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LIFE SCIENCES DIVISION
PROGRESS REPORT FOR THE PERIOD
CYs 1997–1998

Reinhold C. Mann
Director

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LIFE SCIENCES DIVISION
PROGRESS REPORT FOR THE PERIOD
February 1, 1997 – December 31, 1998

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Foreword

This is the first formal progress report issued by the ORNL Life Sciences Division. It covers the period from February 1997 through December 1998, which has been critical in the formation of our new division. The legacy of 50 years of excellence in biological research at ORNL has been an important driver for everyone in the division to do their part so that this new research division can realize the potential it has to make seminal contributions to the life sciences for years to come.

This reporting period is characterized by intense assessment and planning efforts. They included thorough scrutiny of our strengths and weaknesses, analyses of our situation with respect to comparative research organizations, and identification of major thrust areas leading to core research efforts that take advantage of our special facilities and expertise.

Our goal is to develop significant research and development (R&D) programs in selected important areas to which we can make significant contributions by combining our distinctive expertise and resources in the biological sciences with those in the physical, engineering, and computational sciences. Significant facilities in mouse genomics, mass spectrometry, neutron science, bioanalytical technologies, and high performance computing are critical to the success of our programs.

Research and development efforts in the division are organized in six sections. These cluster into two broad areas of R&D: systems biology and technology applications. The systems biology part of the division encompasses our core biological research programs. It includes the Mammalian Genetics and Development Section, the Biochemistry and Biophysics Section, and the Computational Biosciences Section. The technology applications part of the division encompasses the Assessment Technology Section, the Environmental Technology Section, and the Toxicology and Risk Analysis Section. These sections are the stewards of the division's core competencies. The common mission of the division is to advance science and technology to understand complex biological systems and their relationship with human health and the environment.

Major thrust areas in the division include functional genomics and proteomics, biomedical technology research, bioanalytical science and technology, computational biology and bioinformatics, toxicology and risk analysis, life cycle analysis, and environmental assessment and remediation. Core programs are in place in functional genomics and in computational biology/bioinformatics. We will build on these programs to develop a strong proteomics effort. Closely related to this thrust is a proposal for a new Center for Structural Molecular Biology (CSMB) that was developed during this reporting period and is undergoing review during the Summer of 1999. The proposed CSMB would be a user facility that would provide access to a new small angle neutron scattering station at the ORNL High Flux Isotope Reactor (HFIR), to the special biological mass spectrometry facility at the Laboratory, and to our computational biology resources. With increased support for biomedical engineering both at the National Institutes of Health (NIH) and at the Department of Energy Office of

Biological and Environmental Research (DOE-OBER), our ongoing projects in this area are being positioned to establish another core research program in the division. Our alliance with the ORNL Instrumentation and Controls (I&C) Division, and record of accomplishments coming from this partnership contribute significantly to our competitiveness in biomedical engineering. In addition we have been forming a partnership with the Biomedical Engineering Department at Vanderbilt University. We are strengthening program development efforts in the toxicology and risk analysis, life cycle analysis, environmental assessment and remediation areas through the Technology Applications Program in the division.

This report describes many technical highlights produced by the researchers in our division. A number of our scientists were recognized by significant honors and awards. A few examples include the election into the National Academy of Sciences of Dr. Audrey Stevens in 1998. Biological research at ORNL has been recognized since 1957 by the election of six researchers to the National Academy of Sciences (Alexander Hollaender, 1957; William Arnold, 1962; William Russell, 1973; Richard Setlow, 1973; Liane Russell, 1986, Audrey Stevens, 1998). Dr. F. F. (Russ) Knapp, leader of our nuclear medicine program, achieved the rank of Corporate Fellow, the highest distinction for scientists at ORNL. John Miller, head of the Biochemistry and Biophysics Section, was elected Fellow of the American Association for the Advancement of Science. Richard Leggett was elected to the National Council on Radiation Protection and Measurements. Annetta Watson accepted an invitation to serve on the U.S. Army Science Board.

