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DOE Merges Genome Center Sequencing Efforts

Elbert Branscomb To Direct Collaborative Work Through Joint Genome Institute

In a major restructuring of its Human Genome Program, the DOE Office of Health and Environmental Research announced the creation of the Joint Genome Institute to integrate work now based at its three major human genome centers. The merger represents a shift toward large-scale sequencing via intensified collaborations for more effective use of unique expertise and resources at Lawrence Livermore National Laboratory (LLNL), Lawrence Berkeley National Laboratory (LBNL), and Los Alamos National Laboratory (LANL). The genome centers are directed by Anthony Carrano (LLNL), Michael Palazzolo (LBNL), and Robert Moyzis (LANL).

"The Joint Genome Institute will enable more efficient cooperation among DOE laboratories to develop the next generation of genome sequencing technologies," said Martha Krebs, director of DOE's Office of Energy Research.

Elbert Branscomb (LLNL), newly appointed scientific director of the DOE Human Genome Program, also directs the joint institute, which begins operations in January 1997. Commenting on the rationale for the merger, Branscomb noted, "We need to focus our resources and integrate our efforts toward making a significant contribution to worldwide sequencing."

"Our goal is to commit an appropriate portion of our genome budget to sequencing a respectable fraction of the human genome with an efficiency at least comparable to that of other labs worldwide," he said.

In addition to production sequencing, a major goal of the joint center is to enrich the sequence data with

(see Joint Institute, p. 2)

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ELSI Report Now on HGMIS Web Site

The Joint NIH-DOE Committee to Evaluate the Ethical, Legal, and Social Implications Program of the Human Genome Project delivered its unanimous report and recommendations on December 16, 1996. The committee was chaired by Mark Rothstein (University of Houston) and M. Anne Spence (University of California, Irvine). The report, now under consideration by the NCHGR and DOE genome programs, is available through the HGMIS Web site (*http://www.ornl.gov/hgmis*).◊

OHER Program Director Reflects on Genome Project Origins, Applications

By Ari Patrinos

Ari Patrinos

At the end of the road in Little Cottonwood Canyon, near Salt Lake City, Alta is a place of near-mythic renown among skiers. In time it may well assume similar status among molecular geneticists. In December 1984, a conference there, cosponsored by DOE, pondered a single question: Does modern DNA research offer a way of detecting tiny genetic mutations—and, in particular, of observing any increase in the mutation rate among survivors of the Hiroshima and Nagasaki bombings and their descendants? In short the answer was, Not yet. But in an atmosphere of rare intellectual fertility, seeds were sown for a project that would make such detection possible in the future—the Human Genome Project.

In the months that followed, much deliberation and debate ensued. But in 1986, DOE took a bold and unilateral step by announcing its Human Genome Initiative, convinced that its mission would be well served by a comprehensive picture of the human genome. The immediate response was considerable skepticism—skepticism about the scientific community's technological wherewithal for sequencing

(see Patrinos, p. 3)

Joint Institute *(from p. 1)*

information about its biological function, dubbed "functional genomics" as compared to the "structural genomics" of generating maps and other resources in the Human Genome Project. Functional genomics projects will focus on studying domains sequenced by the institute.

As the joint institute, the three laboratories will work together to define major tasks, each of which will be overseen by a manager. "This is a very high level of integration and merger," Branscomb said. "The managers and the joint institute will work together to make the best use of collective resources to achieve particular tasks." Palazzolo of LBNL will manage the genomic sequencing component.

The joint institute's budget will be task based, with allocations determined by external reviews of the proposed activities and contributions of each laboratory. Initially, the bulk of the funds will go toward large-scale sequencing, including production and technology development. The remainder will be used to develop and apply technologies for functional genomics.

Sequencing Targets, Quality, and Data Release

Gene-rich regions of around 1 to 10 Mb will be targeted for sequencing. Considerations include gene density, gene families (especially clustered families), correlations to model organism results, technical capabilities, and relevance to the DOE mission (e.g., DNA repair, cancer susceptibility, and impact of genotoxins). Use of mapped markers and Web sites will help avoid duplications in work. Targeting high-payoff regions will make data available to the broader research community.

Although the joint institute will strive for very high sequencing accuracy (around 99.99%), Branscomb pointed out that "there is much more to accuracy than just a number. You may get all the bases just right, but some clones may have been rearranged or aren't really from human DNA or may have other problems. The integrity of the sequence you generate is much more difficult to measure and presents a substantial challenge to all groups involved in production-scale work."

Data release will be immediate, comparable to procedures established by such major production-sequencing centers as Washington University, MIT-Whitehead, and Sanger Centre. Results will be posted daily on the Web; as data progresses to finished quality, it will be submitted to public databases. *[Denise Casey, HGMIS]* ◊

Maximizing the Value of Sequence Data

Annotation Critical, says Branscomb

Elbert Branscomb
Director
Joint Genome Institute

"Obtaining a functional understanding of sequence data is truly a profound challenge," Elbert Branscomb said recently. One method for determining the function of anonymous stretches of sequence data is by computer analysis. Some programs like GRAIL (Gene Recognition and Analysis Internet Link) help detect certain kinds of functional features in sequence data, while others (e.g., BLAST) allow searching for homologies to sequences of known function. This can be done in a systematic and fairly automated way, Branscomb observed, noting the work of a new annotation consortium headed by Edward Uberbacher (Oak Ridge National Laboratory).

"But the highest payoffs and yet the most difficult path to functional understanding," he continued, "come not from anything you can get by computer analysis but from added biological experimentation such as expression analysis. It would be of tremendous value to be able to search for all genes known to be expressed only in the liver or in the forebrain or in early gestation, and so on. This kind of data can be acquired systematically in different ways."

"People are struggling hard to automate the capture of all sorts of related expression-type data," he pointed out. "Some of these approaches compare expression patterns of different genes in cells and tissues as a function of a physiological condition. For example, you could assess the expression pattern of all genes in a certain cell type and compare that with the same cell type after it has undergone some stage of carcinogenic induction. Researchers at the National Cancer Institute, under the direction of Richard Klausner, are trying to develop technologies and databases that collect these data for investigators."

All this makes the Human Genome Project but a prelude to the insights beckoning just beyond the horizon. "We are just chipping a hole into the sarcophagus of knowledge and peering into the darkness," Branscomb said.

But for any kind of annotation to be useful, he emphasized, it must be stored robustly in a computer-searchable way. This has been one of the most difficult problems to approach, and one that many people are trying to address. Another issue is whether and how sequence annotation should be added to a database after the original sequence submission, either by the submitting lab or by others who find out information about that sequence. Ex post facto annotation not only should be allowed, said Branscomb, it should be made easy and automatic. "It changes the flavor of the databases, making them less archival and more a dynamic record of current knowledge," he said. Both Genome Database and Genome Sequence Data Base have recently introduced promising new schema to support this type of after-the-fact and third-party annotation. GenBank and others are approaching the same basic user needs in interesting ways as well, he noted. ◊

Patrinos *(from p. 1)*

the genome at a reasonable cost and about the value of the result, even if it could be obtained economically.

Things have changed. Today, a decade later, a worldwide effort is under way to develop and apply the technologies needed to completely map and sequence the human genome, as well as the genomes of several model organisms. Technological progress has been rapid, and it is now generally agreed that this international project will produce the complete sequence of the human genome by the year 2005.

And what is more important, the value of the project also appears beyond doubt. Genome research is revolutionizing biology and biotechnology and providing a vital thrust to the increasingly broad scope of the biological sciences. The impact that will be felt in medicine and health care alone, once we identify all human genes, is inestimable. The project already has stimulated significant investment by large corporations and prompted the creation of new companies hoping to capitalize on its profound implications.

But DOE's early, catalytic decision deserves further comment. Organizers of the DOE's genome initiative recognized that the information the project would generate—both technological and genetic—would contribute not only to a new understanding of human biology but also to a host of practical applications in the biotechnology industry and in the arenas of agriculture and environmental protection. A 1987 report by a DOE advisory committee provided some examples. The committee foresaw that the project ultimately could lead to the efficient production of biomass for fuel, to improvements in the resistance of plants to environmental stress, and to the practical use of genetically engineered microbes to neutralize toxic wastes. The department thus saw far more to the genome project than a promised tool for assessing mutation rates. For example, understanding the human genome will have an enormous impact on our ability to assess, individual by individual, the risk posed by environmental exposures to toxic agents. We know that genetic differences make some of us more susceptible, and others more resistant, to such agents. Far more work must be done before we understand the genetic basis of such variability, but this knowledge will directly address DOE's long-term mission to understand the effects of low-level exposures to radiation and other energy-related agents—especially the effects of such exposure on cancer risk. And the genome project is a long stride toward such knowledge.

The Human Genome Project has other implications for DOE as well. In 1994, taking advantage of new capabilities developed by the genome project, DOE formulated the Microbial Genome Initiative to sequence the genomes of bacteria of likely interest in the areas of energy production and use, environmental remediation and waste reduction, and industrial processing. As a result of this initiative, we already have complete sequences for two microbes that live under extreme conditions of temperature and pressure. Structural studies are under way to learn what is unique about the proteins of these organisms—the aim being ultimately to engineer these microbes and their enzymes for such practical purposes as waste control and environmental cleanup. (DOE-funded genetic engineering of a thermostable DNA polymerase already has produced an enzyme that has captured a large share of the several-hundred-million-dollar DNA polymerase market.) ➠

This article was reprinted from the 1996 DOE booklet, *To Know Ourselves*, edited by Douglas Vaughan at Lawrence Berkeley National Laboratory. *TKO* reviews the role, history, and achievements of DOE in the Human Genome Project and introduces the reader to the science and other aspects of the monumental undertaking. [Requests for booklet: HGMIS at the address on page 12. Full text of *TKO* is on the Web (*http://www.ornl.gov/hgmis/tko*).]

