Track on Artificial Intelligence Applications to Molecular Biology"** at the **The Seventh IEEE Conference on Artificial Intelligence Applications**; Miami Beach [*David Searls, (215) 648-2146*]
March	19–21	**Sessions on "Development and Application of Electrophoresis Techniques in Molecular Biology"** at the **International Electrophoresis Society Meeting**; Washington, DC; [*J. Cunningham, (301) 898-3772, Fax: (301) 898-5596*]
July	22–26	**13th IMACS World Congress on Computation and Applied Mathematics with sessions on High Performance Computing** in Biology and **Medicine**; Dublin, Ireland; [*M. Witten, USA, (512) 471-2449*]
August	18–22	**11th International Workshop on Human Gene Mapping** (HGM 11); London, U.K. [*M. Probert, (44-71) 269 3052, Fax: (Int.) (44-71) 430-1787*]
	25–31	**XXII International Conference on Animal Genetics**; East Lansing, MI [*R. Bull, (517) 355-4616, Fax: (517) 353-5436*]
October	6–11	**8th International Congress of Human Genetics**; Washington, DC [*ICHG, (301) 571-1825, Fax: (301) 530-7079*]

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

Training Calendar: Workshops and Coursework

September	10–14	**Transfection Techniques**; Germantown, MD [*BRL Life Technologies, Inc., (800) 828-6686*]
	17–21	**Recombinant DNA Techniques**; Germantown, MD [*see contact: Sept. 10–14*]
October	1–5	**Recombinant DNA Techniques and Applications**; Rockville, MD (also offered Oct. 8–12 [*American Type Culture Collection, (301) 231-5566*]
November	7–9	**Online Information Resources for the Research Biologist**; Rockville, MD [*see contact: Oct. 1–5*]
December	11–14	**Basic Cloning Techniques**; Miami, FL (also offered simultaneously in Ames, IA; Portland, OR; and Nashville, TN) [*David F. Betsch, Biotechnology Training Programs, (515) 232-8306*]

Acronym List

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

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

ACM-SIGMOD	Association for Computing Machinery–Special Interest Group on Management of Data
AMHPS	Association of Minority Health Professional Schools
ASM	American Society for Microbiology
BAC	Bacterial artificial chromosome
cDNA	Complementary DNA
CEPH	Centre d'Etude du Polymorphisme Humain
CF	Cystic fibrosis
DHHS	Department of Health and Human Services (U.S.)
DNA	Deoxyribonucleic acid
DOE	Department of Energy (U.S.)
ESI	Electrospray ionization
HERAC	Health and Environmental Research Advisory Committee
HGCC*	Human Genome Coordinating Committee
HGN*†	**Human Genome News**
HGMIS*	Human Genome Management Information System (ORNL)
HHMI	Howard Hughes Medical Institute
HUGO	Human Genome Organisation [International]
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)
NCRR†	National Center for Research Resources (NIH)
NF1	von Recklinghausen neurofibromatosis
NIH†	National Institutes of Health
NLGLP*	National Laboratory Gene Library Project (LANL, LLNL)
NSF	National Science Foundation
OER*	Office of Energy Research
OHER*	Office of Health and Environmental Research (OER)
ORAU*	Oak Ridge Associated Universities
ORNL*	Oak Ridge National Laboratory, Oak Ridge, Tenn.
PACHG†	Program Advisory Committee on the Human Genome (NIH)
PCR	Polymerase chain reaction
PNL*	Pacific Northwest Laboratory, Hanford, Wash.
RCMI	Research Centers in Minority Institutions
RFLP	Restriction fragment length polymorphism
STS	Sequence tagged site
TWAS	Third World Academy of Sciences
UNESCO	United Nations Educational, Scientific, and Cultural Organization
VNTR	Variable number of tandem repeats
YAC	Yeast artificial chromosome

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