A few personnel changes had impact on programs in the division. Richard Woychik, who was instrumental in launching the ORNL functional genomics initiative, took a position at Case Western Reserve University in 1997, and moved from there to Parke-Davis Pharmaceutical in 1998. Monica Justice accepted an offer from Baylor College of Medicine in 1998. Lisa Stubbs left the Laboratory to join Lawrence Livermore National Laboratory. Eugene Rinchik accepted the leadership position for our mouse mutagenesis program and joined the division in 1998. Yun You moved from Jackson Lab to join our mouse genomics program. DOE funding for our fundamental and applied cryobiology effort was significantly reduced and some of it reoriented in scope and direction. As a result, Peter Mazur, Corporate Fellow, and founder and leader of the program retired from the Laboratory and established his research laboratory at the University of Tennessee. Similarly, DOE funding for the protein engineering group was terminated. Fred Hartman, Director of the former Biology Division, Corporate Fellow, and founder and leader of this program, retired from the Laboratory and established a research laboratory at The University of Tennessee (UT). Charmaine Foltz joined the Laboratory as Institutional Veterinarian. In the division, she heads the Laboratory Animal Resources Section, which operates the Mouse Genetics Research Facility, a DOE user facility with a current average daily occupancy of 70,000 mice. At the end of this reporting period, Michelle Buchanan, leader of the biological mass spectrometry laboratory in the Chemical and Analytical Sciences Division (CASD) joined our division as Associate Director with special focus on providing leadership to our functional genomics program and on building our core efforts in proteomics and structural biology.

During this reporting period, we initiated a number of partnerships that are becoming more and more important for the future of our research programs. The Joint Institute for Biological Sciences (JIBS) was established between ORNL and UT to promote and develop support for collaborative education and research in biological sciences. UT organizations involved in this effort include the Medical Complex, the College of Veterinary Medicine, and the Institute of Agriculture. Barry Berven, Associate Director of our division, was named acting director of JIBS in September 1998. Work is under way to develop a strategic plan outlining specific goals for R&D, staffing, facilities and equipment, and funding. As part of JIBS, the UT/ORNL Graduate Program for Biomedical Sciences has been restructured into the Graduate Program for Genome Science and Technology. This program has been realigned under Life Sciences at both UT and ORNL to have greater involvement and relevance to research initiatives and educational needs at both institutions.

An April 1998 conference, "Partnering for Functional Genomics Research," attracted representatives from 14 pharmaceutical and biotechnology companies. All participating companies expressed interest in further interactions, and several new projects are being discussed. The Merck Genome Research Institute initiated a research project through JIBS. Other follow-on activities are under way to establish collaborative efforts and to pursue the development of an R&D consortium involving several industry partners.

On December 3, 1998, ORNL signed a memorandum of cooperation with a number of medical institutions in Tennessee. Participants include the University of Tennessee (Knoxville and Memphis), Meharry Medical College, Vanderbilt University Medical Center, and St. Jude Children's Research Hospital. This partnership, called the Tennessee Mouse Genome Consortium, is designed to facilitate collaborations among the participating institutions, using the ORNL Mouse Genetics Research Facility (MGRF) as a resource and partner in the research programs under the consortium umbrella.

We have been investing considerable effort into moving research labs out of obsolete facilities at the Y-12 site to the main ORNL campus. At the end of this reporting period only some 60 employees remain at the Y-12 site. These are researchers and staff whose work is associated with the MGRF. Groundbreaking for a new $2.8-million laboratory building at the ORNL site is occurring as this report is being finalized. A $12-million construction line item project, the Laboratory for Comparative and Functional Genomics (LCFG), is being planned for fiscal year 2001. The LCFG will be a modern animal facility that will house our mouse colony, rederived from frozen sperm and embryos, in a specific pathogen-free environment. Upon completion of these two construction projects, we will be able to close down the life sciences complex at Y-12. The LCFG is the first item of a planned $38-million investment by DOE-OBER into a Center for Biological Sciences (CBS) at ORNL. The CBS is planned as a modular complex of buildings, equipment, and infrastructure that will house current and future research programs in the areas of functional genomics, structural biology, proteomics, and systems biology. It will provide the environment for the ORNL biological research program to make significant contributions to biology during the next decade and beyond, with a special focus on complex biological systems research. Development of the CBS will enhance the

advantages gained from the program's recent restructuring to embrace not only the biological sciences but also allied disciplines in information science and computing, analytical methodologies, and chemistry.

Life Sciences Division

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Overview

The Life Sciences Division was created in February 1997 by merging the Biology and Health Sciences Research Divisions. It continues the ORNL tradition of excellence in biomedical research that started 50 years ago. Building on strong and often unique competencies and special facilities in Mammalian Genetics, Molecular Biology, Biochemistry and Biophysics, Structural Biology, Bioinformatics, Biomedical Technology, Biotechnology, Environmental Assessment Technologies, Risk Analysis, and Toxicology, the division pursues research and development to understand the impact of energy production and use on biological systems in general and on human health in particular. The division provides a stimulating R&D environment for a multi-disciplinary group of approximately 480 staff members, including researchers, support staff, subcontractors, guests, and students who pursue challenging research at the intersection of the Biological, Physical, Medical, Engineering, and Computational Sciences. The division operates the MGRF, an official Department of Energy User Facility. It consists of a colony of approximately 500 genetic strains of mice with a total of approximately 70,000 animals, and co-located well equipped laboratory space. This mutant collection is a resource for research in analyzing gene function and identifying mouse models of human genetic diseases. The division has modern experimental research laboratories that support research in the core biosciences and technology development in biosensing, molecular imaging, and high-throughput genotyping. State-of-the-art computing and information processing facilities are part of the division infrastructure supporting Bioinformatics and Computational Biology research programs.