Ramping Up for Production Sequencing

The year 1996 marked an early transition to the third and final phase of the U.S. Human Genome Project as pilot programs aimed at refining large-scale sequencing strategies and resources were funded by DOE and NIH. In October, DOE funded two projects for 2 years to test the feasibility, cost, and technological requirements for implementing an end-sequencing strategy using BAC and PAC clones [HGN 8(1), 8]; see URL (*http://www.ornl.gov/meetings/bacpac/95bac.html#bac*). Earlier in the year, NIH awarded 3-year grants to six pilot large-scale sequencing projects [*HGN* 7(6), 20].

Until this year, the Human Genome Project focused on creating such resources as physical and genetic maps, software, and automated technologies to enable implementation of cost-effective, large-scale sequencing. The ultimate goals of the Human Genome Project, scheduled for completion in 2005, are to sequence all human DNA and identify every gene. To date, close to 1% of the 3 billion base pairs in the human genome have been sequenced.

Internationally, large-scale human genome sequencing was kicked off in late 1995 when the Wellcome Trust announced a 7-year, $75-million grant to the Sanger Centre to ramp up its sequencing capabilities (*http://www.sanger.ac.uk/humanseq*). French investigators have also announced intentions to begin production sequencing.

Discussions in the genome research community now focus on the significant challenges presented by large-scale sequencing. Most major laboratories use a combination of random and directed strategies with fluorescent-based, four-color chemistries. The general consensus is for generating very high quality data, with less than 1 error in 10,000 bases, or 99.99% accuracy. Most funding agencies and researchers agree that rapid and free release of the data is critical. Other issues include the types of annotation that will be most useful to biologists and how to maintain the reference sequence.

HUGO Web Site

HUGO has created a Web page (*http://hugo.gdb.org/hsmindex.htm*) to provide information on current and future sequencing projects and links to sites of participating groups. (E-mail to *hugo@gdb.org* to add a project or request information.) The site also links to a list of resources developed by participants at the February 1996 international meeting on human genome sequencing sponsored by the Wellcome Trust.◊

And other little-studied microbes hint at even more intriguing possibilities. For instance, *Deinococcus radiodurans* is a species that prospers even when exposed to huge doses of ionizing radiation. This microbe has an amazing ability to repair radiation-induced damage to its DNA. Its genome currently is being sequenced with DOE support, with the hope of understanding and ultimately taking practical advantage of its unusual capabilities. For example, it might be possible to insert foreign DNA into this microbe that will allow it to digest toxic organic components found in highly radioactive waste, thus simplifying the task of further cleanup. Another approach might be to introduce metal-binding proteins onto the microbe's surface that would scavenge highly radioactive isotopes out of solution.

Biotechnology, fueled in part by insights reaped from the genome project, will also play a significant role in improving the use of fossil-based resources. Increased energy demands, projected over the next 50 years, require strategies to circumvent the many problems associated with today's dominant energy systems. Biotechnology promises to help address these needs by upgrading the fuel value of our current energy resources and by providing new means for the bioconversion of raw materials to refined products—not to mention offering the possibility of entirely new biomass-based energy sources.

We have thus seen only the dawn of a biological revolution. The practical and economic applications of biology are destined for dramatic growth. Health-related biotechnology is already a multibillion-dollar success story—and is still far from reaching its potential. Other applications of biotechnology are likely to beget similar successes in the coming decades. Among these applications are several of great importance to DOE. We can look to improvements in waste control and an exciting era of environmental bioremediation; we will see new approaches to improving energy efficiency; and we can even hope for dramatic strides toward meeting the fuel demands of the future. The insights, technologies, and infrastructure that are already emerging from the genome project, together with advances in such fields as computational and structural biology, are among our most important tools in addressing these national needs. *[Ari Patrinos, director of the DOE Human Genome Program, also heads the DOE Office of Health and Environmental Research.]* ◊

Focus Moves from Transcriptional Mapping to Gene-Function Studies

1996 Meeting Proceedings

- *http://www.ornl.gov/meetings*

The Sixth International Workshop on the Identification of Transcribed Sequences was held October 2–5, 1996, in Edinburgh, Scotland. The meeting attracted 46 speakers with 20 posters to discuss topics including the generation of regional and chromosomal transcriptional maps, functional analysis of gene expression, techniques for isolating and analyzing genes, use of model organisms, and informatics. The workshop was supported by the Cancer Research Campaign, European Commission, HUGO Europe, Lothian and Edinburgh Enterprise, Wellcome Trust, and DOE. Selected presentations are summarized below.

Bioinformatics, Computational Biology

A number of speakers addressed bioinformatics and computational biology needs for transcriptional analysis. Characterization of potential regulatory elements in genomic DNA remains a difficult task.

Laurent Duret (Geneva University Hospital) described the use of large-scale comparative analysis of metazoan noncoding sequences to identify such elements. His study has found hundreds of long, highly conserved regions (HCRs) in noncoding parts of genes. HCRs retain at least 70% identity in sequences of 50 to 200 bases in DNA of species that diverged 300 million to 550 million years ago. Some of these sequences may play roles in gene regulation and mRNA localization. A database with more than 300 such sequences is available.

James W. Fickett (SmithKline Beecham) reported progress in recognizing transcriptional regulatory regions from their context within a DNA sequence. In particular, he has devised a system that can discriminate among myotubulin-specific regulatory regions, other regulatory regions, and nonregulatory regions. This is an important step toward being able to infer possible functions of a newly discovered gene from its DNA sequence.

Thomas Werner (GMBH Institut für Säugetiergenetik) presented an approach to identifying transcriptional control regions. Using two types of retroviral control regions (LTRs) as models, he showed that this robust technique found all known LTRs in the Primate division of GenBank (95 Mb) and identified five previously unknown LTRs. The false-positive rate was reported to be quite low.

Richard Mural (Oak Ridge National Laboratory) commented on the challenge of automated annotation of DNA sequences. As the analysis of genomes moves into large-scale sequencing, identification and annotation of biologically relevant features in the sequence become increasingly complex and important. Annotation must be updated continually, particularly in light of the rapid rate of new data acquisition. Ideas were discussed for new systems to provide a user-defined view of a DNA sequence as well as data-mining tools for complex querying of multiple data resources.

Comparative Genomics

Among mammals, the mouse is clearly the model organism of choice for "surrogate" human genetics, and information resources for mouse genetics and developmental biology are critical. Martin Ringwold (Jackson Laboratory) reported work on the Gene Expression Database. This database not only contains information on the expression of various mouse genes but also is being linked to a mouse-anatomy database that will allow the user to follow gene expression through the course of development.

The accumulating data from a number of other model organisms are providing

new insights into genome structure and function. With nearly half of its 100-Mb genome sequenced, the nematode *Caenorhabditis elegans* is becoming increasingly important for gene discovery. Steven Jones (Sanger Centre) presented some results of gene prediction in the *C. elegans* genomic sequencing project. The project has identified about 9700 proteins, 46% of which clearly are related to proteins already in public sequence databases.

Because of its small genome size and the compact nature of its genes, the puffer fish *Fugu rubripes* is another important model organism. Greg Elgar (HGMP Resource Centre) described the Fugu Landmark Mapping Project, which aims to sample sequence 1000 *Fugu* cosmids to provide resources for a number of different applications, including gene identification. Some physical linkage data also are expected to come out of this project because of the likelihood of finding more than one *Fugu* gene per cosmid clone. Nearly 200 *Fugu* cosmids have been scanned.

Learning the patterns of gene expression is a necessary first step to understanding gene function and interaction. *C. elegans* is particularly well suited to studying gene-expression patterns because the animal develops rapidly and the fates of all its cells have been mapped. Donna Albertson (Lawrence Berkeley National Laboratory) reviewed a preliminary study in which the expression pattern of nearly 200 *C. elegans* genes was examined using FISH on whole animals. Petra Ross-Macdonald (Yale University) described an approach for yeast that determines when a gene is expressed during the yeast life cycle, subcellular localization of the gene product, and the phenotypic effect of disrupting the gene. This technique is helping to determine functions of large numbers of yeast genes that have been identified by sequencing but have no relatives with known function in current databases.

One hope of comparative genomics is to use information from well-characterized model systems to provide candidates for genes implicated in human diseases. One such application was presented by Guiseppe Borsani (Téléthon Institute of Genetics and Medicine), who found 66 human ESTs with significant homology to known *Drosophila* genes. All these genes, which are well characterized in *Drosophila*, are candidates for genes involved in human pathology. For example, an EST that was homologous to a gene causing retinal degeneration in the fruit fly was mapped to a human genome region near genes for three different types of human retinopathology.

Gene Identification and Mapping

A number of speakers presented data that begin to elucidate genome organization and function. Stephen Scherer (University of Toronto) described progress in gene identification on human chromosome 7q. Around 2500 genes are expected to be found on the long arm of chromosome 7. Three strategies for isolating and mapping these genes were discussed: (1) initial assignment of all known chromosome 7 genes and ESTs from the public domain to the map, (2) genomic DNA sequencing of selected chromosomal regions to identify genes, and (3) direct cDNA selection on chromosome-specific cosmids. The current 7q map contains over 1600 DNA markers, including 170 known genes, 200 ESTs, and more than 500 selected cDNA fragments.

Mammalian genomes are a mosaic of regions (isochores) of varying base composition. Katheleen Gardiner (Eleanor Roosevelt Institute) showed data on the isochore structure of human chromosome 21 and the nature of the boundaries between different isochores. Sequences at a number of these boundaries are homologous (>80% identity) to the pseudo-autosomal boundary of the sex chromosomes' short arms (as described for chromosome 6 isochore boundaries, Fukagawa et al.). One interesting feature of these sequences is that some appear to be transcribed.

