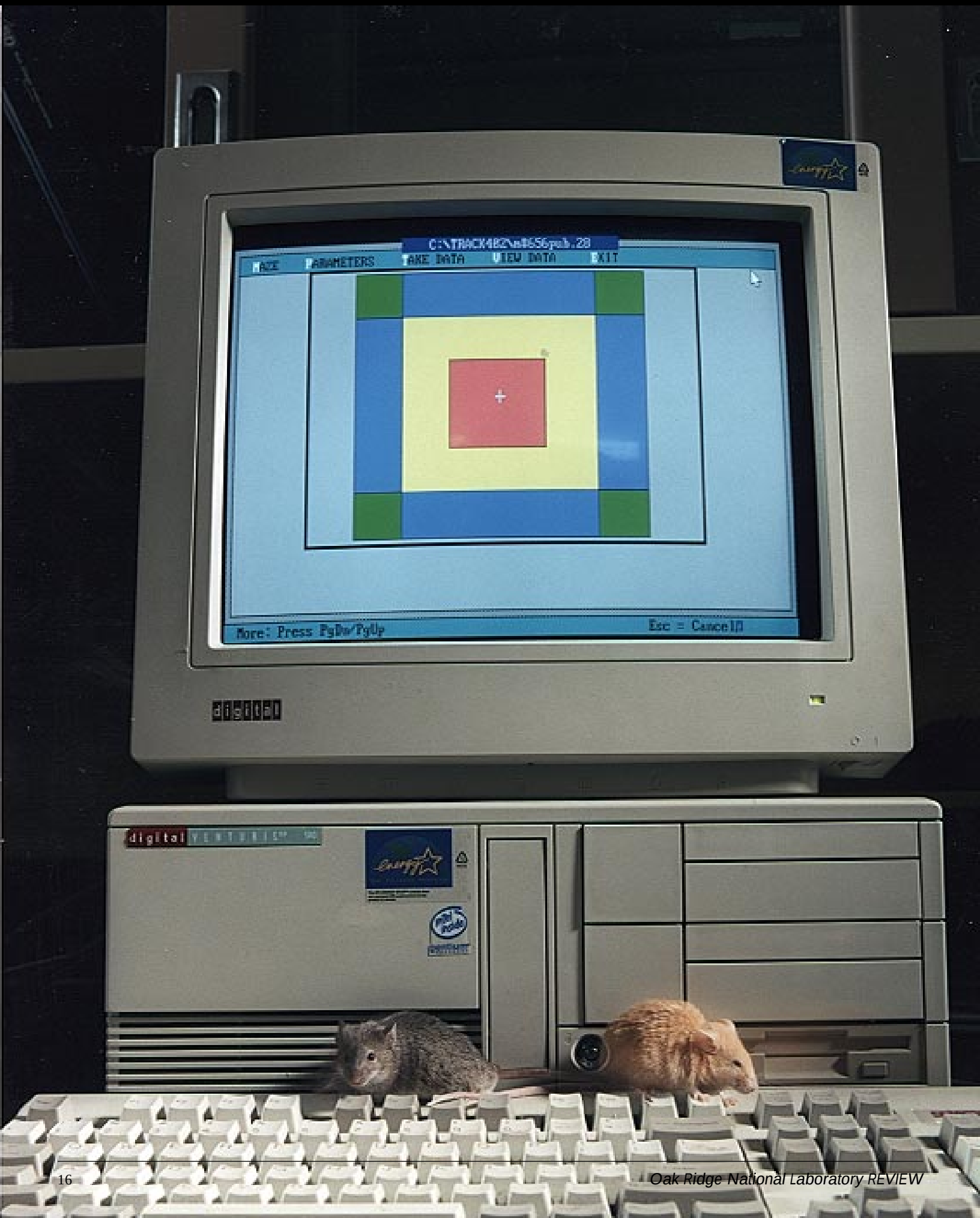
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Functional Genomics

Large-scale human genome sequencing now under way is expected to produce several million base pairs every month for the next 5 to 10 years. This major effort will provide the biomedical research community with a computerized catalog of the names, locations, and nucleotide sequences of the 80,000 to 100,000 genes on human chromosomes. Based on the rate at which sequence data are being produced, some 75 new human genes could be discovered every day. Significant advances are required in our ability to determine the function of these genes to unlock all the information hidden in the output from sequencing and gene searches. Biologists have been studying gene function for many years, but most of their research has been slow, costly, and directed at single genes. Access to the powerful reagents from the genome program is changing all of this. In this new era of biomedical research, in addition to studying the function of individual genes, it will be possible to perform experiments in functional genomics—gene function on a genome-wide scale.

Gene function is determined by (1) analyzing the effects of DNA mutations in genes on normal development and health in the whole organism, (2) analyzing a variety of signals encoded in the DNA sequence, and (3) studying the proteins produced by a gene or system of related genes. Functional genomics at ORNL is a comprehensive effort that leverages strong expertise and facilities in mammalian genetics, bioinformatics and computational biology, and biochemistry, as well as the Laboratory's resources for structural biology and cutting-edge technology development. Functional genomics in humans is becoming tractable by using genome information from other model organisms that provide rich scenarios for experimental research.

