Human Genome news

Linking Interdisciplinary Contributors and Users of Genome Data and Resources

U.S. Department of Energy Office of Biological and Environmental Research www.ornl.gov/hgmis/project/about.html

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In This Issue

From DNA Sequences to Living Systems

Genomes to Life, Microbial Cell Project—Complementary New DOE Programs Explore Critical Life Processes

The complete DNA sequences for organisms ranging from humans to mice and microbes are presenting an even greater scientific challenge—to understand how life's component parts function together and are influenced by environmental factors in creating and operating dynamic living systems. DOE, a key player in the genomics revolution, is poised to make important contributions to this next grand scientific quest through the Microbial Cell Project (MCP) and the proposed Genomes to Life (GTL) program.

The MCP takes a whole-genome approach to understanding the function and regulation of all genes for a single living system and the pathways in which the protein products interact. The MCP will play a leading role in GTL, DOE's major new undertaking.

The GTL will build on previous Office of Science research that includes the Human Genome Program and the Microbial Genome Program initiated in 1994. The plan for GTL is to use DNA sequences from both microbes and higher organisms, including humans, to systematically tackle questions about essential life processes conserved across species. Advanced technological and computational resources tested and modeled in the MCP will be used to identify and understand the underlying mechanisms that enable organisms to function in diverse environmental conditions.

In a sense, the MCP is advance reconnaissance for GTL, and the two programs are and will remain closely entwined.

Both GTL and the MCP contribute toward the shifting of biology to a more quantitative science, involving the collection, integration, and dissemination of diverse data and the development of appropriate tools. The two programs will formulate more high-throughput methodologies for simultaneously studying many components of living systems.

The extraordinary applications of this holistic approach will help DOE fulfill its broad missions in energy, environmental remediation, and protection of human health. [For more details on GTL, see color centerfold and *http://DOEGenomesToLife.org;* for information on MCP, see article, p. 2, and *http://microbialcellproject.org.*] ◊

OASCR Joins OBER in Genomes to Life Program

The DOE Office of Biological and Environmental Research (OBER) and Office of Advanced Scientific Computing Research (OASCR) have formed a strategic alliance to meet the challenges of studying complex systems. OASCR fosters and supports fundamental research in advanced scientific computing and computational science—applied mathematics, computer science, and networking—and operates supercomputer, networking, and related facilities. These tools enable researchers to analyze, model, simulate, and predict complex phenomena relevant to DOE's biological missions. The proposed Genomes to Life program fits readily into this portfolio. ◊

In the News

DOE Microbial Cell Project

A Perspective by Daniel Drell

Daniel Drell
DOE Human Genome Program

More than 50 complete microbial genome sequences have been deciphered since the publication of the first in 1995. These sequences offer scientists an unprecedented opportunity to study cellular life in its simplest form and to begin understanding how nature orchestrates the activities of living systems.

This opportunity is at the root of DOE's new Microbial Cell Project (MCP), begun in 2001 by the Office of Science's offices of Biological and Environmental Research (OBER) and Basic Energy Sciences (OBES), allied with the Office of Advanced Scientific Computing Research (OASCR). OBER and OBES contributed $12 million and OASCR $3 million through its Advanced Modeling and Simulation of Biological Systems Program.

The challenges are great. Although the complete list of life's working parts for sequenced genomes is now online, many perform unknown functions. Additionally, little is understood about how and when the parts function together in living cells and respond to environmental changes. Gaining an understanding of the complexities of systems-level functioning also requires new ways of thinking and collaborations with scientists from such other disciplines as engineering; chemistry; physics; and the computer, imaging, and even management sciences.

Why Microbes?

Microbes have evolved for 3.7 billion years and have colonized almost every environment on earth. In the process, they have developed an astonishingly diverse collection of capabilities that can be used to help DOE meet its challenges in toxic-waste cleanup, energy production, global climate change, and biotechnology.

Additionally, their internal organization and complex regulatory systems allow microbial cells to adapt to a myriad of environments. They work as miniature chemistry laboratories, making unique products and carrying out functions specific to their environmental conditions.

Understanding the complex functioning of a single microbial cell ultimately will enable science to go far beyond just exploiting the beneficial capabilities of microbes to meet DOE's missions. Much of the knowledge gained will apply to cells in all living organisms. The MCP thus represents a first step in moving from cataloguing molecular parts to constructing an integrative view of life at the level of a whole organism—microbe, plant, or animal.

Goals

The MCP has four main goals:

- Determine how microbial proteins combine into molecular machines that fulfill many of life's important intracellular processes.
- Characterize the internal cell environment and its effects on the proteins and protein machines that perform functions relevant to DOE missions.
- Characterize the intracellular distribution, quantities, and fluxes of the proteins and protein machines inside a microbial cell.
- Use high-end computing to model gene-to-gene, gene-to-protein, and protein-to-protein interactions and the cell's internal biochemistry.

In addition to working with academic, nonprofit, and industrial partners, DOE will take advantage of the scientific capabilities of its national laboratories. These capabilities include high-throughput genomic DNA sequencing, microbial biochemistry and array development and analyses; physiology; very high resolution imaging; and structural biology. National user facilities such as synchrotrons will play important roles, as will high-performance computing.

The MCP's ultimate aim is to learn enough about cellular functions so they can be manipulated knowledgeably to enhance beneficial and suppress unintended effects. MCP planners are well aware that it is premature to explore manipulations or interventions. Given the complexity of metabolic networks in even the simplest cell, such actions would be analogous to throwing the proverbial monkey wrench into a complex machine; the outcomes most likely would not be useful and informative. When greater knowledge is gained about the parts, their interactions, the functional pathways to which they belong, their partners in biochemistry, and their temporal and spatial distribution within the cell, these interventions—if and when they merit exploratory research—can be more precise and predictable.

The MCP is as bold and major an undertaking as DOE's Human Genome Initiative was in 1987. Much of the MCP's research appeal stems from the simple fact that this is where the science is leading. Like fortunate children with their first Lego set who have seen the pictured item and know it can be built, we have opened the box and found the pieces. The instructions are missing, however, so we must complete the construction through experimentation. Fortunately, we can build on decades of intense biological research to make the job easier.

The MCP makes its first grant awards this summer. A list will be available via the Web (*http://microbialcellproject.org/funding*) and will be the subject of an article in the next issue of *HGN*. *[Daniel Drell, 301/903-4742, daniel.drell@science.doe.gov]* ◊

☛ Image Galleries

High-quality, original graphics can be downloaded from the HGMIS Web site. No permission is needed, but please let HGMIS know where they were used.

- Human Genome Project Information: *www.ornl.gov/hgmis/graphics/slides/images1.html*
- Genomes to Life Program: *http://doegenomestolife.org/gallery/images1.html*

Please cite the U.S. Department of Energy Human Genome Program and list the Web site's home page. ◊

In the News

Human Genome Working Draft: First-Edition Travel Guides

In February, scientists from the public Human Genome Project and the private company Celera Genomics published the long-awaited details of the working-draft DNA sequence achieved less than a year before. Although the draft is filled with mysteries, the first panoramic view of the human genetic landscape has revealed a wealth of information and some early surprises. Papers describing research observations in the journals *Nature* (Feb. 15) and *Science* (Feb. 16) are freely accessible via the Web (*www.ornl.gov/hgmis/project/journals/journals.html*).

Although clearly not a Holy Grail or Rosetta Stone for deciphering all of biology—two early metaphors commonly used to describe the coveted prize—the sequence is a magnificent and unprecedented resource that will serve as a basis for research and discovery throughout this century and beyond. It will have diverse practical applications and a profound impact upon how we view ourselves and our place in the tapestry of life around us.

One insight already gleaned from the sequence is that, even on the molecular level, we are more than the sum of our 35,000 or so genes. Surprisingly, this newly estimated number of genes is only one-third as great as previously thought and is only twice as many as those of a tiny transparent worm, although the numbers may be revised as more computational and experimental analyses are performed. At once humbled and intrigued by this finding, scientists suggest that the genetic key to human complexity lies not in the number of genes but in how gene parts are used to build different products in a process called alternative splicing. Other sources of added complexity are the thousands of post-translational chemical modifications made to proteins and the repertoire of regulatory mechanisms controlling these processes.

The draft encompasses 90% of the human genome's euchromatic portion, which contains the most genes. In constructing the working draft, the 16 genome sequencing centers produced over 22.1 billion bases of raw sequence data, comprising overlapping fragments totaling 3.9 billion bases and providing sevenfold coverage (sequenced seven times) of the human genome. Over 30% is high-quality, finished sequence, with eight- to tenfold coverage, 99.99% accuracy, and few gaps. All data are freely available via the Web (*www.ornl.gov/hgmis/project/journals/sequencesites.html*).

The entire working draft will be finished to high quality by 2003. Coincidentally, that year also will be the 50th anniversary of Watson and Crick's publication of DNA structure that launched the era of molecular genetics (*www.nature.com/genomics/human/watson-crick*). Much will remain to be deciphered even then. Some highlights from *Nature*, *Science*, and The Wellcome Trust follow (*www.ornl.gov/hgmis/project/journals/insights.html*).

What Does the Draft Human Genome Sequence Tell Us?

By the Numbers

- The human genome contains 3164.7 million chemical nucleotide bases (A, C, T, and G).
- The average gene consists of 3000 bases, but sizes vary greatly, with the largest known human gene being dystrophin at 2.4 million bases.
- The total number of genes is estimated at 30,000 to 35,000—much lower than previous estimates of 80,000 to 140,000 that had been based on extrapolations from gene-rich areas as opposed to a composite of gene-rich and gene-poor areas.
- Almost all (99.9%) nucleotide bases are exactly the same in all people.
- The functions are unknown for over 50% of discovered genes.

The Wheat from the Chaff

- Less than 2% of the genome codes for proteins.
- Repeated sequences that do not code for proteins ("junk DNA") make up at least 50% of the human genome.
- Repetitive sequences are thought to have no direct functions, but they shed light on chromosome structure and dynamics. Over time, these repeats reshape the genome by rearranging it, creating entirely new genes, and modifying and reshuffling existing genes.
- During the past 50 million years, a dramatic decrease seems to have occurred in the rate of accumulation of repeats in the human genome.

How It's Arranged

- The human genome's gene-dense "urban centers" are predominantly composed of the DNA building blocks G and C.
- In contrast, the gene-poor "deserts" are rich in the DNA building blocks A and T. GC- and AT-rich regions usually can be seen through a microscope as light and dark bands on chromosomes.
- Genes appear to be concentrated in random areas along the genome, with vast expanses of noncoding DNA between.
- Stretches of up to 30,000 C and G bases repeating over and over often occur adjacent to gene-rich areas, forming a barrier between the genes and the "junk DNA." These

CpG islands are believed to help regulate gene activity.

- Chromosome 1 has the most genes (2968), and the Y chromosome has the fewest (231).

How the Human Compares with Other Organisms

- Unlike the human's seemingly random distribution of gene-rich areas, many other organisms' genomes are more uniform, with genes evenly spaced throughout.
- Humans have on average three times as many kinds of proteins as the fly or worm because of mRNA transcript "alternative splicing" and chemical modifications to the proteins. This process can yield different protein products from the same gene.
- Humans share most of the same protein families with worms, flies, and plants, but the number of gene family members has expanded in humans, especially in proteins involved in development and immunity.
- The human genome has a much greater portion (50%) of repeat sequences than the mustard weed (11%), the worm (7%), and the fly (3%).
- Although humans appear to have stopped accumulating repeated DNA over 50 million years ago, there seems to be no such decline in rodents. This may account for some of the fundamental differences between hominids and rodents, although gene estimates are similar in these species. Scientists have proposed many theories to explain evolutionary contrasts between humans and other organisms, including those of life span, litter sizes, inbreeding, and genetic drift.

Variations and Mutations

- Scientists have identified about 1.4 million locations where single-base DNA differences (SNPs) occur in humans. This information promises to revolutionize the processes of finding chromosomal locations for disease-associated sequences and tracing human history.
- The ratio of germline (sperm or egg cell) mutations is 2:1 in males vs females. Researchers point to several reasons for the higher mutation rate in the male germline, including the greater number of cell divisions required for sperm formation than for eggs.

HGP Sequenced Genomes

Organism	Size (Mb)	Yr. Seq.	No. of Genes*	Gene Density**
Saccharomyces cerevisiae yeast (eukaryote)	12.1	1996	6034[1]	483
Escherichia coli bacterium (prokaryote)	4.6	1997	4200[2]	932
Caenorhabditis elegans roundworm (eukaryote)	97	1998	19,099[1]	197
Arabidopsis thaliana plant (eukaryote)	100	2000	25,000[1]	221
Drosophila melanogaster fruit fly (eukaryote)	180	2000	13,061[1]	117
Homo sapiens human (eukaryote)	3000	2000 draft	35,000–45,000[1]	12

Sources

1. *Nature* **409**, 819 (Feb. 15, 2001) (*www.nature.com/nature/journal/v409/n6822/fig_tab/409818a0_F1.html*)

2. Entrez Genomes (*www.ncbi.nlm.nih.gov/PMGifs/Genomes/micr.html*)

*Gene predictions are made by computational algorithms based on recognition of gene-sequence features and similarities to known genes. Current gene estimates await further confirmation, including characterization of their protein products and functions.