CpG islands are short (1-kb) regions of genomic DNA with a high GC content and reduced methylation of C residues. About 60% of genes have these islands at their 5′ ends, making CpG islands useful markers for transcriptional units. Sally Cross (Edinburgh University) discussed the construction of whole-genome CpG island libraries from human, mouse, and chicken. These libraries should be a valuable resource for isolating the 5′ ends of a large number of genes, regardless of their level of expression.

Complexities of deducing mRNA structure from genomic sequences were described by Sherman Weissman (Yale University). Comparing full-length cDNAs to genomic sequences reveals a number of limitations in current methods using genomic sequence to predict the structure of mRNAs and proteins. One problem involves large introns that contain other transcribed sequences. Weissman also described a gene, B144, which has a 700-base mRNA that exists in at least 30 alternatively spliced forms.

Quantitative PCR is becoming an important technique for studying gene expression. Michael McClelland (Sidney Kimmel Cancer Center) addressed a broad range of issues connected to the effective use of quantitative PCR, particularly as it applies to differential display. These issues include relative quantitation by low-stringency PCR, the *Cot* effect, and problems of target vs standard titration. The *Cot* effect is particularly interesting because it demonstrates that low-abundance and high-abundance products accumulate at different rates. Very abundant products are formed more slowly than expected because product reannealing competes with priming. The need to

(see Gene Function, p. 6)

Next Workshop

The seventh workshop in the series is planned for late October or early November of 1997 at Asilomar in California. Watch the Meetings Web site for information (*http://www.ornl.gov/meetings*).

Correction for Caption

***HGN* regrets the omission of two lines from the picture caption on page 5 of the last issue. The full caption should read:**

David Bing (Center for Blood Research, Boston) demonstrates DNA profiling to the '96 Working Conversation attendees during a laboratory workshop. Observing, from left, are Judges Ricardo Urbina and Gladys Kessler (U.S. District Court for the District of Columbia) and Barbara Rothstein (U.S. District Court for the Western District of Washington).

Arabidopsis Sequencing Scales Up

Scientists soon will have access to the first complete genetic information of a flowering plant. DOE, the National Science Foundation (NSF), and the Department of Agriculture (USDA) are funding three groups of researchers to begin systematic, large-scale genomic sequencing of *Arabidopsis thaliana*. It has the smallest genome (about 120 Mb) and the highest gene density known in a flowering plant. The ultimate goal is to sequence the entire *Arabidopsis* genome by the year 2004 at a rate of about 200 genes per month.

The three groups, whose grants total around $12 million, are Institute for Genomic Research; a consortium of Cold Spring Harbor Laboratory, Washington University in St. Louis, and Applied Biosystems; and a consortium of Stanford University, University of Pennsylvania, and University of California, Berkeley.

The U.S. effort, which will contribute about two-thirds of the sequence, will dovetail with other large-scale sequencing projects in Europe and Japan through the Multinational Coordinated *Arabidopsis thaliana* Genome Research Project. The project was launched in 1990 by an international group of scientists who recognized the need to study a plant having the basic properties of all plants.

"Decoding the DNA of this model plant will provide a complete catalog of all the genes involved in the life cycle of a typical plant, from seed to flower and fruit," said Martha Krebs, director of the DOE Office of Energy Research. Potential applications of this knowledge could lead to improvements in the quality and quantity of alternative fuels and chemical feedstocks, as well as the use of plants to clean up contaminated soil.

What investigators learn from the study of *Arabidopsis* genes will be immediately applicable to economically important plant species, according to Mary Clutter, NSF assistant director for biological sciences. "Because plants are vital to our existence, increased understanding of the biology of plants will impact every facet of our lives, from agriculture to energy to the environment to health," Clutter said.

Catherine Woteki, USDA acting undersecretary of agriculture for research, education, and economics, added, "Mapping the *Arabidopsis* genome will enable us to use biotechnology to develop a host of new plant varieties for agriculture and other purposes. This research is like exploring a continent for the first time; each step leads to several others, with tremendous possibilities. We're going to see productive results for years to come."◊

Arabidopsis thaliana Database Project (AtDB):

- *http://genome-www.stanford.edu/Arabidopsis*

GRAIL Version 1.3 *Arabidopsis* exon/gene–finding algorithm:

- *ftp://arthur.epm.ornl.gov*

Gene Function *(from p. 5)*

control these various parameters was stressed in this presentation.

J.G. Sutcliffe (Scripps Research Institute) reported a form of differential display called TOGA (Total Gene Expression Analysis). TOGA uniquely identifies nearly every mRNA from an organism, including mRNAs not previously described, and does not require that the mRNA has been characterized previously. This automated PCR-based technique can detect messages of <0.001% prevalence, thus providing a powerful means for comparing mRNA expression profiles.

Wai-Choi Leung (Tulane University School of Medicine) described architectural elements of mRNA molecules. Energy maps can be constructed that describe the location, size, and energy density of closed regions of mRNA molecules. Closed regions reflect the secondary structure of mRNA that may be related to a number of processes, including RNA translocation, nuclear export, transcription termination, and translational control.

cDNA Libraries

M. Bento Soares (Columbia University) discussed strategies for constructing cDNA libraries for both gene discovery and characterization. To clone genes represented by low-abundance transcripts, subtractive hybridization strategies are being developed to eliminate pools of sequenced cDNAs. In addition, techniques are being optimized to produce libraries enriched for full-length cDNAs. These libraries will be very useful for increasing gene representation and therefore the utility of dbEST.

Bernhard Korn (German Cancer Research Center) reported progress in constructing and gridding a full-length cDNA library from human fetal brain. His institution's current library has 120,000 clones with an average insert size of 1.8 kb. Some problems inherent in making such libraries were discussed.

Y Chromosome

The Y chromosome presents a number of unique problems to both genetic mapping and gene identification. Yun-Fai Chris Lau (University of California, San Francisco) presented two approaches to identifying Y chromosome–specific genes by en masse terminal exon trapping. Analysis of these methods showed that such an approach is very feasible and >50% of exon clones were derived either from known Y genes or potential functional sequences. *[Richard Mural, Oak Ridge National Laboratory* (muralrj@ornl.gov) *and Katheleen Gardiner, Eleanor Roosevelt Institute* (gardiner@eri.uchsc.edu)] ◊

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Gene Watch

DOE Clone Resources Spur Disease-Gene Discoveries

Information on National Laboratory Gene Library Project's chromosome-specific libraries:
- *http://www-bio.llnl.gov/bbrp/genome/html/nlglp.home.html*

Migraine

Two research groups report results suggesting a common genetic cause for migraine and epilepsy and the availability of an animal model that may be useful for further studies. Both groups used the chromosome 19 physical map and selected clones supplied by the Human Genome Center at Lawrence Livermore National Laboratory (LLNL).

Researchers led by Lisa Stubbs at Oak Ridge National Laboratory (ORNL) reported the isolation, mapping, and expression analysis of the chromosome 8 *CACNL1A4* gene found in the mutant "tottering" mice studied extensively as models for human epilepsy and cerebeller ataxia. The mouse CACNL1A4 region is homologous to a human chromosome 19 region previously implicated in episodic ataxia type 2 and familial hemiplegic migraine (an inherited form of migraine). Now the ORNL studies indicate that mutations in the human *CACNL1A4* gene are indeed the causative factor in both disorders. Tottering mutants may thus represent mouse models of both diseases, according to the authors of the *Mammalian Genome* article in press. In the November 15 issue of *Cell*, Fletcher et al. published evidence that a calcium channel gene is responsible for tottering and leaner alleles.

Roel A. Ophoff and colleagues at Leiden University in The Netherlands, in collaboration with LLNL genome center scientists, reported cloning the human gene *CACNL1A4*. This gene contains two different mutations that they associated with familial hemiplegic migraine and episodic ataxia type 2. The research findings were included in the November 1, 1996, issue of the journal *Cell*. The authors noted that although these kinds of migraine are rare, variations in the same gene may predispose people to the more common migraine, which affects an estimated 24% of women and 12% of men.

The implicated gene affects the transport of calcium into specific classes of brain cells. This calcium movement regulates the release of neurotransmitters—critical elements in the communication network among cells of the nervous system. Further explorations into the structure and function of the gene will improve diagnosis and may aid in development of new treatments for migraine.

In addition to the role of genes suggested by family, twin, and population studies, such other factors as emotional stress and certain foods and additives have been associated with migraine attacks.

Chromosome Resources a Boon to Gene Hunters

The physical map spanning the candidate region was constructed from the chromosome 19 flow-sorted library generated by LLNL as an early part of the National Laboratory Gene Library Project. In this project, researchers at LLNL and Los Alamos National Laboratory (LANL) used flow sorters equipped with lasers to separate human DNA into individual collections (libraries) of each of the 24 different human chromosomes.

LLNL chromosome 19 libraries also have been important in studies leading to the identification of other genetic mutations, including those associated with a syndrome characterized by recurrent strokes and progressive dementia (see "Stroke and Dementia," p. 8).

