

## Model Organism Sequence and Function Studies Flourish

**M**odel 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

**S**cientists 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](http://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



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

Jazz, a new sequence assembler written at JGI.

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

**R**esearchers 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

**U**sing 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). ◇

## Plant Genome Significant to Agriculture, Energy, Human Health

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](http://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



*Arabidopsis thaliana*

Source: National Science Foundation

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](http://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](http://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](http://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](mailto:smithky@ornl.gov), or [zhouj@ornl.gov](mailto:zhouj@ornl.gov)] ◇

# 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

### 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.



Dabney Johnson and friend.  
Source: ORNL

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.

### 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](mailto:johnsondk@ornl.gov), <http://bio.lsd.ornl.gov/mgd>] ◇

## 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](http://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](http://www.celera.com)).

The NCBI Mouse Genome Resources page ([www.ncbi.nlm.nih.gov/genome/guide/M\\_musculus.html](http://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](http://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](mailto:emrubin@lbl.gov)] ◇

## MGI Release 2.7 Enhances Allele 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](http://www.informatics.jax.org)). Release 2.7 incorporates the following enhancements to the "Allele 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](http://www.informatics.jax.org/searches/allele_form.shtml)

Help document on Using the Allele Query Form: [www.informatics.jax.org/userdocs/allele\\_help.shtml](http://www.informatics.jax.org/userdocs/allele_help.shtml) ◇

## 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](http://www.doemedicalsciences.org)).

**N**uclear 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

## 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.

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)

## 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](http://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.

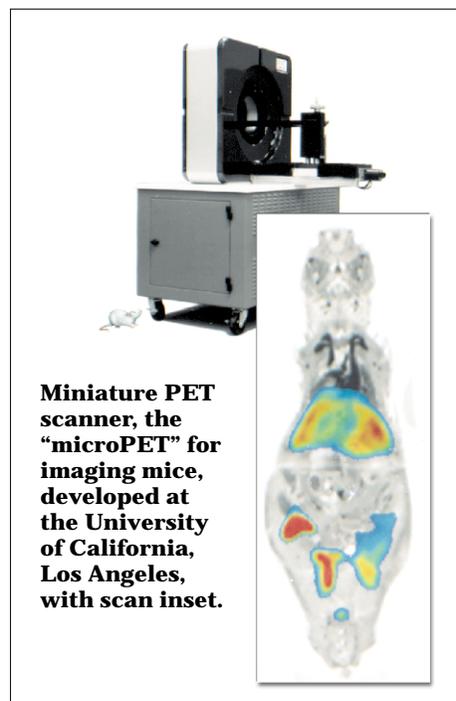
Since mice can be engineered biologically to carry genes that produce disease, molecular probes such as microPET allow the imaging of disease initiation and progression in a living mouse. In concert with this research, scientists are investigating highly sophisticated drugs designed to correct the molecular 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. ♦

## 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. ♦



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