**Gene density = Number of genes per million sequenced DNA bases.

Applications, Future Challenges

Deriving meaningful knowledge from the DNA sequence will define research through the coming decades to inform our understanding of biological systems. This enormous task will require the expertise and creativity of tens of thousands of scientists from varied disciplines in both the public and private sectors worldwide.

The draft sequence already is having an impact on finding genes associated with disease. Over 30 genes have been pinpointed and associated with breast cancer, muscle disease, deafness, and blindness. Additionally, finding the DNA sequences underlying such common diseases as cardiovascular disease, diabetes, arthritis, and cancers is being aided by the human variation maps (SNPs) generated in the HGP in cooperation with the private sector. These genes and SNPs provide focused targets for the development of effective new therapies.

One of the greatest impacts of having the sequence may well be in enabling an entirely new approach to biological research. In the past, researchers studied one or a few genes at a time. With whole-genome sequences and new high-throughput technologies, they can approach questions systematically and on a grand scale. They can study all the genes in a genome, for example, or all the transcripts in a particular tissue or organ or tumor, or how tens of thousands of genes and proteins work together in interconnected networks to orchestrate the chemistry of life.

Post-sequencing projects are well under way worldwide (see related articles, pp. 1 and 7). These explorations will result in a more comprehensive, new, and profound understanding of complex living systems, with applications to human health, energy, global climate change, and environmental cleanup, among others. *[Denise Casey, HGMIS]* ◊

Take a Genome Tour

National Center for Biotechnology Information (NCBI) tutorial on how to use the publicly available DNA sequence data and analysis tools:
www.ncbi.nlm.nih.gov/Tour

NCBI Human Genome Map Viewer:
www.ncbi.nlm.nih.gov/cgi-bin/Entrez/hum_srch

Guide to online information resources:
www.ncbi.nlm.nih.gov/genome/guide/human

In the News

Genomes: 15 Years Later

A Perspective by Charles DeLisi, HGP Pioneer

Charles DeLisi

A common question asked by incredulous audiences 15 years ago was, "Whose genome will you sequence?" After all, there are several billion human genomes, we were reminded, all of them different.

I often answered somewhat cryptically that we would sequence everyone's and no one's. We were after a reference human genome—the organizational and structural properties of the genome that are invariant across our species. With this reference sequence now in hand, we are in a position to return to the more subtle and complex problem of diversity and to approach it with a power that scarcely could have been imagined 15 years ago.

Understanding diversity was in fact a central motivation of the Human Genome Project from the start. I recall in 1985 Mark Bitensky, then Director of Biological Sciences at Los Alamos National Laboratory, arguing passionately for genomic tools to characterize the molecular basis of disease predisposition and resistance and to develop an understanding that would make possible individualized medicine—what we now call pharmacogenomics.

Characterizing human polymorphisms would require rapid and accurate technologies for differential sequencing to detect that rare 1 in 1000 base substitution that on average distinguishes different genomes. The required technology was not available in 1985, but today mass spectrometry techniques can be used to perform 250,000 assays a day for single base substitutions at an error rate of less than one part in 10,000, thus providing the gold standard for single nucleotide polymorphism verification. We now are beginning to assemble the database required for the arduous task of associating complex disorders with sets of common alleles (that is, different versions of the same gene).

In a very real sense, much of biology is about change. Reference genomes, along with various machine-learning algorithms developed and adapted during the genome project, also are bringing microarray technologies to full power. In a few years, annotation of the human genome will be complete, and probes for every gene will be arrayed on a solid phase substrate of a few square centimeters. What microarray technology does better than any other current method is to monitor and characterize change, whether it is the result of normal cell growth and development, progression toward disease, or response to exogenous ligands. Diversity thus will be characterized with a precision and breadth that may well revolutionize medicine during the coming decades.

But, perhaps, an even more fundamental change has begun. The high-throughput computational and experimental methods of the post-HGP era are forcing molecular biology away from its spectacularly successful reductionist roots back toward the integrative systems physiology required to understand cell behavior. High-throughput genomic methods, which are a revolution for global characterization, are a start in that direction. The long leap from characterizing to understanding, however, will be possible only after analogous technologies are developed for proteins.

Although massively parallel technologies for protein profiling are not yet available, ideas are abundant and fledgling methods are proliferating. In the next 5 to 10 years we can expect the emergence of high-throughput technologies for profiling proteins in various states of modification. Since many patterns of information processing, feedback control, memory, and the like will be widely conserved across species, bioinformatics tools—many yet to be developed—will amplify what is revealed. The result will be a ➠

> We shall not cease from exploration
> And the end of all our exploring
> Will be to arrive where we started
> And know the place for the first time.
>
> —T. S. Eliot, "The Four Quartets, Little Gidding"

DeLisi Honored by President

Charles DeLisi (Boston University), DOE Associate Director for Health and Environmental Research in the mid-1980s, was one of 28 honorees to whom President Bill Clinton presented the Presidential Citizens Medal on January 8. According to the award citation, DeLisi was the first government scientist to conceive and outline the feasibility, goals, and parameters of the Human Genome Project. He helped to galvanize an international team of researchers to pool resources, create new technologies, and launch the monumental task of gene mapping and sequencing.

At the presentation ceremony President Clinton added, "Charles DeLisi's imagination and determination helped to ignite the revolution in sequencing that would ultimately unravel the code of human life itself. Thanks to his vision and leadership, in the year 2000 we announced the complete sequencing of the human genome. Researchers are now closer than ever to finding therapies and cures for ailments once thought untreatable."

Established in 1969 by Executive Order 11494, the medal is awarded at the president's sole discretion to U.S. citizens (living or dead) who have performed exemplary deeds of service for the nation or for their fellow citizens. The 2001 award winners were recognized for their remarkable service and accomplishments in a variety of areas, including civil rights, medicine and health, sports, human rights, religion, education, disability advocacy, government service, journalism, and the environment. They include Hank Aaron, Muhammad Ali, Elizabeth Taylor, Ronald Brown, Archibald Cox, Robert Rubin, Warren Rudman, and Charles Ruff. ◊

very rapid increase in the rate of pathway and network discovery, classification, and correlation with cell behavior. We thus will begin to build a deep understanding of the molecular correlates of change, of the differences and similarities between cells, and of the differences between identical cells under varying chemical and physical conditions. These will include some largely overlooked conditions such as stress imposed by mechanical forces and the constraints of geometry.

At the heart of biological processes, whether thermodynamically or kinetically driven, is molecular structure. The ability is well within reach to determine the structure of almost any protein domain computationally—and therefore rapidly and inexpensively.

There are two reasons for such optimism. First, the number of folds is relatively small. The best estimate, based on rigorous statistical sampling theory, is about 1300 for water-soluble domains. The same calculation indicates that, with an increase of 20% a year in protein-structure determination, 95% of all such folds can be determined in the next 15 years, even if we continue to select sequences at random. That's a generous estimate on time because, by using the right type of information, we can readily choose sequences in a way that increases the odds of finding a new fold. The second reason for optimism has to do with advances in algorithms for structure determination and, more important, the development of accurate and rapidly evaluatable free-energy functions that include solvation.

A fold provides only a first approximation to geometry, but, with the fold in hand, the detailed structure can be determined computationally. The ability to obtain virtually any structure at will opens the way to cell-system design, pathway modification, and selection by directed mutations in proteins.

Although humans took center stage in the genome project, every scientist recognized the universality of the methods. In particular, their potential applicability to DOE's environmental programs was of great interest from the outset.

Indeed, the new DOE plan, Genomes to Life, reminds us that microbes are ". . . the largest reservoir of . . . diversity on the planet." Specify an environmental condition, whether in a deep sea vent where temperatures hover above 100°C or in a waste site where radiation levels greatly exceed lethal human doses, and there will be found an ecological niche with microbial communities that have learned to accommodate and flourish. Among the most important challenges of post-HGP biology will be characterizing, understanding, preserving, and exploiting life's robustness.

As experimental methods become increasingly powerful, the mathematical and computational methods of systems engineering will be essential for converting data to knowledge, and yet another discipline will be drawn into the biological sciences. The dexterity with which the computer science community responded to the genomic challenge and the increasing acceptance of computation in the bench scientist's tool kit constitute one of the most extraordinary developments in the recent sociology of science. These trends no doubt will continue and become more pervasive as the abstractions underlying life processes are revealed and data generation continues to accelerate. The recently added Centers of Excellence in Biomedical Computing at the National Institutes of Health and similar programs at the National Science Foundation and DOE are excellent initial steps in preparing for the future of a science whose culture is changing almost as rapidly as the science itself. ◊

New Institute at NIH

On April 20, the Secretary of the U.S. Department of Health and Human Services approved the establishment of the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and, at the same time, the Office of Bioengineering, Bioimaging, and Bioinformatics (called OB3) was abolished. NIH is now proceeding with the selection of a NIBIB staff, director, and advisory council; and a Web site will be in place before the end of 2001.

Meeting Summary, Slides Available

A summary of the March 23 Bioengineering Research Partnership Grantee Meeting can be downloaded from the Web (*grants.nih.gov/grants/becon/brpannualmeet2001.pdf*). Slides from meeting presentations are at *grants.nih.gov/grants/becon/brppresentations/*. ◊

¶ NSF Quantitative Systems Biology Report

The report of the National Science Foundation Workshop on Quantitative Systems Biotechnology (QSB), held in September 2000, is on the Web (*www.wtec.org/qsb*). QSB is defined as engineering research to augment the prediction of a living organism's phenotypic behavior from genomic information and environmental conditions. Workshop objectives were to suggest the scope of a new QSB program solicitation and to examine the possibility of conducting an international study in this area. ◊

¶ Booklet on Structural Biology Basics

The Structures of Life, a new 60-page, full-color booklet from the NIH National Institute of General Medical Sciences, explains how structural biology provides insight into health and disease and is useful in creating new medications. Geared toward an advanced high-school or early college-level audience, the booklet also features "Student Snapshots" designed to inspire young people to consider careers in biomedical research (order through *www.nigms.nih.gov/news/publist.html*). ◊

In the News

International Group Coordinates Structural Genomics Efforts

Shapes of Biomolecules Offer Clues to Their Function

As the human genome sequence nears completion, new projects are under way to determine the 3-D shapes of all proteins and other important biomolecules encoded by the human genome and those of key model organisms. The goals of investigators in the international structural genomics community are to discover, analyze, and disseminate 3-D shapes of protein, RNA, and other biological macromolecules representing the range of nature's structural diversity. Currently, there is significant funding for such research in the United States, Canada, European Union, Israel, China, and Japan.

Airlie Meeting, Agreement

In April, a group of some 150 people from 4 continents met at Airlie Center near Washington, D.C., to discuss the general principles and coordination of research in structural genomics (*www.nigms.nih.gov/news/meetings/airlie.html*). The meeting was sponsored by the NIH National Institute of General Medical Sciences, Institute of Physical and Chemical Research (called RIKEN) in Japan, and U.K.'s Wellcome Trust. The resulting "Airlie Agreement" builds on one produced at the first such meeting held at the Wellcome Trust a year before (*www.nigms.nih.gov/news/meetings/hinxton.html*).

The Airlie group reached general agreement on collaboration in a number of areas, including standards for early data release, criteria for assessing the quality of structures, sharing of targeted protein lists, and archiving and curating data.

Specifically, the "Airlie Agreement" provides for open sharing of scientific data and technological expertise. The consensus conditions for data sharing reflect the balance between two different goals—timely and unrestricted release of all data and consideration for intellectual-property regulations that vary significantly in different countries. For projects with public funding, all data on biomolecular shapes are to be made freely available in all countries soon after their determination. In addition, the agreement recognized the potential for collaboration among researchers in academia and industry.

The group elected an executive committee to establish an international organization for structural genomics and to plan the next meeting, scheduled for October 2002 in Berlin. The executive committee consists of Thomas Terwilliger (Los Alamos National Laboratory), Udo Heinemann (Max-Delbrück-Center for Molecular Medicine, Berlin), and Shigeyuki Yokoyama (RIKEN Genomic Sciences Center, Yokohama, Japan). ◊

Imaging Biological Structures

Because molecular shape often provides clues to function in biological systems, obtaining a detailed knowledge of structure can help elucidate the basic principles of cell and organism function and the role of faulty structures in disease. A broad collection of structural data will provide valuable information beyond that available from individual structures and will have applications in the life sciences, biotechnology, and medicine.