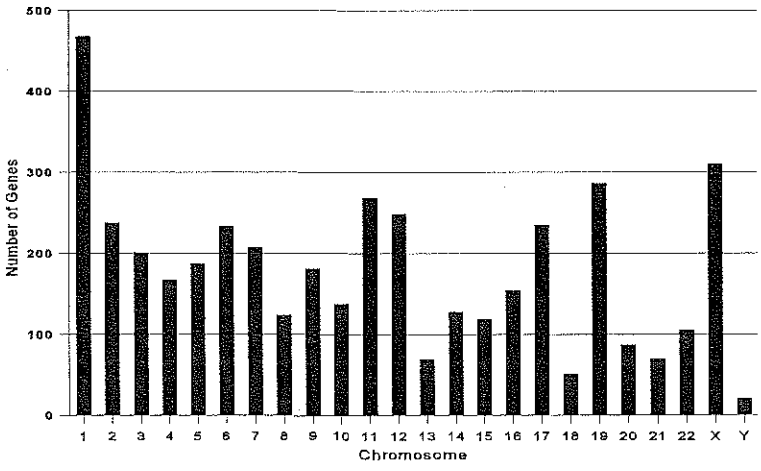
"These clones have proven invaluable to biologists and medical scientists who are conducting more focused and specialized studies," observed Harvey Mohrenweiser, senior biomedical scientist at the LLNL Human Genome Center. "It's exciting to be participating in such collaborations, especially when these discoveries may have a significant, positive impact on a sizable portion of the population."

Fanconi Anemia

Chromosome 16 resources generated by scientists at LLNL and LANL were instrumental to the recent isolation of a mutated gene associated

Count of Genes in GDB by Chromosome

This chart reflects the count of mapped and characterized genes stored in GDB. Gene characterization has been approved by the nomenclature and chromosome committees of the Human Genome Organisation. These counts are run weekly and can be accessed through *http://gdbwww.gdb.org/gdbreports/CountGeneByChromosome.html*. ◊



with Fanconi anemia (FA). FA is a rare autosomal recessive disease characterized by skeletal abnormalities, bone marrow failure, and a predisposition to cancer. In the November 1996 issue of *Nature Genetics* (**14**, 240–42, 320–28), researchers reported finding a gene associated with FA, subtype A, one of five subtypes described for the usually fatal disorder.

In addition to the discovery's considerable impact on the diagnosis and eventual treatment of FA patients, researchers hope that a better understanding of the FA gene pathway will shed light on developmental processes. The multiple clinical abnormalities associated with the disorder suggest that FA proteins play an important part in the development of many organ systems, and researchers believe faulty cellular defense or DNA repair mechanisms are to blame. The protein predicted by the *FAA* gene has no homology to other known proteins, which suggests a novel pathway not related to known mechanisms of defense and repair.

An international consortium composed of research groups from Australia, Italy, The Netherlands, South Africa, United Kingdom, and United States was responsible for the *Nature Genetics* report.

Stroke and Dementia

In the October 24, 1996, issue of *Nature* [**383** (673), 707–10], researchers reported finding mutations in *Notch3*, a chromosome 19 gene associated with CADASIL, a hereditary adult-onset condition causing recurrent strokes and progressive dementia. The chromosome 19 map from LLNL was an important resource for the initial studies.

Symptoms of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) appear at about age 45, with patients usually dying by 65. The number of affected individuals is unknown, and the condition is thought to be largely undiagnosed. The *Nature* authors noted that stroke is the third leading overall cause of death, and vascular dementia is the second leading cause of dementia after Alzheimer's disease.

Notch3, the gene implicated in CADASIL, belongs to a gene family whose functions are essential to embryonic development; Notch genes are found in species as diverse as insects, roundworms, and mammals. Involvement of *Notch3* in CADASIL suggests that disruption of the Notch signaling pathway may be a key factor in adult-onset conditions causing dementia, such as Alzheimer's disease. Researchers hope that studies on the function of the protein encoded by the *Notch3* gene will yield further clues into the pathogenesis of adult-onset dementia and stroke.◊

Want Notification of *HGN* Web Version?

Readers wishing to be notified when the latest issue of *HGN* is placed on the Web should send their request and e-mail address to *yustln@ornl.gov*. A table of contents and URL will be e-mailed to requestors when each issue is posted. This electronic version usually is available at least 2 weeks before readers receive the printed copy.

Planning a Meeting?

To avoid conflicts, see genome calendars on pp. 14–15 and a more extensive listing on the HGMIS Web site (*http://www.ornl.gov/hgmis*).◊

Closing in on a Prostate Cancer Gene

Susceptibility Locus Identified

For the first time, researchers have found direct evidence that an inherited change can lead to prostate cancer. With about 340,000 new cases diagnosed each year, this disease is the most common cancer in men and is responsible for some 40,000 deaths annually. African-American men suffer the world's highest incidence and death rate for this cancer. Results of the study were published in the November 22, 1996, issue of *Science* (**274**, 1371–74).

Scientists at NCHGR, Johns Hopkins University, and Umeå University (Umeå, Sweden) collaborated in the study involving 91 families, each having at least 3 members with prostate cancer. The team estimates that the faulty chromosomal region accounts for about one-third of hereditary prostate cancers or about 3% of the total number of cases. It may also play a role in other types of prostate cancer that do not have a hereditary component.

The implicated region, on the long arm of chromosome 1 (1q24-25), is now the object of intense scrutiny to identify the responsible gene, already named *HPC-1* (hereditary prostate cancer 1). Researchers expect that identification of the gene and its alterations along with elucidation of its function will lead to the development of a susceptibility test and new insights into prevention and management of the disease, which can be treated effectively if discovered early.

Success in finding evidence of a genetic susceptibility came as a surprise to some researchers. "There have been arguments up to the present day that this type of study would be a total failure. Prostate cancer is so common and so complex that finding genes that predispose to the disease was thought to be impossible," said Jeffrey Trent (NCHGR), head of the laboratory that did most of the genotyping.

Another example of such a discovery, noted Trent, is the recent report of a major gene for Parkinson's disease [*Science* **274**, 1197–99 (November 15, 1996)]. "And the same thing has been said about multiple sclerosis, diabetes, schizophrenia, hypertension, and other complex diseases," he continued. "These diseases are so common that in the past geneticists have said we can't address them. But a study like this shows that they really are approachable. And the information we get from them ultimately will be of tremendous benefit to patients."◊

Should the Public—Minorities in Particular—Be Concerned About the Human Genome Project?

Leading genome scientists and bioethicists, concerned about the societal impacts of genetic discoveries from the Human Genome Project, met in September at Tuskegee University to address some of the project's implications for African Americans. Attendees noted the significance and appropriateness of the location in that Tuskegee is the county seat of Macon County, Alabama, site of the most infamous government medical experiment gone awry.* Supported by the DOE and NCHGR human genome programs, the 3-day Conference on the Human Genome Project attracted nearly 300 participants to the campus.

The conference brought together internationally recognized scientists, bioethicists, and legal scholars from government, industry, and academia to discuss the ethical, legal, and social implications (ELSI) of the use and misuse of genetic information. Focused particularly on how the data might affect African Americans, the meeting was also a vehicle for students from Tuskegee and other historically black institutions to meet with genome scientists, hear the issues, and explore career possibilities in genomics.

Discussions about Technical, Social, Ethical Implications

In rare "both-sides-of-the-argument" discussions, speakers expressed apprehension about the project and the use of its resulting genetic information. Concerns ranged from the fear of actuarial classifications of "genetic exceptionalism" to the burden African Americans would face if they were among those labeled by some as a biological underclass.

Keynote speaker Ari Patrinos of DOE discussed the current status of the project and DOE's role in this unique biological undertaking. Addressing a concern of most participants, Patrinos stated that, based on molecular evidence, variations among individuals are due to 1 difference in 1000 bases. At the molecular level, therefore, what unites us dwarfs what divides us.

In one of the most discussed presentations, featured speaker and molecular geneticist David Botstein (Stanford University) took on the myths and power of genetic information. Taking exception to the most extreme interpretations of the impacts of the project, he declared that "it ain't going to happen—all this sexy stuff about 'perfect babies'!" He said that those apprehensive about the genome project should recognize that genetic information has limited uses. The reality, he stated, is that the project has provided the infrastructure for wholesale, systematic discovery of disease genes, including those for some cancers, at a fraction of the cost and time it previously took to find just one gene. This capability has led insiders to refer to the genome project as the infrastructure on which a whole new industry is being built.

Patricia King (Georgetown University Law Center), an original member of the NIH-DOE Joint ELSI Working Group, recognized the enormous promise of the Human Genome Project. However, she defined two categories of potential problems. The first is whether everyone will share in the expected health benefits, or just those who can afford genetic testing and possible medical intervention. Second is the real danger that simple genetic explanations will be given for human characteristics that actually involve complex social, cultural, and environmental influences. Such simplistic explanations have already been offered (and debunked) with regard to intelligence and violent behavior, she said. King further stated that genetic information might be used to define a biological underclass, consisting primarily of minorities, as unemployable, uneducable, and uninsurable.

Although he agreed that these are very legitimate considerations, Rick Myers, director of the Stanford Human Genome Center, indicated that possible misapplications should not derail current work to develop a highly useful genetic map and to sequence the entire genome. Efforts should be made, however, to make changes in our social system that will minimize these problems in such areas as health care and insurance.

Contact for additional information, video and audio tapes, and conference proceedings: Ed Smith; 109 Milbank Hall; Tuskegee University; Tuskegee, AL 36088 (334/727-8028, Fax: -8552, *edsmith@acd.tusk.edu*)

Georgia Dunston (Howard University) and Fatimah Jackson (University of Maryland) brought up other questions. Dunston described her genomic research in the African-American Pedigrees (G-RAP) project at Howard University, developed in response to the absence of such pedigrees in the CEPH DNA panel. Dunston's project has as its primary objective the identification and characterization of DNA polymorphic markers that will be useful in mapping genes underlying diseases or susceptibility to diseases common in African Americans. The long-range goal of G-RAP is to improve the health of African Americans through research on DNA variability. The G-RAP program also provides Howard students an opportunity to receive training and conduct research in genetics, thus increasing the pool of African-American scientists participating in human genome research.