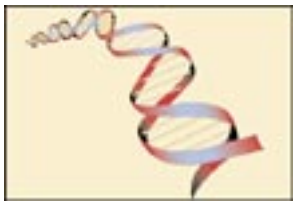
Mouse Genetics Research Facility

The mouse, because of its genetic and physiological similarities to the human and its extensive comparative genetic linkage map, is one of the leading model organisms for determining human gene function. A wide variety of genetic and molecular manipulations are possible in the mouse, making it a powerful research organism for studies of functional genomics. Mouse geneticists may "target" a specific gene to eliminate or alter its function in the whole animal or only in a specific cell population. They may add normal genes to a mutant mouse to correct an abnormality. They can engineer rearrangements in large regions of the genome and then create mutations gene by gene in the region using the chemical mutagen ethylnitrosourea (ENU) to make single-base changes in DNA. ORNL's Bill Russell discovered that ENU is a "supermutagen" and established the parameters for its effective use in mutagenesis experiments in the mouse. ENU has proven quite useful for making multiple mutant forms of a single gene, thereby providing more exact human disease models that mimic the subtle genetic variations characteristic of human populations. These strategies for creating mutations in mice can easily be expanded to a genome-wide scale, generating genetic reagents essential for the entire research community.

ORNL's Laboratory for Comparative and Functional Genomics, formerly called the Mouse Genetics Research Facility, represents one of the largest facilities in the world for carrying out experimental research in functional genomics using the mouse as a model organism. This newly designated DOE user facility currently houses some 90,000 mice representing a variety of mutations.

Just as you rarely see a computer without a mouse, you rarely see mice on a computer keyboard—a symbol for computational biology. ***Photograph by Tom Cerniglio.***

Mitch Doktycz checks the alignment of a robot's dispensing probes as he prepares to construct a set of flow-through genosensors. The dispensing probes transfer DNA sequences from microtiter plates to individual wells of the genosensors. Each genosensor measures less than half an inch on a side and contains almost 100 wells. A potential use of flow-through genosensors is rapid detection of genetic disease and other mutations. *Photograph by Tom Cerniglio.*