Key advances making structural genomics research possible include the availability of synchrotrons and high-field NMR (nuclear magnetic resonance) instruments; the MAD (multiwavelength anomalous diffraction) method of phase determination; high-throughput cloning and recombinant expression; a flood of information from genome sequencing projects; and bioinformatics methods for protein-fold assignment, model building, and function prediction. ◊

Biologists Driving Synchrotron Use Rate

Life scientists (some 2400 of 6000) accounted for 40% of the users of the four DOE synchrotron light sources in 2000, according to DOE Associate Director for Biological and Environmental Research Ari Patrinos. Because of this demand, as many as 15 new synchrotron stations for protein crystallography are expected to open in the United States alone by 2003, and more stations are under consideration. If half the protein crystallography stations were devoted to high-throughput structure determination, Patrinos estimated, 30,000 such structures could be generated each year. [*Genome Technology*, 21 (May 1, 2001).] ◊

Human Proteome Organisation Formed

On June 25, the recently launched Human Proteome Organisation (HUPO) announced the election of Sam Hanash (University of Michigan) as its Inaugural President (*www.hupo.org*). Proteomics is the high-throughput study of protein expression and function. HUPO's goals are to increase awareness of the Human Proteome Project (HPP) and the importance of proteomics in the diagnosis, prognosis, and therapy of disease; foster international cooperation; and promote scientific research. HUPO's inaugural meeting, sponsored by Cambridge Healthtech Institute (CHI), was held in April in Virginia (*www.healthtech.com/2001/hpr/*), where topics included HPP, HUPO goals and objectives, and nominations for the first president. CHI is planning the next meeting for January 2002 in San Diego. ◊

Model Organism Sequence and Function Studies Flourish

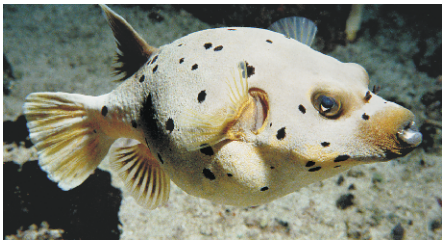
Model organism genomes sequenced in the Human Genome Project (HGP) have helped researchers identify many functionally important human DNA regions, including genes, and further studies will help elucidate fundamental biological processes common to all species. These organisms include the mouse, fruit fly, yeast, the bacterium *Escherichia coli*, and the roundworm. Outside the HGP, vast amounts of genomic data are being generated for a variety of microbial, animal, and plant systems. In this section are articles on the flowering plant *Arabidopsis thaliana* and the pufferfish *Fugu rubripes*, followed by those on the laboratory mouse and an algorithm for comparisons of model organisms. ◊

New Genome Project Tackles Sushi Delicacy

Scientists searching human genome data for genes and the DNA sequences that control their activity soon will have a valuable new resource, courtesy of the Japanese delicacy known as *Fugu* (*Fugu rubripes*) or pufferfish. An international consortium, led by researchers at the DOE Joint Genome Institute (JGI), has announced a collaborative agreement to sequence the *Fugu* genome (*www.jgi.doe.gov/programs/fugu.htm*).

Although the *Fugu* genome contains essentially the same genes and regulatory sequences as the human, it comprises only about 400 million bases as compared with the 3.2 billion bases that make up human DNA. With far less noncoding (sometimes known as "junk") DNA to sort through, identifying biologically important regions in the *Fugu* genome should be a much easier task. Comparing such DNA sequences from different species is an effective method because evolution tends to conserve these regions.

JGI is generating draft sequences for the *Fugu* genome project and applying Jazz, a new sequence assembler written at JGI.



Black-Spotted Pufferfish*. Photo by Jeff Jeffords, *http://divegallery.com

Sequence finishing and computational annotation are being done with other consortium members: U.K. Human Genome Mapping Project (*www.hgmp.mrc.ac.uk*); Institute of Molecular and Cell Biology, Singapore (*www.imcb.nus.edu.sg*); Molecular Sciences Institute, Berkeley (*www.molsci.org/welcome.shtml*); and Institute for Systems Biology, Seattle (*www.systemsbiology.org*).

Pufferfish are raised in bulk on farms in Japan, where the taste is considered addictive. If prepared improperly, however, the flesh can be lethal due to a highly potent neurotoxin present in *Fugu* ovaries, intestines, and livers. Eating pufferfish claims the lives of about 70 to 100 adventuresome (or unsuspecting) diners each year, most in rural areas and from fish improperly cleaned at home. It is the only food forbidden to be served to Japan's royal family.

Fugu's deadly effects have caught the imagination of many authors, including Ian Fleming. Near the end of *From Russia with Love*, the fictional James Bond is almost killed by *Fugu* toxin. ◊

In the News

Role of Key Breast Cancer Gene Identified

Researchers Genevieve Nonet, Martha Stampfer, and Paul Yaswen at Lawrence Berkeley National Laboratory and Joe Gray, Koei Chin, and Colin Collins at the University of California, San Francisco, published an article focusing on the functional characterization of the gene *ZNF217* in the February 15th issue of *Cancer Research* **61**. The gene is located in a region of chromosome 20 found to have an increased copy number in many tumors, including 40% of breast cancer cell lines. Reintroduction of the *ZNF217* gene into normal human breast cells in culture enables the cells to grow past the point at which they would normally stop. In addition to becoming immortal, the epithelial cells containing *ZNF217* gain several other features characteristic of tumor cells, such as the ability to express telomerase. These results support the hypothesis that *ZNF217* plays a role in breast cancer by allowing the cells to continue growing and accumulating other changes necessary for malignant progression. ◊

Breast Cancer Researchers Use Gene Expressions

Using gene-expression profiling, an international group of researchers led by Jeffrey Trent (NIH National Human Genome Research Institute) has made it possible to distinguish between hereditary and sporadic breast tumors for the first time. Simultaneous microarray assessments of some 6000 genes within breast cancer cells revealed clear and unique differences in activity patterns, leading to a new test that shows exactly which genes are active in a tumor cell. This capability may have important implications for both diagnosis and treatment. The findings were published in the *New England Journal of Medicine* **344**(8), 539–48 (February 22, 2001). ◊

Comparative Genomics

Plant Genome Significant to Agriculture, Energy, Human Health

Arabidopsis thaliana
Source: National Science Foundation

For the first time, scientists have sequenced the complete genetic material of a plant, that of the mustard weed *Arabidopsis thaliana*. The international *Arabidopsis* Genome Initiative (AGI) consortium published the results and early analyses in the December 14, 2000, issue of *Nature*, and articles are freely available on the Web through *Nature's* Genome Gateway (*www.nature.com/genomics/papers/a_thaliana.html*).

Scientists expect that systematic studies will illuminate numerous features of plant biology, including those of significant value to agriculture, energy, environment, and human health.

AGI, a collaboration of research groups in the United States, Europe, and Japan, is funded by government agencies on three continents. U.S. research was supported in large part by DOE's Office of Basic Energy Sciences, the U.S. Department of Agriculture, and the National Science Foundation (NSF).

Related to broccoli and cauliflower, *Arabidopsis* has emerged as a powerful tool in plant molecular biology because of its rapid life cycle, small physical size, and relatively small genome (125 Mb). The genome is organized into 5 chromosomes containing some 26,000 genes. Genes are compact and closely spaced (about 4.6 kb apart), suggesting short regulatory regions compared with animal genomes.

Potential Applications

Having the entire genome will help researchers identify plant-specific gene functions and develop rapid, systematic ways to locate genes important for growing larger crops that are more resistant to disease and weather and produce useful chemicals more efficiently. Plants also hold great potential as sources of renewable energy, although they currently represent just 3% of U.S. energy resources. Completion of the *Arabidopsis* genome sequence is revealing new information on how photosynthesis converts solar energy and carbon dioxide into biomass, helping scientists develop better plants for fuel and chemical uses.

The complete sequence of *Arabidopsis* is directly relevant to human biological functions as well, because many fundamental life processes at the molecular and cellular levels are common to all higher organisms. Some of those processes are easier to study in *Arabidopsis* than in human or animal models. *Arabidopsis* contains numerous genes similar to those that prompt human diseases ranging from cancer and premature aging to ailments such as Wilson's disease, in which the human body's inability to excrete copper can be fatal.

Gene Function Project

To help researchers capitalize on the genome sequence, NSF has begun the "2010 Project" to study the function of 26,000 *Arabidopsis* genes over the next decade. Thus far, scientists have determined experimentally the roles of only about 1000, with another 14,000 estimated using computational methods to identify similarities of genes with known functions. Strategies will involve inactivating or over expressing each gene, one at a time, and observing the consequences. The NSF 2010 Project is part of a worldwide *Arabidopsis* functional genomics effort that will be coordinated in a manner similar to the *Arabidopsis* genome sequencing project.

Data

For news, data, an interactive MapViewer, analysis tools, laboratory protocols, and useful links, see The *Arabidopsis* Information Resource (TAIR, *www.arabidopsis.org*). *[Denise Casey, HGMIS]* ◊

Drosophila Researchers Win Prize

At its annual meeting in San Francisco on February 17, the American Association for the Advancement of Science presented the prestigious Newcomb Cleveland Prize to five researchers representing the teams that completed the sequence of the fruit fly. Gerald Rubin and Susan Celniker accepted the prize on behalf of the Berkeley *Drosophila* Genome Project (BDGP), and J. Craig Venter, Gene Myers, and Mark Adams represented Celera Genomics. BDGP is a partnership among Lawrence Berkeley National Laboratory; the University of California, Berkeley; and Baylor College of Medicine.

The 2000 prize, which recognized an outstanding paper published in *Science* between June 1, 1991, and May 31, 2000, was awarded for "The Genome Sequence of *Drosophila melanogaster*." The paper is a series of articles jointly authored by hundreds of scientists, technicians, and students from 20 public and private institutions in 5 countries. It appeared in the March 24, 2000, special issue (*www.sciencemag.org/content/vol287/issue5461*).

Celera and BDGP began a collaboration in 1998 to determine whether the whole-genome shotgun-sequencing method pioneered by Venter could be used on organisms having many thousands of genes encoded in millions of DNA base pairs. The technique, previously tested successfully in much smaller bacterial genomes, proved in the larger fruit fly genome to be faster and more efficient than traditional methods. ◊

Microbial Conference Set for Tennessee

The Ninth International Conference on Microbial Genomes will be held October 28–November 1 in Gatlinburg, Tennessee (*www.esd.ornl.gov/microbial_genomes*). Hosted by Jizhong Zhou and Oak Ridge National Laboratory, the meeting will focus on DNA sequence, sequence comparison analysis, and recent advances in functional genomics. [Contact: Web site, *smithky@ornl.gov*, or *zhouj@ornl.gov*] ◊

Comparative Genomics

ORNL Mouse Program Provides Powerful Tools for Studying Human Genes

Connecting Sequence and Function

Sequencing genomes was the easy part. Some major challenges facing the new era of post-sequencing biology include finding all genes and deducing their functions, elucidating the connections between mutations and disease, and untangling the complex networks of interactions controlling all these processes in living systems. Model organisms such as the mouse, whose genes and DNA regulatory regions are remarkably similar to those of humans, provide powerful tools for illuminating our own genetic material.

Researchers in the Mouse Genetics and Genomics (MGG) section at Oak Ridge National Laboratory (ORNL) are using mouse genetics and mutagenesis strategies to annotate biologically important features of the DNA sequence and to provide functional information for parts of the genome that are expressed or that regulate gene expression (*http://bio.lsd.ornl.gov/mgd*). A complementary effort exploits genome data for a better understanding of normal and abnormal biological processes defined by genetic and phenotypic analyses of mouse mutations.

Mouse Mutations

MGG is screening about 10% of the mouse genome for chemically induced recessive mutations affecting a wide variety of physiological, neurological, behavioral, morphological, developmental, reproductive, cancer, aging, and other genetic phenotypes (*http://bio.lsd.ornl.gov/mgd/mutagenesis/mutagenesis.htmlx*). This activity expands on previous studies that identified over 50 mutations associated with visible or lethal phenotypes in 1% of this genome. The group is integrating microarray and proteomics technologies into these and other mutagenesis crosses for a molecular-based set of assays to complement whole-organism phenotypic screening. Point-mutation maps describing single-base changes of the target mutagenized regions are being merged with DNA sequence maps to correlate mutant phenotypes with specific genes.

Human Disease Models

Two allelic mutations were recently discovered that serve as models for human acute and chronic tyrosinemia (Aponte et al., *Proc. Nat. Acad. Sci. USA* **98**, 641–45, 2001). The group also has identified a significant candidate gene for an obesity-associated quantitative trait locus that may have an imprinted or maternal-effect component (Dhar et al., *Physiol. Genomics* **4**, 93–100, 2000).