Jackson, an anthropologist, suggested that the genome project is the most important molecular taxonomic effort of this century because it will by definition set the taxonomic norms or baselines for *Homo sapiens sapiens* (*Hss*). African Americans should be concerned, added Jackson, about whether their sequence data will be included in the reference taxonomic description of *Hss* and whether the genome project has followed the best procedures of population biology to ensure equal representation.

Tom Murray (Case Western Reserve University) expressed the fear that genetic information might be misused, especially in insurance decisions and risk classification. Murray

*Between 1932 and 1972 the U.S. Public Health Service conducted the "Tuskegee Study of Untreated Syphilis in the Negro Male" to observe the course of the disease. In this study, 600 low-income African-American men, 400 of whom were found to be infected with syphilis, were monitored but treated only with placebos. Participants received no treatment even after a proven cure, penicillin, became available in the late 1940s.

indicated that the concept of actuarial fairness requires payment of premiums according to risk. This creates a "catch 22" for individuals who either have a disease or a risk of disease, such as might be suggested by a genetic test. In response, actuary Dave Christianson (Lutheran Brotherhood) stated that insurance factors often are exaggerated and that alternatives exist to lessen the impact of actuarial decisions based on genetics.

In his presentation Luca Cavalli-Sforza (Stanford University), author of *The Great Human Diasporas*, said genetic evidence suggests that differences among groups are less than those within groups, indicating that racism is a "human sin" not supported by biology. Human population genetics tells us, he continued, that "the enormous continuity in variation makes it almost impossible to define race except in a very, very approximate way. And you would have to say that there are thousands of races."

Summarizing the importance of the meeting, Daniel Drell (DOE Human Genome Program) said, "Rapid progress toward obtaining a reference human genome sequence has heightened the urgency of dealing with the challenging and complex ELSI considerations arising from the Human Genome Project. While many of these issues are not novel, they nonetheless remain difficult and need to be addressed. Nowhere is it more appropriate to acknowledge this than here at Tuskegee University." *[Ed Smith, Tuskegee University]* ◊

Teens Collaborate in DNA Sequencing

Unique Program Teaches Via Research Participation

Sequencing the human genome may seem an unlikely activity for teenagers, but Maureen Munn says it's a great way to get them really thinking about genome science and the implications of genetic testing.

Contact:
- Maureen Munn (206/616-4538 or *mmunn@u.washington.edu*)

"We're making research real for them," says Munn, director of the High School Human Genome Program at the University of Washington in Seattle. The program is partially supported by a grant from the Ethical, Legal, and Social Issues sector of the DOE Human Genome Program. "Students participate in actual research with scientists, many of whom are not much older than the kids and who wear the same T-shirts and backward caps. Along with learning the fundamentals of DNA sequencing, the students hear stories about how they became scientists."

Science and Ethics

In the science component of the instructional module, the classes sequence DNA isolated from a region on human chromosome 5. This region appears to carry a gene associated with a form of hereditary deafness that haunts a large Costa Rican family who can trace their lineage—and the disorder—back to the mid-18th century. Each student group determines the sequence of a small fragment taken from a 6.8-kb piece of DNA that was isolated from the genome of a nonaffected family member. They use standard Sanger sequencing methods to generate sets of DNA fragments, which are then separated on a polyacrylamide gel and stained to create purple bands on the gel. "There's probably no better way of conveying the information than by seeing the bases laid out on the gel ladder," Munn says.

The entire sequence of the DNA piece eventually will be assembled from all the partial sequences generated by the students, using the same basic method genome researchers use—finding overlapping sequences that identify the segments adjacent to each other in a whole, uncut genome.

Maureen Munn demonstrates a sequencing technique at the National Association of Biology Teachers annual meeting in Charlotte, North Carolina.

Students in the program also learn about the impact of genetic research on the lives of real people. Developed by ethicists from the University of Washington Department of Medical History and Ethics, the ethics portion of the module focuses on issues raised by presymptomatic testing in patients at risk for Huntington's Disease (HD). This inherited, severe neurological disorder usually doesn't become symptomatic until midlife. The module provides a scenario about a family that carries the HD allele, descriptions of the clinical and genetic aspects of the disorder, an exercise in drawing pedigrees, and an autoradiograph showing the PCR assay used to detect HD. Students use an ethical decision-making model to decide whether or not they would be tested for the HD allele, and those who choose to be tested are given mock laboratory results.

Teacher Workshops

Munn holds a week-long workshop in the summer for teachers to learn about the program, which was conceived in the Department of Molecular Biotechnology laboratories of Maynard Olson and Leroy Hood. During the school year, the program furnishes local teachers with equipment, supplies, and technical support to carry out DNA sequencing with their students. Teachers from other regions link with scientists in their communities who help provide equipment and expertise.Twenty teachers from the Seattle area are involved with a team of 50 volunteer scientists in the expanding program. Munn also distributes the module to teachers and scientists throughout the country and will send DNA samples to those wishing to participate. ➠

In October 1996 Munn presented a 1-day version of the workshop at the National Association of Biology Teachers meeting in Charlotte, North Carolina. She was accompanied by two of her lead teachers from the Seattle area, Barbara Schulz and Peggy O'Neill Skinner, who explained most of the scientific and ethical issues to participants while Munn readied water baths and electrophoresis gels.

Although benefits of the program to high schoolers are obvious, Schulz pointed out a somewhat hidden advantage for scientists. "This is a good opportunity for them to reach out," she said. "We help them explain their work to the community. We know the kids talk about this experience at home, because their parents come back to us with questions about the Human Genome Project."

Munn and other participating investigators emphasize to the students the need for accuracy and a sense of responsibility because the data will be entered into the same public databases the scientists use. "This sequence eventually will be compared with one from an affected individual in a search for mutations that may be responsible for the disorder," she said. "When students ask how they can be sure their data is correct, it illustrates beautifully the nature of research: you have to go back and verify your results; there's no answer waiting in the back of a book!" she laughed.

Although she hopes the project will interest some students in science careers, Munn points to a broader goal. "We hope it encourages the development of a new generation of adults who can think creatively and constructively about the implications of science findings and how to make judicious decisions that could someday affect public policies," she said. *[Denise Casey, HGMIS]* ◊

This newsletter is prepared at the request of the DOE Office of Health and Environmental Research by the Biomedical and Environmental Information Analysis Section of the Health Sciences Research Division at Oak Ridge National Laboratory, which is managed by Lockheed Martin Energy Research Corp. for the U.S. Department of Energy, under Contract DE-AC05-96OR22464.◊

Science Features Genome Project

Full Text of Articles on Web

Much of the October 25, 1996, issue of *Science* is devoted to the human genome. Following are selected highlights from this annual "Genome Issue" edited by Barbara Jasny.

New Gene Map. The magazine's centerpiece is the first version of the new transcript map of the human genome pinpointing over 16,000 gene locations, more than tripling the total number of genes mapped by 1994. The international mapping consortium observed that "the gene map unifies existing genetic and physical maps with nucleotide and protein sequence databases in a fashion that should speed the discovery of genes underlying inherited human disease." The map is in a fold-out chart with accompanying article in *Science,* and it is available on the Web (*http://www.ncbi.nlm.nih.gov/SCIENCE96*).

Rising to the Occasion: Yeast Genome Analysis and Functional Biology. In the article "Life with 6000 Genes," A. Goffeau (Catholic University of Louvain, Belgium) discusses early analysis of the complete *Saccharomyces cerevisiae* genome. The sequence was completed last year in an international effort involving about 600 scientists in Europe, North America, and Japan. Goffeau also explains the excellent potential this organism represents for functional-analysis studies of a eukaryotic genome. This work will be aided, he notes, by the availability of "very efficient techniques . . . that permit any of the 6000 genes to be replaced with a mutant allele, or completely deleted from the genome, with absolute accuracy."

Have You Ever Wanted to Play With a Genome? This is a user-friendly guide to yeast databases on the Web (*http://www.sciencemag.org/science/feature/data/genomebase.htm*).

How Soon Should Sequence Data Be Released? In the "Policy Forums" section, an article by David R. Bentley (Sanger Centre) argues for release "directly upon completion . . . with an earlier prerelease of unfinished sequence and additional mapping information." Taking the opposing view, Mark D. Adams and J. Craig Venter (The Institute for Genomic Research) argue that data generated by lengthy sequencing projects should be made available only when "they have passed a series of rigorous quality-control checks and have been annotated."

Full text of all articles:
- *http://www.sciencemag.org/science/content/vol274/issue5287*

Global Genomics. In "The New Genomics: Global Views of Biology," Eric Lander (MIT–Whitehead Institute) proposes goals for the next phase of genomics: using genome project data to study gene function. Lander's goals focus on developing infrastructure, inventories, and technologies. Comparing genome data to the periodic table, Lander explains that the information will offer biologists "not 100 elements, but 100,000 genes; not a rectangle reflecting electron valences, but a tree structure depicting ancestral and functional affinities among the human genes," enabling genome-wide questions for a global perspective of the cell.