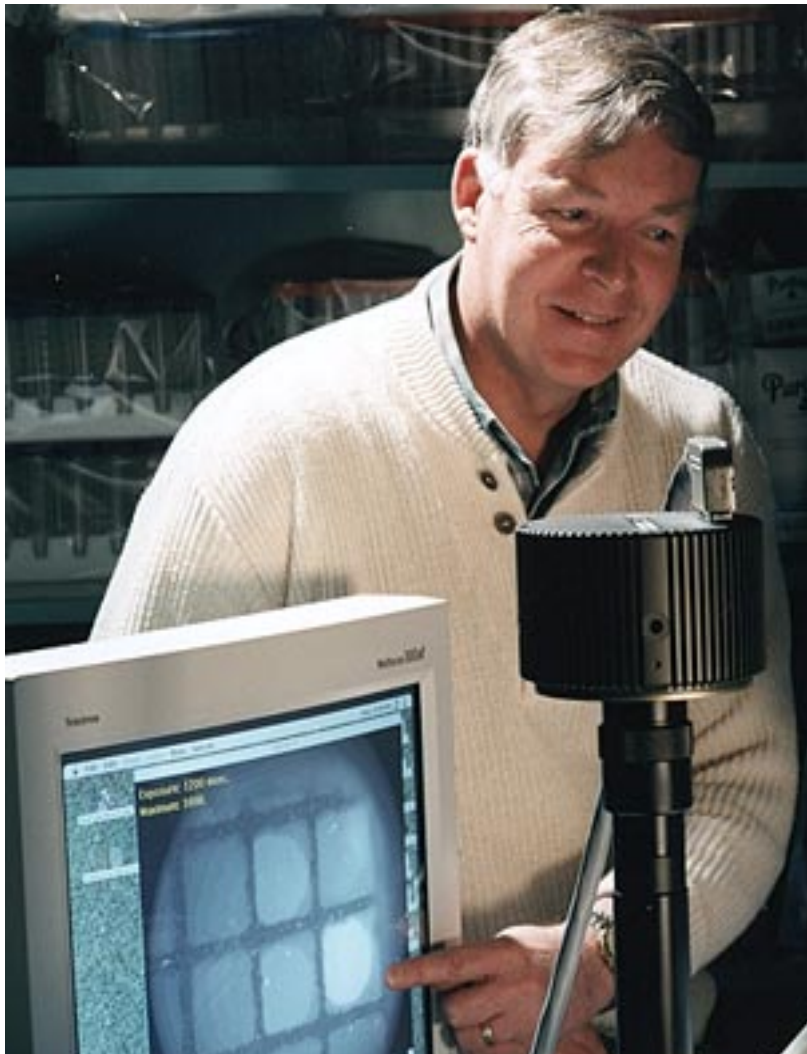


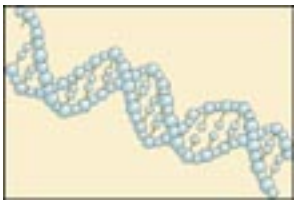
Bioinformatics Resource

Since 1989, ORNL has been developing a bioinformatics resource for the genome research community, starting with the DNA pattern analysis system called the Gene Recognition Analysis Internet Link (GRAIL™). GRAIL™ is a suite of tools designed to provide analysis of DNA sequences both interactively and through the use of automated computation. The capabilities of GRAIL™ are available by several methods, including an electronic mail server at ORNL that processes DNA sequence(s) contained in e-mail messages, and an interactive graphical X-based client-server system called XGRAIL™, which supports a wide range of analysis tools such as gene modeling. The ORNL genome informatics resource is being used by thousands of researchers worldwide. ORNL informaticists and computational biologists lead the Genome Annotation Consortium, a collaborative effort involving several bioinformatics groups that work toward providing the analysis tools, information access, and processing environment appropriate to manage effectively the enormous amounts of data produced by large-scale genome sequencing.

Protein Analysis

Another critical component of the functional genomics research program at ORNL is the ability to quickly characterize the structure and function of the proteins that genes encode. This analysis involves a comprehensive effort to integrate protein engineering and enzymology, mass spectrometry, neutron-based structural biology, and computational approaches to the prediction of protein structure and function based on structure.



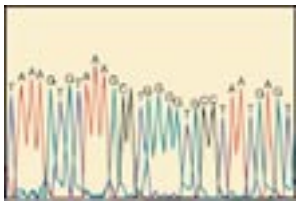


High-Throughput Analysis and Screening Systems Development

The large number of genes to be analyzed and the extraordinary complexity of analyzing the function of a system of genes and their interrelationships make it necessary to develop high-throughput technologies that can lead to truly genome-wide determination of gene function. The ORNL program includes a number of technology-oriented efforts that include flow-through genosensor-type chip arrays, fast DNA analyses employing the "lab-on-a-chip" concept, and other microinstrumentation developments for genome analyses.

This comprehensive effort is now in the second year of a three-year start-up period supported by ORNL's internally funded Laboratory Directed Research and Development Program. The team of researchers includes members of ORNL's Life Sciences, Chemistry and Analytical Sciences, Instrumentation and Controls, and Robotics and Process Systems divisions.

After focusing the fluorescence microscope, Mitch Doktycz discusses the image on the computer screen with Ken Beattie. A once freely moving DNA sequence containing a fluorescent tag binds strongly to complementary sequences immobilized on the flow-through genosensor. Blue visible light from the microscope excites the fluorescent tag, producing the array of bright and dark spots. ***Photograph by Tom Cerniglio.***



Selected First-Year Achievements

Several key milestones have been met during the first year of ORNL's Functional Genomics Program. Efforts have resulted in the establishment of new programs in ENU mutagenesis and the testing of potential mutants for changes in behavioral and biochemical parameters. To date, behavioral aberrations in four existing mutant strains of mice have been documented for publication by Dabney Johnson's mammalian genetics laboratory, and 176 new litters have been screened for induced mutations in a large segment of mouse chromosome 4. ENU was used by Monica Justice to generate multiple alleles at two mouse loci involved in immune function. New recessive alleles of each locus were obtained, and eight new dominant mutations with relevant human disease phenotypes have proven to be heritable. These dominant mutations include ones that cause anemia, craniofacial abnormalities, neural tube defects, skin disorders, and cataracts.

Under Ed Michaud's direction, the transgenics laboratory has developed more efficient molecular systems for creating made-to-order mutations in specific genes or regions of the genome. Researchers in ORNL's Instrumentation and Controls Division are developing new technologies to automate screening techniques that are currently bottlenecked by a reliance on manual testing protocols. A database cataloging the entire Oak Ridge collection of mutant strains was created to make available information about the genes and genome regions in the mouse as research tools for the research community. The database has a Java interface so users can view the deletion complex and the mouse function data and make correlations and comparisons with human data.

An online resource about mouse mutant strains at ORNL was made available. Genome sequences become meaningful and useful if the information they contain is found, extracted, made explicit, and made accessible to the research community. The Genome Channel is a unique information resource and Web browser that gathers the distributed output of sequencing centers and provides a fully assembled view of the human genome, its chromosomes, clones, sequences, and experimentally known and computationally predicted genes. The initial version of the Genome Channel was well received at its debut at the 1997 DOE Genome Contractor's meeting in Sante Fe, New Mexico, by both the user community and sponsors. It is being developed by the ORNL-led Genome Annotation Consortium, whose mission is to bring biological meaning to the DNA sequence output of the Human Genome Project. This research tool captures sequence as it is generated worldwide, analyzes the sequence for new genes, and makes the information accessible to the genome community via the Genome Channel Browser. This work also addresses the development of a system that uses the World Wide Web's intelligent agents to dynamically locate and link to remote information about the function of known genes.—*Reinhold Mann, director of ORNL's Life Sciences Division*