MGG is evaluating specific candidate genes for induced mutations leading to (1) abnormal hematopoiesis (production of red blood cells), iron transport, and skeletal development; (2) abnormal brain function, resulting in epilepsy; (3) defective kidney function, resulting in juvenile death; (4) perinatal death, possibly due to skull or brain abnormalities; (5) early embryonic death due to a failure of yolk-sac hematopoiesis; (6) defective skin function, leading to alopecia and increased risk of skin cancer; and (7) modification of the agouti signaling pathway involved in pigmentation, obesity, diabetes, and cancer.

Screening Libraries

High-throughput mutation scanning is central to these gene-discovery efforts, so MGG is producing a large bank of 3000 to 5000 inbred C57BL/6JRn mice. They will carry point mutations induced in their sires by N-ethyl-N-nitrosourea and cryopreserving both tissues and gametes. DNA or RNA from these mice can be used to screen for point mutations in any gene. The mutations are identified by high-throughput heteroduplex analysis followed by DNA sequencing of PCR products from this large bank. Stocks of mice carrying the specific gene mutation can be reconstituted from the frozen gametes. An allelic series of mouse mutations for any preselected gene then can be used to test specific hypotheses about the structure-function relationships of the gene product in the context of a specific genetic network or environmental response. Initial targets for this type of analysis will include DNA-repair and other types of radiation- and stress-response genes; intracellular-transport genes; regulatory regions of selected genes, including imprinted ones; signaling molecules; and cancer-susceptibility genes.

Dabney Johnson and friend. Source: ORNL

User Facility

The Mouse Genetics Research Facility is a DOE Biological and Environmental Research User Facility, offering expertise in mouse genetics and mutagenesis, molecular biology, and functional genomics. Mutant mouse stocks, mutagenesis and phenotyping protocols, and genomic expression and phenotype data are available to the functional genomics and wider biological research communities through database, cryopreservation, and mouse-distribution efforts at ORNL. The Mutant Mouse Database provides searchable, one-stop shopping for new and archived mutant-mouse stocks created over the program's 50-year existence. *[Dabney Johnson, ORNL, johnsondk@ornl.gov, http://bio.lsd.ornl.gov/mgd]* ◊

MicroCAT Scanner Used for Screening

A high-resolution X-ray–computed tomography (CT) system developed at ORNL by Mike Paulus and Shaun Gleason provides researchers with a high-throughput method of internally screening mice for defects and damage resulting from mutations. The MicroCAT scanner, which generates 3-D images in 7 to 20 minutes, eliminates the need to sacrifice and dissect the mice. This allows researchers to monitor ongoing changes in animals, thereby facilitating studies on disease progression, consequences of aging, and responses to therapies.

Comparative Genomics

Consortium Achieves Draft Mouse Sequence

In May the international Mouse Sequencing Consortium (MSC) announced the completion of a draft map (3× coverage) representing at least 95% of the mouse DNA sequence. MSC plans to use longer DNA stretches of known map position and assemble the sequence fragments into a finished, highly accurate form. The mouse is an invaluable resource for interpreting human genome data and finding human genes and other functionally important DNA regions conserved by evolution.

"The success of MSC and other public-private research consortia no doubt will lead to future cooperative efforts to solve big problems quickly, especially when the resulting data belong in the public domain," said Arthur Holden, cochairman of MSC. Comprising three private companies and six NIH institutes, MSC was formed in October 2000.

At 3 billion bases, the mouse genome is comparable in size to that of humans. Even more important, almost every human gene appears to have a counterpart in the mouse; among 4000 genes studied, fewer than 10 are present in only one of the two species. Researchers expect to find that about 85% to 90% of gene sequences are similar in mouse and human, with similarities ranging from 60% to 90%.

In addition to highlighting gene sequences, mouse-human DNA comparisons will help identify other regions responsible for turning gene expression on and off. Genome comparisons also will provide insights into the evolutionary mechanisms underlying overall gene organization.

Like all mammals, humans and mice share the same physiological systems and develop many of the same diseases. Because of its small size, high fertility rate, and ease of manipulation, the laboratory mouse offers great promise in the study of the genetic bases of disease susceptibility, development, and progress. Biotechnological methods now allow DNA sequences containing gene mutations associated with human diseases to be introduced directly into the genomes of mouse embryos. Many will develop into mice that show symptoms similar to those of affected humans, thus facilitating studies and the development of new therapies.

The new mouse data already have been used to locate the mouse equivalent of a human gene that may be related to schizophrenia. The discovery may help researchers develop a mouse model to study further the gene's association with this devastating mental disorder. ◊

☛ NCBI Mouse Resources

Raw MSC data are freely available in the National Center for Biotechnology Information Trace Archive (*www.ncbi.nlm.nih.gov/Traces/trace.cgi*) and in the Ensembl Trace Server (*http://trace.ensembl.org*). The private company Celera Genomics also has generated a draft mouse genome sequence, which is accessible by subscription (*www.celera.com*).

The NCBI Mouse Genome Resources page (*www.ncbi.nlm.nih.gov/genome/guide/M_musculus.html*) includes the Graphical Mouse Genome Map Viewer for searching data by map position, gene symbol, gene name, or marker name; Human-Mouse Homology Map; and special BLAST form to facilitate searches of finished mouse genome sequence.

Human-Mouse Comparisons Identify Candidate Sequences

A more detailed version of this article appeared in Science *on July 6.*

Less than 5% of the 3.2 billion bases in the human genome sequence is thought to be occupied by genes, regulatory elements controlling gene expression, and other DNA regions that serve important known biological functions. One of the most efficient ways to identify these rare sequence features is to compare human DNA sequence with that of a related but divergent species such as the mouse. The power of the mouse model in studying human disease and in dissecting gene function adds an important dimension to such comparisons.

A clone-based physical map assembled by scientists at Lawrence Livermore National Laboratory (LLNL) provided the framework for completing the draft sequence of human chromosome 19 (HSA19) nearly a year ago. Since then a DOE Joint Genome Institute (JGI) team headed by Lisa Stubbs at LLNL has focused on functionally annotating this chromosome, beginning with an effort to identify and delineate all functional components of resident genes.

Spanning some 65 to 70 million bases and containing an estimated 1100 genes, HSA19 is one of the smallest, yet most gene-dense, of the 24 human chromosomes. To provide a tool for functional annotation and evolutionary studies, the JGI-LLNL group isolated and sequenced sets of overlapping BAC clones spanning mouse DNA sequences related to HSA19. The draft sequence's high quality and solid anchorage between human sequence and related mouse clones enabled an unusually comprehensive view of the conserved (common to both mouse and human) and nonconserved features distributed across the chromosome.

Comparison of related mouse and HSA19 DNA identified more than 12,000 conserved sequence elements, including candidate undiscovered human exons (protein-coding gene fragments) as well as whole novel genes and an estimated 4000 candidate regulatory DNA sequences. Analyses showed that highly conserved versions of virtually all single-copy human genes are found in mouse DNA and that mouse and human genes are organized in very similar ways.

However, Stubbs and her team also noted striking species-specific differences in the content and functional capacity of certain types of genes, including those encoding zinc-finger transcription factors, olfactory

(see Comparisons, p. 12)

Comparisons (from p. 11)

receptors, pheromone receptors, cytochrome P450, serine proteases, and many other types of proteins. These types of genes, which often are found organized into tandem clusters of 5 to more than 60, are present in different numbers and types in mouse and human DNA. This reflects the very active duplication, divergence, and either functional or total loss of genes since separation of rodent and primate lineages. Stubbs and her colleagues estimate that these changes have given rise to at least 100 actively expressed genes that are unique to either humans or mice. These lineage-specific genes are likely to have significant impacts on biology, defining at least some of the major physiological, morphological, and behavioral differences between rodents and primate species.

HSA19 is related to mouse DNA found in 15 conserved segments from different portions of mouse chromosomes 7, 8, 9, 10, and 17. Because both human and mouse sequences were derived from precisely mapped clones, the JGI team could identify the boundaries or "breakpoints" of these 15 homology segments and examine the sequence content and structure of the chromosome-rearrangement sites. Repeated sequences including clustered gene family members, LINE1, retrovirus sequences, and local duplications were found at all breakpoint sites. Results of this study indicate that, throughout evolution, "illegitimate" recombination (i.e., recombination of related DNA sequences at nonhomologous chromosomal sites) between gene families and other duplicated sequences has driven evolutionary changes in chromosome structure.

The JGI team is now extending these studies to comparisons of related regions in a nonmammalian vertebrate species, the chicken. Together with JGI's emerging sequence of the pufferfish and other vertebrate genomes being sequenced by public efforts worldwide, these studies will provide the basis for deeper evolutionary and functional studies of the estimated 1200 HSA19 genes. The resulting data and resources will be used to identify all HSA19 genes and their regulatory elements and pave the way for studies of biological function in model organisms. *[Lisa Stubbs, DOE JGI and LLNL]* ◊

VISTA Software Widens Comparative View

With the increasing availability of human and mouse genomic sequence, a challenge confronting biologists is how to convert these large amounts of data into useful biology. One of the more powerful algorithms for identifying functional regions in genomic DNA, including both genes and surrounding regulatory elements, involves comparative sequence analysis.

Confronted by a scarcity of tools for such studies, investigators led by Inna Dubchak and Edward Rubin in the Genome Sciences Department at Lawrence Berkeley National Laboratory (LBNL) have developed a suite of software tools called VISTA (VISualization Tools for Alignment). Incorporating a novel global-alignment procedure and components for visualization and analysis, VISTA enables large-scale comparisons between DNA sequences of two or more species. Its visual output is clean and simple, allowing for easy identification of conserved regions. Similarity scores are displayed for the entire sequence, thus helping in identification of shorter conserved regions or regions with gaps.

Various modifications of VISTA deal with particular biological problems. cVISTA (complementary VISTA) is used to look at differences between such recently evolved species as mice and rats or humans and chimpanzees. rVISTA (regulatory VISTA) combines a search of the transcription-factor binding-sites database with comparative sequence analysis, thus greatly reducing the number of predicted binding sites and suggesting plausible hypotheses for further biological studies. Used extensively in LBNL's Genome Sciences Department, VISTA also has become the main comparative sequence analysis tool of several large sequencing centers.

Individuals can use VISTA by anonymously sending sequence data to the Web site (*www-gsd.lbl.gov/vista*) or requesting a stand-alone computer program (free for academic institutions; modest licensing fee for private industry). More than 250 investigators have used VISTA online since it became available in July 2000, and close to 150 copies of the program have been distributed in academic institutions of 20 countries. *[Edward Rubin, LBNL, emrubin@lbl.gov]* ◊

MGI Release 2.7 Enhances Allelle Detail Searching

Mouse Genome Informatics (MGI) provides integrated access to data on the genetics, genomics, and biology of the laboratory mouse (*www.informatics.jax.org*). Release 2.7 incorporates the following enhancements to the "Allelle Detail" page.

- New query field for "Promoter Notes" can be used to search for when and where a transgene is expressed.
- "Molecular Information" (previously "Molecular Description") section may include mutations, ES cell line and strain, promoter, notes (molecular), and reference (molecular).
- References associated with a phenotypic allele used experimentally or included as a major part of a review article are added. The page also displays three other kinds of references ("Original Reference" reporting the creation or discovery of a spontaneous or genetically engineered allele; "Molecular Information" reference describing or identifying the molecular nature of the mutation responsible for a given phenotypic allele; and "Synonym References" containing an allele synonym).
- "Gene Expression in This Mutant" includes the number of assays, with a link to a display on the "GXD Expression Summary" page of all expression data assayed in mice carrying the allele. The "Allele Detail" page no longer displays the mode of inheritance if it is not applicable.

Allele Query Form: *www.informatics.jax.org/searches/allele_form.shtml*

Help document on Using the Allele Query Form: *www.informatics.jax.org/userdocs/allele_help.shtml* ◊

In the News

Converting Energy to Medical Progress

Although typically focused on only one part of DOE's Biological and Environmental Research (BER), Human Genome News *will now include material from the Medical Sciences Division (MSD), which shares the same mission. MSD's nuclear imaging has all but eliminated the need for exploratory surgeries.*

Following is a summary of MSD's new booklet, Converting Energy to Medical Progress *(April 2001). The booklet is available from HGMIS and can be downloaded from the Web (www.doemedicalsciences.org).*

Some Highlights of BER-Funded Research in Nuclear Medicine

Brookhaven National Laboratory, New York

One of the world's leading laboratories for the design, synthesis, and application of radiopharmaceuticals for such priorities as substance abuse, aging and degenerative diseases, and the biology of tumors.

Lawrence Berkeley National Laboratory, California

Specialized instrument development to improve detection of prostate, breast, and other cancers for such priorities as SPECT imaging for brain studies of mental illness. New radiotracers to study aging, heart disease, and cancer.

Oak Ridge National Laboratory, Tennessee

Genesis of BER when ORNL made available a vast selection of radionuclides for nuclear medicine research. Studies of new radiopharmaceuticals' potential for diagnostic and therapeutic applications in cancer and coronary artery disease.