The Genome Project's Conscience. A "News & Comment" article discusses some aspects of the Human Genome Project's ethical, legal, and social component, deemed "the world's biggest bioethics program." A portion of the article focuses on preliminary findings related to wide-scale genetic screening for cystic fibrosis.◊

Whole-Genome Transcript Maps in GDB

The whole-genome transcript maps published in *Science* (Schuler et al., 1996) and displayed in GDB at the American Society of Human Genetics meeting in San Francisco have been loaded into GDB's production database (map list: *http://gdbwww.gdb.org/gdb-bin/genera/genera/hgd/IntegratedMap?!action=query&displayName=RH**). These maps can be viewed using GDB's Mapview helper application.◊

MGD 3.1 Release Update

Enhancements to the Mouse Genome Database (MGD) Release 3.1 are now online (*http://www.informatics.jax.org*). These include a new search engine to improve full-text searching within MGD; revised documentation and an online symbol-submission form from the Mouse Nomenclature Committee; modifications to several query forms, including a new option to search for EST probes; updates to the DNA Mapping Panel data sets; and available 1996 Chromosome Committee reports. [User Support: 207/288-6445, *mgi-help@informatics.jax.org*] ◊

GenPept Release 97.0

Release 97.0 of the GenPept (GenBank Gene Products) Database is available via ftp (*ftp.ncifcrf.gov*). GenPept is a searchable database containing known or potential coding regions identified by GenBank sequence submitters. Release 97.0 is not an official GenBank release but an attempt to provide a data file format compatible with existing software products. [Contact: Gary Smythers (*gws@ncifcrf.gov*)] ◊

Human Genome news

This newsletter is intended to facilitate communication, help prevent duplication of research effort, and inform persons interested in genome research. Suggestions are invited.

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Contact: Daniel W. Drell
301/903-6488, Fax: -8521
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TORCH Institutes for Teachers

Teacher OutReaCH (TORCH) institutes are 1-week workshops for middle- and high-school teachers of biology, physics, physical science, chemistry, mathematics, and history. Designed to increase knowledge of general content, applications, and teaching techniques, the courses are led by teams of teachers who have completed month-long institutes under the Woodrow Wilson National Fellowship Foundation. Colleges, universities, school districts, or local education agencies may apply to sponsor and locally host an institute. [Contact for sponsoring or attending an institute: Geri Marchioni (609/452-7007 ext. 21, *marchioni@woodrow.org*) or Mary Apodaca (ext. 19, *apodac@woodrow.org*), Fax: -0066] ◊

BES Program References, Web Sites

Information on BAC End Sequencing (BES) described in the last issue of *HGN* [**8**(1), 8] can be found in P. Ioannou and P. de Jong, *Current Protocols in Human Genetics*, Supplement 9, Unit 5.15 (1996), and C. Wu., S. Zhu, S. Simpson, and P. de Jong, *Nucleic Acids Research* **24**, 2614–15 (1996).

Related Web Sites

- BES project: *http://www.ornl.gov/meetings/bacpac/95bac.htm#bac*
- Roswell Park Cancer Institute: *http://bacpac.med.buffalo.edu*

See *HGN* article cited above for other related sites.◊

New Addresses for Genetic Linkage Analysis Laboratory

Jurg Ott's Statistical Genetics Lab, formerly at Columbia University and New York Psychiatric Institute, has moved to Rockefeller University. Below are new electronic addresses.

- Ftp: *ftp://linkage.rockefeller.edu*
- Web: *http://linkage.rockefeller.edu*
- Bibliography on Computational Gene Recognition: *http://linkage.rockefeller.edu/wli/gene*
- Chromosome 1 home page: *http://linkage.rockefeller.edu/chr1*

Linkage and pedigree analysis in large complex pedigrees (block V0.1.2):

- *http://www.cs.auc.dk/~claus/block.html* or *ftp.cs.auc.dk/pub/packages/* ◊

Notice to DOE Contractors, Grantees

The sixth DOE Human Genome Program Contractor-Grantee workshop will be held November 9–13, 1997, in Santa Fe, New Mexico. At least one investigator from each funded project is expected to attend the entire meeting and represent the project at poster sessions. Some projects also will be represented in platform presentations. More information on registration and abstracts will be forthcoming from Sylvia Spengler; Human Genome Program Coordination; 459 Donner Laboratory; Lawrence Berkeley National Laboratory; Berkeley, CA 94720 (510/486-4879, Fax: -5717, *sjspengler@lbl.gov*).◊

Biological Data Transport Upgrade

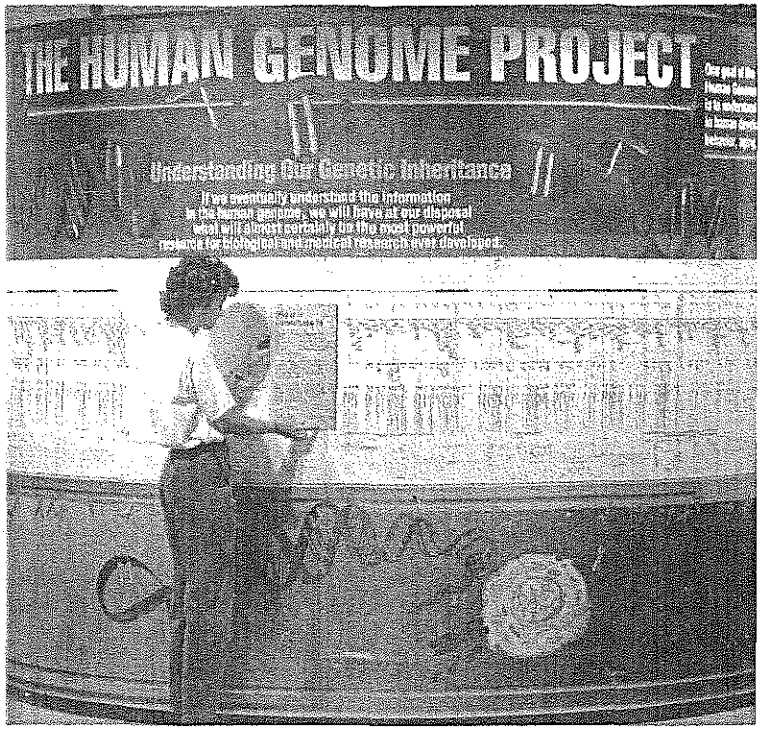
Recent upgrades of the Biological Data Transport bioinformatics resource (*http://www.data-transport.com*) include additions to the Query Depot. The site provides a central location to conduct bioinformatics-related searches of public data. These searches, which can be requested simultaneously for the same query to save time, provide access to such resources as GenBank, Entrez, BCM Search Launcher, BLAST, Genome Database, Human Gene Mutation Database, and several vendors. [Contact: Scott Jokerst, 510/648-8229, *scott_jokerst@data-transport.com*]◊

Journal Changes Name and Scope

The journal *Genome Science & Technology* [*HGN* **8**(1), 12] has changed its name to *Microbial & Comparative Genomics*. Due to recent accomplishments in sequencing the complete genomes of representatives from the three domains of life, the journal will focus on true comparative genomics. [Contact: Mary Ann Liebert, Inc., 800/654-3237 or 914/834-3100, Fax: -1388, *liebert@pipeline.com* or Darrell Doyle, Senior Editor, 301/838-3500, Fax: -0209, *djdoyle@tigr.org*] ◊

Genetics Exhibit Opens in Los Alamos

"Understanding Our Genetic Inheritance" officially opened September 30 at the Bradbury Science Museum in Los Alamos, New Mexico. This exhibit explains the contributions of the Center for Human Genome Studies at Los Alamos National Laboratory (LANL) to the Human Genome Project—the international effort to map all the genetic information in human cells. The exhibit was planned and executed by Julie Meyne (LANL).



The centerpiece of the museum exhibit is a 16-foot-long version of LANL's map of human chromosome 16. Center researchers continually update the laboratory version of this map, which is used worldwide by scientists to locate specific genes on the chromosome and to determine which sections are associated with various diseases.

Also at the museum is the first robot designed and built at LANL to help biologists map the human genome. It can be activated to demonstrate some of the steps it once performed in the laboratory. In addition, two interactive computer programs developed by the Exploratorium in San Francisco help visitors learn more about the world of genetic research and discover their own inherited characteristics. Another activity allows matching of DNA "fingerprints" to see how missing persons can be identified. Wall panels give background information about DNA, chromosomes, DNA fingerprinting, and specific LANL research; benefits to human health through understanding the human genome; and ethical, legal, and social implications of genetic research.◊

IMGT Database

The international ImMunoGeneTics database (IMGT) specializes in immunoglobulins (Ig), T-cell receptors (TCR), and the major histocompatibility complex (MHC) of all vertebrate species. Comprising annotated sequences and alignment tables, IMGT includes two databases: LIGM-DB contains more than 19,000 Ig and TCR sequences from 78 species, and MHC/HLA-DB contains alignment tables for Class I and Class II human leucocyte antigens. [IMGT contact: Marie-Paule Lefranc (*lefranc@ligm.crbm.cnrs-mop.fr*)]

IMGT Database Access

- WWW at CNUSC (Montpellier, France): *http://imgt.cnusc.fr:8104*; informatics, *denys.chaume@cnusc.fr*; bioinformatics; *giudi@ligm.crbm.cnrs-mop.fr*
- WWW at European Molecular Biology Laboratory–European Bioinformatics Institute (Hinxton, U.K.): *http://www.ebi.ac.uk/imgt*; contact, *malik@ebi.ac.uk*
- Sequence Retrieval System: *http://www.ebi.ac.uk/srs/srsc* (Select "Search sequence libraries"; on the next screen, click off the "Swissprot" box and click on "IMGT.")
- Ftp: *ftp//ftp.ebi.ac.uk/pub/databases/imgt*
- CD-ROM: Database accompanying the Nucleotide Sequence Database of EMBL.◊

Five-Year Status of Gene Therapy Evaluated

Long-Term Efficacy, Adverse Consequences Not Yet Known

An overview of challenges facing gene therapy is presented in a special feature of the September 10, 1996, issue of *Human Gene Therapy* (**7**, 1781–90). "Gene Therapy in the United States: A Five-Year Status Report" concludes that it clearly is too early to assess the therapeutic efficacy of gene therapy or even to predict its promise. Although the public is excited about novel medical cures and some measure of success has been achieved in certain technical aspects of gene transfer, the report says that gene therapy is still at an early stage. Nearly all the gene-therapy studies consist of Phase I trials, with the goal of establishing the procedure's safety rather than its effectiveness. [Article reprints: Brian R. Smith; Yale University School of Medicine; 333 Cedar Street, P.O. Box 208035; New Haven, CT 06520-8035] ◊

GDB Access, User Support

- **United States** *http://gdbwww.gdb.org; help@gdb.org*
- **Australia** *http://morgan.angis.su.oz.au/gdb/gdbtop.html; bucholtz@angis.su.oz.au*
- **France** *http://gdb.infobiogen.fr; gdb@infobiogen.fr*
- **Germany** *http://gdbwww.dkfz-heidelberg.de; gdb@dkfz-heidelberg.de*
- **Israel** *http://gdb.weizmann.ac.il; lsprilus@weizmann.weizmann.ac.il*
- **Japan** *http://www2.gdb.gdbnet.ad.jp/gdb/gdbtop.html; mika@gdb.gdbnet.ad.jp*
- **Netherlands** *http://www-gdb.caos.kun.nl/gdb/gdbtop.html; post@caos.caos.kun.nl*
- **Sweden** *http://gdb.embnet.se:gdb; help@gdb.embnet.se*
- **United Kingdom** *http://www.hgmp.mrc.ac.uk/gdb/gdbtop.html; admin-gdb@hgmp.mrc.ac.uk*

Calendar of Genome and Biotechnology Meetings*

More comprehensive lists of genome-related meetings and organizations offering training are available at *http://www.ornl.gov/hgmis* or from HGMIS (see p. 12 for contact information).

February 1997

1–5. Miami Nature Biotechnol. Winter Symp.—Advances in Gene Technology: Biomolecular Design, Form, and Function; Fort Lauderdale, FL [Meeting Coordinator, 800/642-4363, Fax: 305/324-5665; *mbws@mednet.med.miami.edu*]

6–7. Oligonucleotide- and Gene Therapy–Based Antisense Therapeutics with New Applications for Genomics; San Diego, CA [IBC, 508/481-6400, Fax: -7911, *inq@ibcusa.com*; *http://www.io.org/~ibc*]

9–12. Techniques at the Genome/Proteome Interface; Baltimore, MD [ABRF '97, 301/530-7010, Fax: -7014; *abrf97@faseb.org*; *http://www.faseb.org/meetings*]

9–14. Quantitative Genetics and Biotechnology; Ventura, CA [GRC, 401/783-4011, Fax: -7644; *grc@grcmail.grc.uri.edu*; *http://www.grc.uri.edu*]

10–11. Molecular Genetic Profiling: Implications for Drug Discovery and Development; Bethesda, MD [C. Sussman, 508/480-6957, Fax: -6976; *carols@nmhcc.com*]

10–11. Display Technologies in Protein Engineering, Drug Discovery, Molecular Evolution and Vaccine Development; Lake Tahoe, NV [see contact: Feb. 6–7]

13–18. AAAS AMSIE '97: Engaging Science, Sustaining Society; Seattle, WA [Meetings Dept., 202/326-6450, Fax: /289-4021; *amsie97@aaas.org*; *http://www.aaas.org/meetings/meetings.htm*]

16–21. Molecular Mechanisms of Evolution: Structure, Function, Expression, and Regulation of Genes and Proteins; Santa Fe, NM (abs. deadline: Oct. 1, 1996) [Keystone Symp., 800/253-0685 or 970/262-1230, Fax: -1525; *keystone@symposia.com*; *http://www.colorado.net/symposia*]

17–21. 19th Annual Lorne Conf.: Organisation and Expression of the Genome; Lorne, Victoria, Australia [R.A. Sturm, +61-7/3365-1831, Fax: -4388; *r.sturm@mailbox.uq.edu.au*]

20. NCHGR Human Genome Lecture Series: Dierdre Meldrum: Capillary Automated Submicroliter Sample Preparation for Genome Analysis; Bethesda, MD [K. Nakamura, 301/402-0838, Fax: /480-2770; *nakamurk@odder.nchgr.nih.gov*]

24–26. Human Genome Project: Commercial Implications; San Francisco [CHI, 617/630-1300, Fax: -1325; *chi@healthtech.com*; *http://www.healthtech.com/conferences*]

27. TIGR/NRC/DOE Distinguished Speaker Series: James Watson, (CSHL); Rockville, MD [D. Hawkins, 301/838-3501, Fax: -0209; *dhawkins@tigr.org*; *http://www.tigr.org/conference/speakers/ds9697.html*]

27–28. Genetic Screening and Diagnosis of Human Diseases; San Francisco [see contact: Feb. 24-26]

28–Mar. 2. 4th Joint Clinical Genetics Meeting: 28th Annu. MOD Conf. and 4th Annu. ACMG Meeting; Ft. Lauderdale, FL [M. Greenfield, 301/571-1887, Fax: -1895; *mgross@genetics.faseb.org*; *http://www.faseb.org/genetics/acmg/ann-meet.htm*]

March 1997

6–8. HGM '97; Toronto [HUGO, 301/654-1477, Fax: /652-3368; *hugo@gdb.org*]

10. First Meeting of Prospective General Membership of Natl. Coalition for Hlth. Professional Educ. in Genetics; Washington, DC [K. Boehm, 301/402-0955; *kboehm@nchgr.nih.gov*]

13. TIGR/NRC/DOE Distinguished Speaker Series: David Botstein, (Stanford Univ.); Washington, DC [see contact: Feb. 27]

16–19. 4th Intl. Conf. on Automation in Mapping and DNA Sequencing; Heidelberg, Germany [I. Fatscher, +49-6224-929-025, Fax: -026; *fatscher@embl-heidelberg.de*; *http://www.embl-heidelberg.de/CourseInfo/AMS97/AMS97.html*]

16–21. Discovery and Development of Novel Therapeutic Agents for the 21st Century; Tamarron, CO [see contact: Feb. 16-21]

17–18. Symp. on Genomic Medicine; Rockville, MD [C. Sadler, 301/838-3509, Fax: -0229; *genmed@tigr.org*; *http://www.tigr.org/conference/genome_series.html*]

21–23. Intl. Workshop on Chromosome 10; Leeds, U.K. [N. Spurr, +44-171/269-3846, Fax: -3802; *spurr@icrf.icnet.uk*]

23–27. Electrophoresis '97; Seattle [D. Wiley, 913/843-1221, Fax: -1274; *dwiley@allenpress.com*]

31–Apr. 3. 11th Intl. Conf. on Math. and Computer Modeling & Scientific Computing; Washington, DC [X.J. Avula, 573/341-4585, Fax: /364-3351; *avula@umr.edu*]

31–Apr. 6. Unstable Triplets, Microsatellites, and Human Disease; Santa Fe, NM [Cambridge Symposia, 617/630-1399, Fax: -1395; *symposia@cambridge.org*; *http://www.cambridge.org/symposia*]

April 1997

4–5. 15th Annu. SERGG Meeting; Atlanta [M. Lane, 404/727-5844, Fax: -5783; *mrl@rw.ped.emory.edu*; *http://www.cc.emory.edu/PEDIATRICS/sergg/meeting/meeting.htm*]

9. TIGR/NRC/DOE Distinguished Speaker Series: Lee Hood, (Univ. of Washington); Washington, DC [see contact: Feb. 27]

13–19. Molecular and Cellular Biol. of Gene Therapy; Snowbird, UT [see contact: Feb. 16–21]

14–16. Genetic Testing for Cystic Fibrosis; Bethesda, MD [J. Ferguson, 301/496-5641, Fax: /402-0420; *jferg@helix.nih.gov*; *http://consensus.nih.gov*]

16–20. 38th Annu. Drosophila Res. Conf.; Chicago [M. Ryan, 301/571-1825, Fax: /530-7079; *mryan@genetics.faseb.org*]

17. NCHGR Human Genome Lecture Series: Wylie Burke: Care of Individuals with Inherited Predisposition for Cancer; Bethesda, MD [see contact: Feb. 20]

17–18. 5th Intl. Nature Genetics Conf.—Functional Genomics: From Genes to Drugs; Washington, DC [see contact: Mar. 31–Apr. 6]

May 1997

8. TIGR/NRC/DOE Distinguished Speaker Series: George Poste (SmithKline Beecham Pharm.); Washington, DC [see contact: Feb. 27]

14–18. Genome Mapping and Sequencing; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845; *meetings@cshl.org*; *http://www.cshl.org/meetings*]

18–20. 29th Meeting of European Society of Human Genetics; Genoa, Italy [Symp. Secretariat, +39-10/570-4092, Fax: -4093]

19–21. HGP Europe: Genomes, Diseases, Drugs, and Diagnostics; Monte Carlo, Monaco [see contact: Feb. 24–26]

28–June 1. AMIA 1997 Spring Cong.; San Jose, CA [AMIA, 301/657-1291, Fax: -1296; *http://www.amia.org*]

29–June 5. 4th Intl. Workshop on Mutation Detection; Brnobanks, Czech Republic [Workshop Secretariat, +44-171/935-8085, Fax: -8341; *hugo@hugo-europe.org.uk*; *http://hugo.gdb.org/mutation.htm*]

June 1997

8–11. Genetics of Common Diseases: 1997 Annu. Meeting of the Molecular Medicine Society; La Jolla, CA [Global Trade Productions, 703/671-1400, Fax: -7695]

21–26. 5th Intl. Conf. on Intelligent Systems for Molecular Biol.; Halkidiki, Greece (abs. deadline: March 21) [Conf. Secretariat, *ismb97@embl-ebi.ac.uk*; *http://www.cse.ucsc.edu/research/compbio/ismb97*]

30–July 2. Genomics: Commercial Opportunities from a Scientific Revolution; Cambridge, U.K. [SCI Conf. Secretariat, +44-171/235-3681, Fax: -7743; *conferences@chemind.co.uk*]