Memorial Sloan-Kettering Cancer Center, New York

Pioneering work in the use of "monoclonal antibodies" to treat cancer. Novel ways to produce a variety of radionuclides to treat lymphoma, leukemia, and prostate cancer.

University of California, Los Angeles

New ways to image the biology and genetics of several diseases, including cancer, diabetes, heart disease, Alzheimer's disease, and Parkinson's disease. Pioneers in PET and microPET, which allows scientists to watch cells at work in the living person or mouse.

Washington University, St. Louis, Missouri

Innovative use of radionuclides in medicine. Important contributions to PET. Development of new organic carrier molecules and a new class of PET radiopharmaceuticals based on metal radionuclides and first hormone receptor agents.

University of Michigan, Ann Arbor

Research in the chemical design and synthesis of radiopharmaceuticals and their implementation in PET and SPECT brain-chemistry studies. Development of computer science for nuclear medicine imaging systems. Insight into several neurological disorders that affect movement, memory, aging, and dementia.

Nuclear medicine is an exciting field in healthcare that provides important information for diagnosing, evaluating, and managing disease. Virtually all hospitals, as well as many clinics and doctors' offices, conduct nuclear medicine tests and scans. About 13 million (35,000 a day) such procedures are performed each year on patients in the United States (and many more in other countries) in cardiology, oncology, neurology, sports and internal medicine, thyroid disorders, surgery, gastrointestinal ailments, pulmonary disorders, infection, and dementia.

Nearly every nuclear medicine scan or test used today was made possible by research funded by BER and its predecessor agencies on radiotracers, radiation-detection devices, gamma cameras, positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scanners, and computer science.

In managing DOE's nuclear medicine research program, MSD pursues two main areas of scientific investigation—imaging systems and radiopharmaceuticals (radiotracers). The aim is to develop beneficial applications of nuclear technologies for medical diagnosis and treatment of many diseases.

Biological Imaging

All human characteristics depend on a galaxy of biochemical reactions that occur many millions of times per minute within the cells and tissues of the body. A deranged chemical process can cause disease, resulting in other abnormal biochemical (physiological) changes. With its unique ability to reveal biochemical processes, nuclear medicine provides crucial information about numerous diseases. Nuclear medicine procedures are different from X rays, scans by computed tomography (called CT) and magnetic resonance imaging (called MRI), and ultrasound, all of which primarily visualize structure and shape (anatomy).

Nuclear medicine images are produced by low levels of energy emitted from medically useful radiotracers introduced into a patient's body. SPECT gives off gamma rays and PET emits positrons, another form of energy that converts to gamma rays. Radiotracers are designed to provide insights about healthy, normal biology, the biological process of disease, and even the molecular errors that cause disease.

Radiotracers interact with such biological processes as bone mineral turnover, potassium transport in heart muscle, or glucose metabolism in various organs or tumors. Highly sensitive scanners detect and process the energy signals, after which computer programs reconstruct them into diagnostic images. PET and SPECT, for example, produce 3-D images that look like multiple slices through the body.

Imaging Gene Expression

BER scientists have successfully created images of genetically altered organ function in animals. Now, MSD has initiated exploratory research to develop

(see Imaging, p. 14)

In the News

National Center for Toxicogenomics

The outpouring of human genome data and the development of large-scale, rapid, efficient technologies to probe them have transformed the field of toxicology and engendered a new specialty—toxicogenomics. Researchers in this new field study gene response to environmental stressors and toxicants and seek to understand the role played in disease by gene-environment interactions. The use of DNA microarray and proteomic techniques to assess changes in gene and protein expression is a rapidly growing research area that will have a large impact in many areas, including the environmental health sciences.

To develop the field of toxicogenomics and coordinate an international research effort, the NIH National Institute of Environmental Health Sciences (NIEHS) created the National Center for Toxicogenomics (NCT). NCT aims to promote advances in toxicogenomics and catalyze their application to the prevention and amelioration of environmentally related diseases (*www.niehs.nih.gov/nct.org.htm*).

The establishment of NCT was announced in December 2000 by NIEHS Director Kenneth Olden and Deputy Director Samuel Wilson. NCT Director is Raymond Tennant, NIEHS.

Toxicogenomic strategies under development through NCT are based on microarrays containing thousands of messenger RNA (mRNA) fragments, the intermediary products of active genes, to create "gene-expression profiles." Using bioinformatics tools, researchers combine these data with those from protein-expression profiles to determine how disease may be influenced by environmental factors. NCT's goal is to combine these microarray-based strategies into a unified approach, together with the informatics infrastructure necessary to understand it.

(see Toxicogenomics, p. 15)

Imaging *(from p. 13)*

new radiotracers based on messenger RNA for dynamic imaging of gene expression in animals in real time. BER researchers at Sloan-Kettering, for example, created iodine-124 FAIU, a highly specific radiopharmaceutical that provides the first nuclear medicine images showing the expression of certain genes in tumors in a live animal.

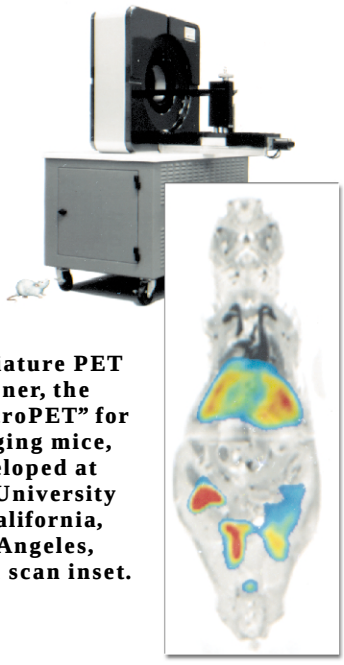
As scientists discover more information about the relationship between genes and disease or behavior, they can identify new molecular targets for imaging the biological activity of disease. In time, drugs may be custom made for individual patients based on genetic "fingerprinting," and nuclear medicine will play a crucial role in this pursuit.

PET imaging techniques developed at Washington University, for example, are helping to identify which patients with breast cancer will respond to tamoxifen hormone therapy. Scientists there also have developed fluorine-18 fluoroestradiol that targets estrogen receptors on breast tumors. The presence or absence of abundant estrogen receptors in breast cancer cells can help doctors select the most appropriate chemotherapy for these patients.

Since mice can be engineered biologically to carry genes that produce disease, molecular probes such as microPET allow the imaging of disease initiation and progression in a living mouse. In concert with this research, scientists are investigating highly sophisticated drugs designed to correct the molecular errors of disease. Combined with the explosive growth of knowledge from genome research, PET and microPET play a major role in the promising new era of molecular diagnostics and therapeutics.

Future Impacts

The nuclear medicine of tomorrow will depend on the discovery of radiopharmaceuticals that seek specific molecular and genetic targets, the design of companion advanced scanners for creating meaningful images, and the promise of new radiopharmaceutical treatments for cancers and genetic diseases. ◊



Miniature PET scanner, the "microPET" for imaging mice, developed at the University of California, Los Angeles, with scan inset.

PET Developers Win Kettering Prize

David Kuhl (University of Michigan, Ann Arbor) and Michael Phelps (University of California, Los Angeles, School of Medicine) are co-winners of the Charles F. Kettering Prize for their involvement in the development of positron emission tomography (PET). The Kettering Prize, sponsored by the General Motors Cancer Research Foundation, recognizes the most outstanding recent contribution to the diagnosis or treatment of cancer. Both researchers have long-standing BER research support involving PET and its medical applications for diagnosis and therapy. ◊

In the News

Exploring the Impact of Genetics Research on Minorities

One of the goals of the National Educational Foundation of Zeta Phi Beta Sorority, Inc., is to emphasize education in minority communities. In keeping with this goal, the foundation has planned and conducted three major informational conferences on the challenges and impacts of the Human Genome Project (HGP) within the last 3 years: New Orleans in April 1999, Philadelphia in July 2000, and Atlanta in July. Follow-up meetings and training sessions all over the country have been carried out by members of the educational foundation. Following is a summary of the Philadelphia meeting, held July 7 and 8, 2000.

Pictured left to right: Kathryn Malvern (Zeta Phi Beta Sorority, Inc.), Ari Patrinos (DOE Office of Biological and Environmental Research), Issie Jenkins (Zeta Phi Beta Sorority, Inc.), and Daniel Drell (DOE Human Genome Program).

The 250 attendees included representatives of minority organizations, civic and religious groups, health communities, government, student groups, and the public. Because the conference was held in conjunction with the sorority's national meeting (July 9–14), minority representatives from states across the country also were present.

The conference took place several weeks after President Bill Clinton's announcement that a rough draft of the human genome sequence had been completed and that differences had been resolved between private and public sectors in the sequencing race. Meeting objectives were to make minority communities more aware of the HGP and its status, to inform them of the project's benefits, and to provide a forum for minority input. Other topics were implications and concerns raised by HGP research, including ethical, legal, and social issues (ELSI). The symposium also addressed the need to expand the pool of minority scientists and the challenge of interesting minority students in science.

Conference Program

The keynote speaker was DOE Associate Director of Biological and Environmental Research Ari Patrinos. He discussed the history and accomplishments of the HGP and provided background information on Clinton's announcement. Indicating that the HGP's outcome will dramatically affect the country's economy, Patrinos emphasized the importance of involving minority communities so that all can share in project benefits and related concerns can be avoided or responsibly addressed.

Presenters included John Quackenbush (The Institute for Genomic Research), who spoke on "Decoding the Book of Life" and how genomics will influence approaches to a variety of problems in modern biology. The challenge for the future, he said, will be to identify specific genes, determine their functions, and explore genetic changes that can lead to disease.

Panels

A panel discussion on the project's implications for minority health issues included Georgia Dunston and Robert Murray (both at Howard University Medical School). In addressing recent programs that screen for genetically determined health

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Toxicogenomics *(from p. 14)*

This challenge exemplifies the ongoing paradigm shift occurring across the life sciences. Researchers are moving toward monitoring cellular events on a large-scale, global level that will facilitate a broader view of how living systems respond to specific stresses, drugs, and toxicants. Data generated by such research will provide extraordinarily detailed information on coordination profiles for cellular networks of responding genes and proteins, help define important target molecules for toxicity studies, and suggest future biomarkers and alternative testing procedures.

Experiments using such microarray technologies also will help define complex regulatory circuitry within a cell, tissue, or organ that is responding to specific stressors. Studies may help pinpoint locations and time points for effectively interceding in a cascade of biochemical and molecular events influenced by environmental stressors, making possible the early diagnosis of cellular responses and the prevention of or intervention in human disease.

Other NCT goals are to increase understanding of the pathways involved in biological response to environmental stressors and how these changes differ with genetic and dose differences; establish a publicly available relational database of toxicogenomics research; and promote collaborative research that will combine toxicology and disease pathology with gene-expression profiling, proteomics, and single-nucleotide polymorphism analysis using the Chemical Exposure in Biological Systems Data Base. A symposium on Gene Expression and Proteomics in Environmental Health Research will be held December 3–4 in Bethesda, Maryland. [James K. Selkirk, Deputy Director NCT, 919/541-2548, Fax: -1460, *selkirk@niehs.nih.gov*] ◊

disorders, Murray spoke of ethical and legal conflicts that can arise when the disorder will not be manifested for a number of years and intervention is unknown or of questionable value. He indicated that such problems often arise when a person is merely placed in a category of increased risk for developing the condition; this situation is more likely to have serious negative consequences for members of minority groups. Finding a solution to this dilemma is imperative before any widespread genetic screening programs are put in place, according to Murray. He and Dunstan agreed that, without protective measures, information from genetic screening could be used to stigmatize or discriminate against minorities.

Dunston questioned the genetic samples being used in human genome research and whether they represent enough variation in populations. Indicating that the genome study deals with the foundation of identity, she expressed concern that current research could be too limited.

Mary Kay Pelias (Louisiana State University Medical School) spoke on genetic problems in clinical practice and biomedical research. Using hereditary traits and diseases as illustrations, Pelias described how they are manifested in Louisiana's diverse population and how relevant historical developments and patterns of immigration can influence health issues.

Fatimah Jackson (University of Maryland) emphasized that consideration of the African-American perspective on human genome research is critical, although it cannot be used as a substitute for those of other groups. Insights of African Americans are important because they so frequently have been victims of "science" and "quasigenetic" inquiries. This group was among the first to call for representative sampling in the HGP, Jackson said, and for the inclusion of African-American genetic sequences in the human genome's template. If all groups were not included in the baseline template, some might not be considered by the big pharmaceutical companies intent on making commercial drugs linked to specific genotypes. Jackson pointed out that minorities cannot assume inclusiveness at any stage of the HGP and that the pattern of sampling often reflects power relationships. Minorities may need to demand such inclusiveness.

Daniel Drell (DOE Human Genome Program) presented a review of the HGP and a recap of the first day's proceedings.