July 1997

20–25. Genetic Vaccinations; Plymouth, NH [see contact: Feb. 9–14]

August 1997

22–27. Human Molecular Genetics; Newport, RI [see contact: Feb. 9–14]

24–29. 17th Intl. Cong. of Biochemistry and Molecular Biol. in conj. with ASBMB 1997 Annu. Meeting; San Francisco [FASEB, 301/530-7010, Fax: -7014; *kmirabal@faseb.org*; *http://www.faseb.org*]

September 1997

13–17. 9th Intl. Genome Sequencing and Analysis Conf.; Hilton Head, SC [see contact: Mar. 17–18]

October 1997

16–19. Gene Therapy; Hilton Head, SC [see contact: Mar. 17–18]

28–Nov. 1. ASHG; Baltimore [see contact: Apr. 16–20]

November 1997

9–13. 6th DOE Human Genome Program Contractor-Grantee workshop; Santa Fe, NM [S. Spengler, 510/486-4879, Fax: -5717; *sjspengler@lbl.gov*] ◊

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

Training Events*

March 1997

14–27. Advanced Genome Sequence and Analysis; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845; *meetings@cshl.org; http://www.cshl.org*]

April 1997

3–4. Workshop on DNA Topology II; Piscataway, NJ [P. Pravato, 908/445-5930, Fax: -5932; *pravato@dimacs.rutgers.edu; http://dimacs.rutgers.edu/Workshops*]

May 1997

4–7. Genetic Analysis Methods for Medical Researchers (focus: human genetic disease mapping); Durham, NC (appl. deadline: Feb. 1) [V. Roberts, 919/684-6274, Fax: -6514; *genclass@genemap.mc.duke.edu; http://www.mc.duke.edu/depts/genetics/courses/index.html*]

25–29. Biotechnology for Business; Durham, NC [B. Maciunas, 919/660-1579, Fax: -1591; *biotech@chem.duke.edu; http://www.chem.duke.edu/special/biotech*]

June 1997

6–26. Advanced Bacterial Genetics; Cold Spring Harbor, NY [see contact: March 14–27]

6–26. Molecular Embryology of the Mouse; Cold Spring Harbor, NY [see contact: March 14–27]

20–August 21. Teaching the Ethical, Legal, and Social Implications of the Human Genome Project (Dartmouth College program for faculty from liberal arts colleges interested in developing a multidisciplinary course for their home institution); Hanover, NH [B. Hillinger, 603/646-1263, Fax: -2652; *barbara.hillinger@dartmouth.edu; http://www.dartmouth.edu/artsci/ethics-inst*]

July 1997

6–11. 18th Wellcome Summer School; "Human Genome Analysis: Genetic Analysis of Multifactorial Diseases"; Oxford, U.K. (appl. deadline: March 27) [J. Davey, +44-171/403-6998, Fax: /407-5281; *wss@umds.ac.uk; http://www.umds.ac.uk/lwlmg*]

24–August 1. 19th Wellcome Summer School. "Human Genome Analysis: From YAC to Gene"; London, U.K. (appl. deadline: March 27) [see contact: July 6–11]

August 1997

3–5. Workshop on Molecular Evolution; Woods Hole, MA (appl. deadline: May 13) [C. Hamel, 508/548-3705; *admissions@mbl.edu; http://www.mbl.edu*] ◊

Deadline for *HGN* Submissions

Calendar. Items for the *Human Genome News* (*HGN*) "Calendar of Genome and Biotechnology Meetings" or "Training Events" should be submitted by mail, e-mail, or fax as soon as information is finalized. See page 12 for HGMIS contact information. *HGN* is published quarterly.

Meeting Reports. In addition to these advance calendar listings, *HGN* staff welcomes reports on past chromosome workshops and sequencing, mapping, informatics, and ELSI meetings.◊

Funding Opportunities

DOE OHER

Computational Molecular Biology

Topic: Ten postdoctoral fellowships to catalyze career transitions into computational molecular biology from other scientific fields. These fellowships are funded by DOE and the Alfred P. Sloan Foundation to give young scientists an intensive 2-year postdoctoral opportunity in an appropriate molecular biology laboratory. Selections will be announced in June 1997, and funding can begin any time after September 1, 1997.

- Applications due April 14, 1997.

Contact: Christine Trance; Alfred P. Sloan Foundation; 630 Fifth Ave., Ste. 2550; New York, NY 10111 (212/649-1649, Fax: /757-5117, *trance@sloan.org*)

NABIR Program

Program Notice 97-04

Topic: Scientific research elements in the Natural and Accelerated Bioremediation Research (NABIR) Program.

Full announcement, guidelines: *http://www.er.doe.gov/production/grants/grants.html* or *http://www.lbl.gov/NABIR*

- Applications due January 30, 1997.

Contact: John Houghton (301/903-8288, Fax: -8519, *john.houghton@oer.doe.gov*)

NIH NCHGR

Genome-Analysis Technologies

RFA HG-97-001 (R01, P01, R21)

Topic: To develop novel genomic-scale technologies for the study of genome function and sequence variation. These technologies will facilitate, among other things, elucidation of the biological roles of gene products and noncoding functional elements, interactions among functional elements in the cell, biological consequences of genome organization, dynamics of polymorphisms in populations, and the functional significance of genomic variation.

- Letters of Intent due February 27, 1997.
- Applications due March 27, 1997.

Contact: Elise Feingold (see NCHGR contact information in box)

RFA: *gopher://gopher.nih.gov/00/res/nih-guide/rfa-files/RFA-HG-97-001*

NIH National Research Service Award Fellowships

Topic: To engage in research relevant to the Human Genome Project. Postdoctoral, senior postdoctoral, and minority predoctoral fellowships are available to U.S. citizens or permanent residents; research in ethical, legal, and social issues (ELSI) is not open to predoctoral students through this program.

- Applications for postdoctoral and senior postdoctoral due December 5, April 5, and August 5.
- Applications for minority predoctoral due May 1 and November 15.

Contacts: ELSI topics, Eric Meslin (301/402-4997, *eric_meslin@nih.gov*); all other topics, Bettie Graham (see NCHGR contact information in box) ◊

U.S. Genome Research Funding

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

DOE Office of Health and Environmental Research (OHER) Human Genome Program

- Contact for funding information or general inquiries: *genome@er.doe.gov* or 301/903-6488
- Relevant documents: *http://www.er.doe.gov/production/oher/hug_top.html*

Alexander Hollaender Distinguished Postdoctoral Fellowships (DOE)

Research opportunities are available in energy-related life, biomedical, and environmental sciences, including human genome, global change, and supporting disciplines.

- Next deadline: January 1998
- Contact: Barbara Dorsey, Oak Ridge Institute for Science and Education (423/576-9975, Fax: /241-5219)

NIH National Center for Human Genome Research (NCHGR)

Program announcements are listed on the Web (*http://www.nchgr.nih.gov/Grant_info/Funding*).

- NCHGR Program Contact: 301/496-7531, Fax: /480-2770, *http://www.nchgr.nih.gov/home.html*
- ELSI: 301/402-4997

Small Business Innovation Research (SBIR) Grants

DOE and NIH invite small business firms (less than 500 employees) to submit grant applications addressing the human genome topic of SBIR programs. The two agencies also support the Small Business Technology Transfer (STTR) program to foster transfers between research institutions and small businesses.

DOE SBIR applications in Genome, Structural Biology, and Related Technologies are due March 3, 1997, for FY 1997.

Contacts:

- Kay Etzler; c/o SBIR Program Manager, ER-16; DOE; Washington, DC 20585 (301/903-5867, Fax: -5488, *kay.etzler@oer.doe.gov*); SBIR, *http://sbir.er.doe.gov/sbir.htm*; STTR, *http://sttr.er.doe.gov/sttr.htm*
- Bettie Graham (see contact, NCHGR). NIH SBIR due April 15, August 15, and December 15. STTR, December 1

National SBIR/STTR conference: Orlando, FL (April 2–4, 1997). Conference information: 203/205-6450.◊

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3. ___ Reprint of "A New Five-Year Plan for the U.S. Human Genome Project" (*Science*, October 1, 1993) by Francis Collins and David Galas

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SELECTED ACRONYMS

AAAS Am.Assoc. for the Advancement of Sci.
ABRF Assoc. of Biomolecular Resource Facilities
ACMG Am. Coll. of Medical Genet.
AMIA Am. Med. Informatics Assoc.
AMSIE Annu. Meeting and Sci. Innovation Expo.
ASBMB Am. Soc. for Biochem. and Mol. Biol.
ASHG Am. Soc. for Hum. Genet.
BAC bacterial artificial chromosome
bp base pair
CHI Cambridge Healthtech Inst.
cM centimorgan
CSHL Cold Spring Harbor Lab.
DHHS NIH Dept. of Health and Human Services
DOE Dept. of Energy
ELSI ethical, legal, and social issues
EST expressed sequence tag
FASEB Fed. of Am. Soc. for Exp. Biol.
FISH fluorescence in situ hybridization
GDB Genome Database
GRC Gordon Res. Conf.
HGM Human Genome Meeting
HGMIS Human Genome Management Information System
HGP Human Genome Project
HUGO Hum. Genome Org.
IBC Intl. Business Communications
MIT Massachussetts Institute of Technology
MOD March of Dimes
NCHGR Natl. Ctr. for Human Genome Research
NIH Natl. Institutes of Health
NRC National Research Council
OHER Office of Health and Environmental Research
PAC P1 artificial chromosome
SERGG SouthEastern Regional Genetics Group
STS sequence tagged site
TIGR The Inst. for Genomic Res.
WWW World Wide Web
YAC yeast artificial chromosome

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