At the panel on HGP ELSI for Minorities, facilitator Issie Jenkins (then foundation chair) raised the issue of confidentiality and uses of individual genetic information; the potential for discrimination in healthcare, health insurance, and employment; the potential for use and misuse of genetic data in the criminal justice system; and the benefits of minority participation in clinical trials. Jeroo Kotval (School of Public Health, New York State University) spoke of ethical issues involved in a market-driven healthcare system and identified the following four principles as central: just distribution and quality of healthcare, cost-effective care, and trust. Each of these principles could

¶ Minorities and the Human Genome Project

The book *Plain Talk About the Human Genome Project*, edited by Edward Smith and Walter Sapp, is a compilation of talks presented during a 3-day conference at Tuskegee University in September 1996 [*HGN* **8**(2), 9–10]. Distinguished leaders, scientists, ethicists, educators, and students spoke on wide-ranging topics related to the Human Genome Project's promise and perils, matters of race and diversity, and education about the project and its implications. 292 pp., 1997. [Ordering Information: *http://agriculture.tusk.edu/Genome2/Plain_Talk_HGP/Plain_Talk.html*]

The Human Genome Project and Minority Communities: Ethical, Social, and Political Dilemmas, edited by Raymond Zilinskas (Monterey Institute of International Studies) and Peter Balint (University of Maryland) addresses the divisions between minority groups and the scientific community, particularly in the area of medical and genetic research. The book consists largely of talks by distinguished speakers at the conference, "The Human Genome Project: Reaching the Minority Communities in Maryland," held in June 1997 at the University of Maryland at Baltimore [*HGN* **9**(1–2), 19–21)]. In an essay that was not part of the conference, the editors argue that, although minorities tend to be skeptical of medical research in general and genetics research in particular, the Human Genome Project has the potential to make dramatic positive contributions to the health of all people. 144 pp., 2000. [Available through bookstores, including online suppliers.] ◊

Human Genome news

This newsletter is intended to facilitate communication and collaboration, help prevent duplication of research effort, and inform persons interested in genome research. Views expressed are not necessarily those of the Department of Energy Office of Biological and Environmental Research. Suggestions are invited.

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Special thanks to Carolyn Krause, ORNL

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be impacted by the new genetic tests and their implications.

Jenifer Smith (DNA Analysis Unit, FBI Laboratory) explained how law enforcement officials use DNA evidence and the Combined DNA Index System (CODIS)—a collection of DNA databases from forensic laboratories around the United States. CODIS includes DNA profiles of individuals convicted of such serious crimes as rapes and homicides. These profiles are compared with those collected in other cases waiting to be solved. All states have legislation allowing the collection of DNA samples from convicted offenders. Questions were raised about the use of such evidence with respect to minorities.

Phyllis Epps (Health Law and Policy Center, University of Houston Law Center) spoke of recent advances in pharmacogenomics (drug targeting to a patient's genetic makeup) that have revealed drug-metabolism differences linked to race, ethnicity, and gender. As a result, drug manufacturers, researchers, and physicians will have legitimate reasons to consider race in judging the effectiveness of medicines. Given past history, patients will regard race-based treatment with suspicion, and the medical community will find it a great challenge to balance the benefits of different treatments against the risks inherent in classifying persons for whatever reason.

Workshops

Three afternoon workshops led to a series of recommendations and concerns that included the following:

- Monitor the status of health insurance coverage for genetic testing and counseling, an important issue for minority communities.
- Create more training opportunities for veteran teachers and encourage mentors for minority students in such scientific developments as genetics.
- Develop career-day presentations to increase minority student awareness of the large number and types of current and future opportunities in the genomic, biomedical, and biotechnology industries.
- Encourage minority students to volunteer, take part-time jobs, and pursue internships in science and related fields.
- Interest minority students in math and science courses in middle and high school; college is too late to begin.

Closing Session

The closing session was conducted by Kathryn Malvern (now foundation chair) on "What Next?" for continued minority involvement in education about genomic research developments. Suggestions were made to continue information sessions at or involving local churches, prepare and disseminate conference proceedings and collaborate with other groups.

Attendees also recommended disseminating factual information written in layman's terms at Black Expo and minority festivals and on videotapes. Information in cartoon form should be developed for children.

They also saw a need to form local HGP Awareness Teams to keep abreast of developments; provide easily understood examples of the project's benefits; develop a Web site with short lists of benefits and positive and negative potentials; and conduct more research into minority issues and concerns.

Leanne Washington (Pennsylvania House of Representatives member) was the closing luncheon speaker. She spoke of state involvement and of the important need for information in minority communities. She committed to sponsoring a state-wide conference on the HGP.

The foundation received many favorable comments on the informative conference. A number of participants expressed the desire to keep abreast of developments and contribute to policy and legislative decisions regarding genetic research and the use of genetic information. The proceedings of this meeting are on the Web (*www.ornl.gov/hgmis/publicat/zetaphibeta/*) *[Issie L. Jenkins, Esq.]*

The conference was supported by DOE and NIH through the ELSI components of their respective human genome programs. The U.S. Equal Employment Opportunity Commission, Philadelphia District Office, provided assistance as a cooperating agency sponsor. Funding also was received from the March of Dimes and Merck Research Laboratories. ◊

Sandia, Celera, Compaq Work on Next-Generation Computing

In January, Sandia National Laboratories and Celera Genomics, Inc., signed a 4-year Cooperative Research and Development Agreement to begin work on the next generation of computer software and hardware for computational biology and a full range of applications in the life sciences. Under contract to Sandia, Compaq Computer Corporation will design the new machine, which is expected to achieve 100 trillion operations per second (100 TeraOps). By sharing some computing technologies developed by Sandia, Celera and Compaq ultimately may reach the "petacruncher" level (1000 TeraOps).

This level of cooperation is necessary to meet the dramatic demands of emerging genomics and proteomics applications at affordable prices by bringing together the capabilities of three leaders in bioinformatics, high-performance computing, and massively parallel systems. Using both public and private resources, the multimillion-dollar arrangement first was suggested by Sen. Pete V. Domenici (R-N.M.) and guided to completion by Ari Patrinos, Associate Director of the DOE Office of Biological and Environmental Research.

J. Craig Venter, Celera's president and chief scientific officer, said, "Just 3 years ago, the computational needs of biology were thought to be minor and irrelevant to the computing industry. Today, biologists are setting the pace of development in the industry."

(see Computing, p. 18)

In the News

Scientists Decode Genes of Microbe that Thrives in Toxic Metals

Understanding the genetic makeup of microbes that thrive in polluted environments may one day help scientists engineer bacteria to clean contaminants from soil. In a step toward that goal, the DOE Joint Genome Institute has released the draft DNA sequence of the toxin-tolerant *Ralstonia metallidurans*. Researchers at DOE's Brookhaven National Laboratory (BNL), in collaboration with a Belgian team, now are seeking to understand and manipulate the sequence. The research was funded in part by DOE's Microbial Genome Program.

This bacterium was first isolated in Belgium in 1976 from settling-tank sludge that was polluted with high concentrations of heavy metals. Examination revealed that, in addition to its chromosomal genes, *Ralstonia* has extra genetic material (plasmids) that house genes conferring resistance to the harmful effects of a wide array of heavy metals. Having the draft genome sequence will make manipulation of these naturally existing resistance factors more feasible. Scientists also are working on ways to limit the ability of bacteria to spread genes inadvertently so they will stay in the bacteria where they are put. This can be done by crippling *Ralstonia*'s ability to transfer genes or by using host strains that normally do not transfer genes.

Potential future benefits include transferring *Ralstonia*'s heavy-metal resistance genes to microbes with capabilities for breaking down other pollutants, thereby engineering strains with a combination of useful traits. Another possible application is to link *Ralstonia*'s heavy-metal uptake to genes that cause bacteria to glow, or bioluminesce, when indicating the presence of heavy metals in the soil. The higher the concentration of metals, the brighter the glow.

"What we're doing is building on the diversity of biology," said BNL's John Dunn. "Here's a bacterium that potentially could be used as a tool to help us clean up the environment and to monitor how well we're accomplishing that goal." ◊

¶ Microbial Genome Program Flyer Available

A brochure on the DOE Microbial Genome Program is available in print from HGMIS and can be downloaded from the Web site (*www.ornl.gov/microbialgenomes/pubs.html*). The text includes information on DOE's reasons for studying and sequencing microbes, possible microbial applications, and related research and Web sites. All current and past DOE-supported microbial projects are listed with details on their status and their potential usefulness.

☛ JGI Planning Another "Microbe Month"

Because of the success of last year's "Microbe Month," DOE's Joint Genome Institute (JGI) in Walnut Creek, California, is planning another such event for this fall. Last October, high-quality draft sequences of 15 bacterial genomes were produced—a rate of more than one genome for every one and a half working days (*www.jgi.doe.gov/tempweb/News/news_11_2_00.html*). In addition to their value in basic research, many microbes have immediate implications for the economy and the environment. *Xylella fastidiosa*, for example, is a pathogen carried by insects that infects grapevines; citrus and almond trees; oleander bushes, used as median strips on California highways; and other important plants. [More information: *http://compbio.ornl.gov/channel*]

Computing *(from p. 17)*

Patrinos noted, "The most fertile ground for scientific discovery lies at the interface of disciplines, with the most important at the junction of biology and information science."

To accomplish the consortium's goal of creating a prototype by 2004, Compaq and Sandia will collaborate on system hardware and software. Celera and Sandia will focus on advanced algorithms and new visualization technologies for analyzing the massive amounts of data generated by high-throughput machines. All three groups will contribute to integrating system hardware and software and on optimizing performance.

The alliance will use Compaq Alpha processors connected in a massively parallel configuration with extremely high bandwidth and low-latency mesh interconnects. Sandia currently operates the most powerful Linux-based supercomputer in existence and is home to ASCI Red, the first TeraOp supercomputer, one of the fastest in the world. ◊

☛ Educational Kit on the HGP

The Human Genome Project and other sponsors have created a multimedia kit as an educational tool for high school students and the general public. *The Human Genome Project: Exploring our Molecular Selves* includes a CD-ROM with seven varied segments; *The Secret of Our Lives*, an award-winning video documentary; a commemorative wall poster; and *Genetics, The Future of Medicine*, an informational brochure. Request a free copy or use the kit online (*www.nhgri.nih.gov/educationkit*). ◊

Resources

☛ HGMIS Notes

HGP Fact Sheet Published

Updating articles drawn from the November 2000 issue of *Human Genome News*, the Human Genome Management Information System (HGMIS) has published the 4-page *Human Genome Project Fact Sheet* to provide quick and timely answers to frequently asked questions. Topics include gene patenting, the "rivalry" between public and private sectors, HGP funding since 1987, and challenges for the future. This free document is available in bulk for meetings and educational purposes (865/576-6669, *mansfieldbk@ornl.gov*).

HGMIS Requests Change of Address, Subscription Status

After each issue of *HGN* is printed and mailed, many copies are returned to HGMIS because the addressee has moved. Some subscribers may wish to drop their print subscriptions. Please use the back page of any issue to notify HGMIS of a change in address or subscription status or to request information.

HGP Handouts

HGMIS will send multiple copies of *HGN* and other genomics-related materials to relevant meetings on request and without charge (see contact, p. 16).

HGMIS Documents, Web Site Win Awards

The DOE *Microbial Genome Program Report*, produced by HGMIS, won a number of awards in the 2000–2001 competitions sponsored by the Society for Technical Communication (STC). HGMIS was initiated in 1989 by DOE to make information about the Human Genome Project accessible to many audiences.

In the STC East Tennessee Chapter (ETC) competition, the microbial report (*www.ornl.gov/hgmis/publicat/microbial*) received a Distinguished (first place) Award in Online Communications and two Merit (third place) Awards, one in Technical Publications and the other in Technical Art. In addition, the document was judged ETC's Best of Show in Online Communications and went on to receive another Distinguished Award at the international level. Only first place winners in chapter competitions were eligible for the international contest.

A HGMIS entry in the News and Trade Articles category, "Genes, Dreams, and Reality: The Promises and Risks of the New Genetics" by Denise Casey, won a Merit Award in Technical Publications. The article appeared in the journal *Judicature* **83**(3) (*www.ornl.gov/hgmis/publicat/judicature*).

STC, the largest organization of its type in the world, is dedicated to advancing the arts and sciences of technical communication. Its 25,000 members include writers, editors, illustrators, printers, publishers, educators, students, engineers, and scientists employed in a variety of technological fields.

Web Awards

HGMIS also has received numerous awards for its Human Genome Project Information Web site (*www.ornl.gov/hgmis*). Some recent ones are from Scientific American, Schoolsnet, BigChalk, KidsHealth, CyberU, sciLINKs, Geniusfind, ISI, Hardin MD, Awesome Library, and ResPool Research Network. ◊

Send article suggestions to Betty Mansfield (mansfieldbk@ornl.gov).

☛ Genetic Testing, Counseling Resources

GeneTests and GeneClinics, companion resources on genetic counseling and testing for hereditary disorders, are freely available on the Web. In the past year, several new features and many disease profiles have been added.

GeneTests (*www.genetests.org*):

Genetics Laboratory Directory: List of about 500 U.S. and international laboratories that are testing for some 820 diseases; searchable by a variety of parameters, including disease name, gene name, affected organ system, and others.

Genetics Clinic Directory: List of 950 U.S. genetics and prenatal diagnosis clinics; searchable by geography, population (age group), and subspecialty, if applicable.

About Genetic Services: Primer of educational materials about genetics counseling and testing; useful for consumers and nongeneticist healthcare providers.

Teaching Tools: Downloadable PowerPoint slide presentation on the availability and use of genetic services; suitable for genetics professionals to teach nongenetics healthcare providers.

GeneClinics (*www.geneclinics.org*)

Contains 113 expert-authored and peer-reviewed full-text articles on specific hereditary diseases, as well as overviews on disease families. GeneClinics contains about 80 disease profiles and overviews.

The two resources gradually are becoming more integrated, with links from GeneClinics profiles to specific testing, counseling, and educational resources in GeneTests. GeneTest search results link to relevant GeneClinics profiles.

One-time registration is required for GeneTests (use the New Users button on the Home Page to register and select your passwords). [Contacts: *genetests@genetests.org* or *geneclinics@geneclinics.org*] ◊

Resources

Web Sites

Biotechnology Business

www.genomeweb.com

News and information on the business and technology of genomics and bioinformatics worldwide.

www.genengnews.com

Information about all facets of the biotechnology field worldwide from *Genetic Engineering News*.

www.bio.com/os/start/

bioOnline site. Industry and research news, reports, education, career center.

www.signalsmag.com

Online magazine of biotechnology industry analysis.

ELSI

www.humgen.umontreal.ca

Database on legal, social, and ethical aspects of human genetics. Organized around a list of international policymaking organizations and bibliographies of policy statements on various topics. ◊

¶ *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology*

In a comprehensive 2-volume, 1160-page reference work, the editorial team of Thomas Murray (The Hastings Center) and Maxwell Mehlman (Case-Western Reserve's Law-Medicine Center) bring together leading experts from a variety of fields to describe ethical, regulatory, and policy issues in biotechnology; analyze their implications; and present public policy options. Published late in 2000, the encyclopedia includes a chapter written by Daniel Drell of the DOE Human Genome Program's Ethical, Legal, and Social Issues program. This is the fourth and final entry in the *Wiley Biotechnology Encyclopedias* series.

Visit the Web site for a detailed description, table of contents, and a sample article, "Human Enhancement Uses of Biotechnology," by Robert Wachbroit *(www.wiley.com/products/subject/reference/murray_index.html)*. [Orders: Web site, 800/225-5945, or *catalog@wiley.com*] ◊

U.K. Scholarships

Marshall Scholarships

Up to 40 scholarships for study toward a degree in the United Kingdom are awarded yearly to U.S. citizens who hold a first degree with a minimum GPA of 3.7 after freshman year. The scholarships pay full costs, including travel and an allowance for a dependent spouse. Candidates must have received an undergraduate degree in any discipline within 3 years of taking up the scholarship, which is tenable at any British university for 2 to 3 academic years. Applications must be made through a regional center in the United States and are due in mid-October of the year preceding tenure.

Marshall Sherfield Postdoctoral Fellowships

Two postdoctoral fellowships will be awarded in 2002 for U.S. scientists and engineers to undertake up to a year of research at British universities or research institutes. Fellowships cover full costs and allowances for travel and accompanying spouse and children. Awardees are expected to engage in a meaningful collaboration with a university or institute whose research is complementary to their areas of expertise. Applications are due October 9.

More information about both programs is on the Web (*www.acu.ac.uk/marshall)*. ◊

¶ *Nature* 2001 Yearbook of Science and Technology

The *Nature Yearbook of Science and Technology 2001* provides a comprehensive view of the major trends and players in the fast-moving world of science. It profiles thousands of institutions and organizations in almost every country in the world, including developing nations, and all U.S. states. The reference work also includes specially commissioned articles and essays by leading experts in their fields. One volume, 2000 pp., 2001. [Orders: *www.nature reference.com/NatureYearbook/nature_yearbookspecial.htm*] ◊

¶ New Report Looks at Small-Scale Solutions

Global Environmental Change: Microbial Contributions, Microbial Solutions, a new report from the American Society for Microbiology (ASM), suggests that microbiology can provide solutions to such serious environmental challenges as the increase in greenhouse gases and other stresses. Written by Gary M. King (University of Maine), James Tiedje (Michigan State University) and the ASM Committee on Environmental Microbiology, the report makes four recommendations for enhancing microbiological solutions to global change:

- Integrate an understanding of microbiological processes at all organizational levels, from individual organisms to ecosystems.
- Discover, characterize, and harness the abilities of microbes that play important roles in transformations of trace gases and various toxic elements.
- Implement policies that promote effective long-term research on the microbiology of global change.
- Establish programs to train people to solve tomorrow's complex environmental problems.

The report can be downloaded (*www.asmusa.org/pasrc/pdfs/globalwarming.pdf*). ◊

Next Wave Online Publication

Next Wave, a weekly online publication from *Science*, covers scientific training, career development, and the science job market. It includes features, news items, career columns, and perspectives in the job market, career transitions, job hunting, diversity and work life, advice for graduate students, science policy, and postdoctoral and faculty issues. Some articles are freely accessible, and others require a modestly priced subscription (*http://nextwave.sciencemag.org*). ◊

Resources

☛ Twisted Ladder Media Issues Two CD-ROMs

Two new groundbreaking CD-ROMs use innovative multimedia and easy navigation techniques to make the genomic revolution understandable and accessible to many audiences.

The New Genetics: Courseware for Physicians is designed for medical doctors who wish to update their knowledge about genetics and genomics. Price includes Continuing Medical Education (CME) credits from Stanford University.

The New Genetics: Medicine and the Human Genome presents the same content, without CME credits, for college students, researchers, nurses, policymakers, attorneys, and others who are interested in the impact of genetics and genomics on healthcare and society.

Both CD-ROMs can be ordered through the Web site, which contains sample text, complete content outline, feature demonstrations, and animations (*www.twistedladdermedia.com*). They were produced by Sara Tobin (Stanford University) and Ann Boughton (Twisted Ladder Media), with support from the Ethical, Legal, and Social Issues component of DOE's Human Genome Program. ◊

☛ BSCS High-School Curriculum Modules

Four high-school curriculum modules produced by the Biological Sciences Curriculum Study (BSCS) and sponsored by DOE can be downloaded free of charge from the BSCS site *(www.bscs.org)*:

- *Genes, Environment, and Human Behavior* (2000)
- *The Puzzle of Inheritance* (1997)
- *The Human Genome Project: Biology, Computers, and Privacy* (1996)
- *Mapping and Sequencing the Human Genome: Science, Ethics, Policy* (1997)

All but the last also are available in print at $5 each for shipping and handling (BSCS, 719/531-5550, *info@bscs.org*). ◊

In the News

Winners of Postdoctoral Fellowships Announced

Since 1995, the Sloan Foundation and DOE have jointly supported up to ten Postdoctoral Fellowships in Computational Molecular Biology each year. The program, which has been renewed for another 3 years, is aimed at catalyzing career transitions into computational molecular biology from physics, mathematics, computer science, chemistry, and related fields. See the Sloan Web site for many other funding opportunities *(www.sloan.org/programs/scitech_fellowships.shtml)*.

Winners of the competition that closed in February are shown below with their Ph.D. institution and field, postdoctoral institution, and sponsoring senior scientist.

Joyce Duan (Baylor College of Medicine; Biochemistry): University of California, Los Angeles; David Eisenberg

Hugh MacMillan (University of Colorado; Applied Mathematics): University of California, San Diego; Andrew McCammon

Jay Storz (Duke University; Biology): University of Arizona; Michael Nachman

Justin Fay (University of Chicago; Population Genetics): University of California, Berkeley; Michael Eisen

Shayan Mukherjee (Massachusetts Institute of Technology; Computational Neuroscience): Whitehead Institute; Todd Golub

Duncan Odom (California Institute of Technology; Chemistry): Whitehead Institute; Richard Young

ANL's Advanced Photon Source Illuminates Ribosomal Activities

Using the Advanced Photon Source at Argonne National Laboratory (ANL) to gain a detailed picture of ribosomal function, a team from the U.K. Medical Research Council Laboratory of Molecular Biology (LMB) has developed insights into how ribosomes manufacture proteins from amino acids to the exact specification of genes on DNA. Led by LMB head Venki Ramakrishnan, the team published its work in *Science* on May 4 [J. M. Ogle et al., *Science* **292**(5518), 897–902].

Such information aids in understanding not only how antibiotics work but also the basis of certain kinds of resistance. If an antibiotic could induce a ribosome to make a "mistake" and add the wrong amino acid onto the protein chain, for example, such incorrectly made proteins would not function. If this happened in bacteria during development, they would be rendered ineffective.

Ramakrishnan stated that pharmaceutical and biotechnological companies are keenly interested in such studies because of their potential usefulness in the design of new antibiotics that can overcome the growing problem of resistance. ◊

In Memoriam

Walter Goad, a pioneer in DNA sequence analysis, died November 2, 2000. After a distinguished career in theoretical physics at Los Alamos National Laboratory, he created the first DNA database, GenBank, a key event in the formulation and success of the Human Genome Project. ◊

*Calendar of Genome and Biotechnology Meetings**

More comprehensive lists of genome-related meetings and organizations offering training are available on the Web (*www.ornl.gov/hgmis*) and from HGMIS (see p. 16 for contact information).

September 2001

10–11. NIH Natl. Advisory Council for Human Genome Research; Bethesda, MD [K. Malone, 301/402-2205, Fax: -0837; kimberly@od.nhgri.nih.gov]

13–15. Computational Challenges in the Post-Genomic Age-II; Durham, NC [A. Komornicki, 650/786-0003; andrew.komornicki@sun.com; *www.sdsc.edu/Workshops/postgenomic*]

17–19. Human Genetic Variation and Pharmacogenomics; Boston [CHI, 617/630-1300, Fax: -1325; chi@healthtech.com; *www.healthtech.com*]

20. Human Genetics, Environment, and Communities of Color: Ethical and Social Implications; New York [S. Prakash, 212/961-1000 ext. 333, Fax: -1015; conference@weact.org; *www.weact.org/conference*]

24–25. Next-Generation Technologies for High-Throughput Proteomics; San Francisco [GBR, 530/478-1523, Fax: -1773; *www.annualproteomics.com*]

28–30. Integrating Genome Sequence, Sequence Variation, and Gene Expression; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845; meetings@cshl.org; *www.cshl.org*]

October 2001

5–6. Genetics Policy and Law: Natl. Forum of the Natl. Conf. of State Legislators; Washington, DC [NCSL, 303/830-2200; ncsl_genetics@ncsl.org; *ww.ncsl.org/programs/health/genetics/oct-meet.htm*]

9–10. Functional Genomics: Using a Systems Biology Approach to Develop Novel Therapeutics; Boston [see contact, Sept. 17–19]

9–12. Genomics Meets Nanoscience; Bar Harbor, ME [N. Place, 207/288-6257, Fax: -6080; nancyp@jax.org; *www.jax.org/courses/documents/courses_2001.html*]

10–12. Genetic Nursing: Cultures, Consumers, Discoveries; San Diego [ISONG, E. Rawnsley, 603/643-5706; eileen.rawnsley@valley.net; *www.nursing.creighton.edu/isong/Bulletin_board/Conferences*]

10–13. SNP and Complex Genome Analysis; Stockholm [A. Brookes, +46-08-7286630, Fax: -331547; cgr_snp2001@kisac.cgr.ki.se; *http://snp2001.cgr.ki.se*]

11–12. Applications of Genomics to Animal Models for Pharmaceutical Studies; Boston [see contact, Sept. 17–19]

12. 11th Intl. HUGO Mutation Database Initiative Meeting; San Diego [R. Horaitis; horaitis@mail.medstv.unimelb.edu.au; *www.genomic.unimelb.edu.au/mdi/meetings/sandiego.html*]

12–16. American Society of Human Genetics; San Diego [M. Ryan, 301/530-7010, Fax: -7014; mryan@genetics.faseb.org; *www.faseb.org/meetings/*]

14–16. Genomic Information: Whitehead Symp. XIX; Boston [G. Cervini, 617/258-0633; cervini@wi.mit.edu; *www.whitehead.mit.edu/cee/cee_conf.html*]

16–18. Functional Genomics; (Environ. Mut. Conf. satellite meeting); Seattle [C. Aaron, 616/833-1399, Fax: -9722; Sid.Aaron@pharmacia.com; *www.genomicfunctions.org*]

17–18. Pharmacogenomics 2; Paris [Institut Pasteur; euroconf@pasteur.fr; *www.pasteur.fr/applications/euroconf*]

18–19. Pharmacogenomics and Population Groups; Louisville, KY [C. Rupf, 502/852-4985; cfrupf01@louisville.edu]

18–19. Biosilico 2001: Scientific American's 2nd Annu. Bioinformatics and Genomics Conf.; New York [BioEdge, 402/996-9185, Fax: 973/429-8234; BioSilicoInfo@bioedge.net; *www.bioedge.net*]

18–21. Bioinformatics and Medicine. From Molecules to Humans, Virtual and Real; 2nd Bioinformatics Industrialization Workshop; Hinxton, Cambridge, UK [N. Clarkson, +44-1223/495002; Fax: /495023; nicky.clarkson@hinxton.wellcome.ac.uk; *www.wellcome.ac.uk/en/1/biosersymhinscibin.html*]

21–24. 15th Intl. Mouse Genome Conf.; Edinburgh [D. Miller, 865/574-0858, Fax: -1283; millerdr@ornl.gov; *www.imgc2001.com*]

24–25. Structural Genomics in Pharmaceutical Design: 15th Annu. Symp. for the Center for Advanced Biotechnol. and Medicine; Princeton, NJ [PTI, 609/987-0586, Fax: -0092; *www.genomics-bioinformatics.com*]

25–28. Genome Sequencing and Analysis Conf.; San Diego [TIGR, 301/610-5959, Fax: /838-0229; www@tigr.org; *www.tigr.org*]

28–Nov. 1. 9th Intl. Conf. on Microbial Genomes; Gatlinburg, TN [J. Zhou, 865/576-7544, Fax: -8646; zhouj@ornl.gov; *www.esd.ornl.gov/microbial_genomes*]

29–Nov. 1. Chips to Hits; San Diego [IBC, 508/616-5550, Fax: -5522; *www.ibcusa.com*]

November 2001

4–7. 20th Annu. NSGC Educ. Conf.; Washington, DC [A. Lombard, 610/872-7608, Fax: /565-6220; *www.nsgc.org*]

4–7. 2nd Intl. Conf. on Systems Biology; Pasadena, CA [ICSB, 626/395-6911, Fax: /796-8914; icsb2001@caltech.edu; *www.icsb2001.org*]

7–8. Uses of Genomic Data in Risk Assessment: State of the Art 2001; Washington DC [Society of Toxicology, 703/438-3115; *www.toxicology.org*]

7–10. NABT 2001 Natl. Conv.; Montreal [NABT, 703/264-9696, Fax: -7778; office@nabt.org; *www.nabt.org/sup/conferences*]

9–12. Beyond the Identification of Transcribed Sequences: Functional and Expression Analysis; Washington, DC [K. Gardiner, 303/336-5652; gardiner@eri.uchsc.edu; *www.ornl.gov/meetings/bits2001*]

15–18. In Silico Biology: Bioinformatics After the Human Genome; Atlanta [Organizing Committee, 404/385-3501, Fax: /894-8925; register@conted.swann.gatech.edu; *http://exon.biology.gatech.edu/conference/*]

16. Chemical Genomics/Chemogenomics: High-Throughput Discovery of Disease Genes and Drugs; Boston [see contact, Sept. 17–19]

16–18. Science and Society: From Genomes to Cures; Heidelberg, Germany [EMBL; courses@embl-heidelberg.de; *www-db.embl-heidelberg.de:4321/CoursesConferences.html*]

27–28. BERAC Meeting; Washington, DC [J. Corcoran, 301/903-6488; joanne.corcoran@science.doe.gov; *www.sc.doe.gov/production/ober/berac.html*]

29–Dec. 1. 5th Annu. Conf. on Computational Genomics; Baltimore [see contact, Oct. 25–28]

December 2001

3–4. Symp. on Gene Expression and Proteomics in Environmental Health Research; Bethesda, MD [J. Selkirk; selkirk@niehs.nih.gov; *www.niehs.nih.gov/nct/workshop.htm*]

6–9. Physiological Genomics & Rat Models; Cold Spring Harbor, NY [see contact, Sept. 28–30]

17–19. 12th Intl. Conf. on Genome Informatics; Tokyo [Secretariat, +81-3/5449-5615, Fax: -5442; giw@ims.u-tokyo.ac.jp; *http://giw.ims.u-tokyo.ac.jp/giw2001/index.html*]

January 2002

3–7. Pacific Symp. on Biocomputing 2002; Kauai, HI [K. Lauderdale, 650/725-0659, Fax: -7944; psb@smi.stanford.edu; *http://psb.stanford.edu*]

5–11. Structural Genomics: From Gene Sequence to Function; Breckenridge, CO [970/262-1230, Fax: /1525; info@keystonesymposia.org; *www.symposia.com*]

5–11. Frontiers of Structural Biology; Breckenridge, CO [see contact, Jan. 5–11]

7–13. Molecular Mechanisms of DNA Replication and Recombination; Snowbird, UT [see contact, Jan. 5–11]

9–11. Second Annu. Human Proteome Project; San Diego [see contact, Sept. 17–19]

12–16. Plant Animal & Microbe Genomes X; San Diego [D. Scherago, 212/643-1750 ext. 20, Fax: 1758; pag@scherago.com; *www.intl-pag.org/pag*]

20–25. Protein Folding Dynamics; Ventura, CA [GRC, 401/783-4011, Fax: -7644; grc@grcmail.grc.uri.edu; *www.grc.uri.edu*]

28–31. Bioinformatics Technol. Conf.; Tucson, AZ [A. Calvo, 707/829-0515, ext. 441; andrewc@oreilly.com; *conferences.oreilly.com/biocon/cfp.html*]

February 2002

2–6. Genomics and Structural Biol. in Medicine: Miami Nature Biotechnol. Symp.; Miami [S. Black, 305/243-3597, Fax: /324-5665; mnbws-biochem@miami.edu; *www.med.miami.edu/mnbws*]

10–14. 27th Annu. Lorne Conf. on Protein Structure and Function; Lorne, Australia [L. Sparrow, +61-3/9662-7284, Fax: -7101; Lorne.Proteins@hsn.CSIRO.au; *www.biochemistry.unimelb.edu.au/lorne*]

*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.

For Your Information

11–12. NIH National Advisory Council for Human Genome Research; Bethesda, MD [see contact, Sept. 10–11]

14–19. AAAS 2002 Annu. Meeting; Boston [AAAS, 202/326-6450, Fax: /289-4021; aaasmeeting@aaas.org; *www.aaas.org*]

19–24. Genotype to Phenotype: Focus on Disease; Santa Fe, NM [see contact, Jan. 5–11]

21–26. Epigenetics in Development and Disease; Taos, NM [see contact, Jan. 5–11]

22–23. The End of Natural Motherhood? The Artificial Womb and Designer Babies; Tulsa, OK [S. Gelfand, 405/744-9238; Fax: -4635; gelfand@okstate.edu; *http://philosophy.okstate.edu/motherhood.html*]

23–24. Genomic Partnering: Emerging and Early Stage Partners; (Genome TriConference); Santa Clara, CA [see contact, Sept. 17–19]

25–27. Human Genome Discovery: Commercial Implications (Genome TriConference); Santa Clara, CA [see contact, Sept. 17–19]

28–Mar. 1. Gene Functional Analysis (Genome TriConference); SantaClara, CA [see contact, Sept. 17–19] ◊

Training Calendar

September 2001

23–Oct. 6. Molecular Biol. Techniques; Chapel Hill, NC [W. Litaker, 919/966-1730, Fax: -6821; litaker@med.unc.edu; *www.med.unc.edu/pmbb/welcome.htm*]

29–Oct. 6. DNA Microarrays: Applications and Data Analysis; Heidelberg, Germany [EMBL; courses@embl-heidelberg.de; *www-db.embl-heidelberg.de:4321/CoursesConferences.html*]

30–Oct. 7. Mathematical Approaches to the Analysis of Complex Phenotypes; Bar Harbor, ME [N. Place, 207/288-6326; nancyp@jax.org; *www.jax.org/courses/documents/courses_2001.html*]

October 2001

10–23. Gene Identification: From Candidate to Phenotype; Cold Spring Harbor, NY [CSHL, 516/367-8346, Fax: -8845; meetings@cshl.org; *www.cshl.org*]

15–28. Bioinformatics: Writing Software for Genome Research; Cold Spring Harbor, NY [see contact, Oct. 10–23]

24–26. Analysis of Gene Expression Data; Piscataway, NJ [G. Stolovitzky, gustavo@us.ibm.com; *http://dimacs.rutgers.edu/Workshops/GeneExpression.html*]

31–Nov. 5. Computational Genomics; Cold Spring Harbor, NY [see contact, Oct. 10–23]

November 2001

14–16. Gene Identification and Protein Functional Analysis; Hinxton, Cambridge, UK [Human Genome Mapping Project Resource Centre, +44-1223/494-513; Fax: -512; training@hgmp.mrc.ac.uk; *www.hgmp.mrc.ac.uk*]

28–30. Protein Structure Prediction; Hinxton, Cambridge, UK [see contact, Nov. 14–16]

☛ Exploring DNA in the Classroom

With the support of the DOE Human Genome Program, the Biotechnology Institute has published an interactive CD-ROM for 7th to 12th grade classrooms. *DNA and Genes Odyssey*, which can be used on PC or MAC, contains seven lectures, numerous animations, and an extensive teacher's guide and is accompanied by a short videotape. Lecture topics are "DNA and Genes Basics," "Uniqueness and Inheritance," "Human Genome Program," "Genetic Testing," "Evolutionary Biology," "Careers," and "Predicting the Future." Lecture overheads and teacher materials can be displayed on screen or printed. A teacher survey is at *http://psych.la.psu.edu/jswim/bioscied/DNAandGenes.htm*.

The spring issue of *Your World* magazine, *Cracking the Code*, explores the impact of the Human Genome Project. Its publication coincided with the release of a 2-hour television special titled "Cracking the Code of Life," produced by NOVA and WGBH-TV and broadcast on PBS stations (*www.pbs.org/wgbh/nova/genome*). Written for 7th to 10th graders, *Your World* is the magazine of biotechnology fundamentals and applications in healthcare, agriculture, the environment, and industry. The publishers are preparing *Cancer and Biotechnology* for the fall issue and *Microbial Genomics* for spring 2002. [Contact for CD-ROM and magazine: 800/796-5806, *jeff@biotechinstitute.org*; *www.biotechinstitute.org*]

Text versions of main articles and the teacher's guide for the 1997 Human Genome issue of *Your World* magazine are on the Web (*www.bio.org/library/yourworld/v5iss2.htm*). ◊

December 2001

3–5. Introd. Molecular Biol. Computing; Cambridge, UK [see contact, Nov. 14–16]

10–14. Advanced Linkage Course; New York [K. Montague, 212/327-7979, Fax: -7996; montagk@rockvax.rockefeller.edu; *http://linkage.rockefeller.edu*]

18–20. Human Linkage Analysis; London [see contact, Nov. 14–16] ◊

Contractor-Grantee Meeting Scheduled for DOE Human Genome Program

- **Jan. 27–Feb. 3, 2002, in Oakland, California (contact: Donn Davy, 510/486-4162, dfdavy@lbl.gov)**

U.S. Genome-Related Research Funding

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

DOE Office of Biological and Environmental Research Human and Microbial Genome Programs

- Funding opportunities: *www.sc.doe.gov/production/grants/grants.html*
- Life Sciences Division: 301/903-6488, *genome@science.doe.gov*
- Medical Sciences Division: 301/903-3213, *sharon.betson@science.doe.gov*

Computational Molecular Biology Postdoctoral Fellowships

Support career transitions into computational molecular biology from other scientific fields. Funded by DOE and the Alfred P. Sloan Foundation.

- Contact: Pat Stanley, Sloan Foundation; 212/649-1628, *stanley@sloan.org*, *www.sloan.org/main.shtml*

NIH National Human Genome Research Institute

- NHGRI program: 301/496-7531, *www.nhgri.nih.gov/About_NHGRI*
- Funding opportunities: *www.nhgri.nih.gov/Grant_info*
- ELSI: 301/402-4997

Small Business Innovation Research Grants

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

Contacts:

- DOE SBIR/STTR Office: 301/903-1414 or -0569, Fax: -5488, *sbir-sttr@science.doe.gov*, *http://sbir.er.doe.gov/sbir*; DOE SBIR and STRR due February 2002.
- Bettie Graham (see ELSI contact, NHGRI). NIH SBIR and STTR due April 1, August 1, and December 1.
- National resources, calendar: *www.zyn.com/sbir*
- National SBIR/STTR conferences: 360/683-5742, Fax: -5391, *sbir@zyn.com*.
- Alerting service: *http://lyris.pnl.gov/cgi-bin/?enter=sbir-alert* ◊