Mission

The mission of the Life Sciences Division is to advance science and technology in order to understand complex biological systems and their relationship with human health and the environment.

Structure

The Life Sciences Division consists of six research sections, an operations support section, and the Laboratory Animal Resources Section, which operates the MGRF.

Systems Biology

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Computational Biosciences Section

Mammalian Genetics and Development Section

Biochemistry and Biophysics Section

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Introduction

Activities in the Biochemistry and Biophysics Section span the fields of biology, chemistry, and physics with particular emphasis on the science at the intersection of these fields; e.g., biochemistry, biophysics, and chemical physics. Basic research is carried out in areas such as protein engineering, establishment of structure-function relationships, x-ray and neutron crystallography of biomolecules, DNA structure, biosensors, disease diagnosis, health effects from chemicals and radiation, plasma physics, microscopy, and optical and mass spectrometry. In addition to the basic research, considerable effort is spent on technology development such as the invention and refinement of novel measurement techniques, instruments, and sensors. Some technologies of recent interest include laser spectroscopy, mass spectrometry, scanning probe microscopies, imaging technology, and biosensors. A recent emphasis has been on potentially high throughput chip technologies and multiplexed sensors. Wireless biomedical devices, developed in collaboration with the I&C Division, represent another important focus for the future.

Biochemistry research focuses on exploration of structure and function relationships of animal and plant proteins. The proteins studies include energy-related enzymes, growth factors important in cancer biology, and DNA repair enzymes. Site-directed mutagenesis, biochemical modification, and genetic techniques are used to produce modified proteins. Extensive studies on the regulation of eukrayotic messenger RNA synthesis and turnover has focused on several exoribonucleases. These enzymes play an important role in regulating RNA levels and function. ORNL has extensive national-resource capabilities for structural biology in neutron scattering and diffraction at the HFIR. The x-ray counterparts of these facilities provide synergistic and complementary structural capabilities. These facilities are being used to determine the structural organization of genomic DNA and associated nuclear proteins through detailed three-dimensional analysis of structures such as the nucleosome core particle. The molecular immunology program focuses on ligands that bind to cell surface molecules to target isotopes to cellular sites. Glycoproteins in the endothelium of tumors are the subject of study of monoclonal antibodies. These target molecules are identified using protein chemistry and molecular biology.

Selected Accomplishments

Flowthrough Genosensor Technology. A high-throughput DNA analysis system based on flowthrough genosensor technology was assembled by researchers in BABS. This system has the ability to monitor thousands of DNA sequences simultaneously, at high speed, due to the unique micro-capillary array design. The flowthrough genosensor chip is comprised of DNA probes attached to the inner walls of micro-capillaries connecting the two faces of a glass or silicon wafer. Robotic technologies for the automated gridding of DNA probes across the genosensor chips have been developed. When a labeled nucleic acid sample is flowed through the chip, the pattern of binding across the chip, analyzed by a CCD imaging system, reveals the presence and relative abundance of specific nucleotide sequences

in the sample. Flowthrough chip technology has been patented and licensed. Applications of the technology in genotyping, gene expression analysis, and microbial identification are under development. The technology is expected to help researchers uncover complicated cellular processes such as metabolic pathways and responses to genotoxic or pathogenic exposure and will facilitate diagnosis of genetic and infectious diseases, and accelerate drug discovery.

New Generation of Intelligent Sensors. The next revolution in microminiature electronic devices will be in the area of intelligent sensors. Exploiting the sensitivity of micromachined springboards used in the atomic force microscope, researchers have shown that a variety of physical, chemical, and biological components in the environment can be perceived at extremely small levels. Arrays of such sensors now combined on a single silicon chip provide a powerful and yet very inexpensive means for simultaneous measurement. Several companies have licensed or are in the process of licensing the cantilever technology, which is expected to impact areas of environmental monitoring, industrial control, and consumer products.

ORNL Technology Puts Knoxville Company in Remediation Fast Lane. Slow and expensive commercial laboratory tests of water or soil may become obsolete because of a new instrument developed by the Advanced Monitoring Development Group and licensed to Environmental Systems Corporation. The Knoxville company has purchased the commercial rights to the technology to be used in the Luminoscope, a field-portable instrument designed to detect, measure, and monitor levels of gasoline, oil, polychlorinated biphenyls (PCBs) and pesticides down to parts per million levels in soil or in water. The instrument fits inside a suitcase-size carrying case and has a battery pack. A laptop computer provides instrument control, data analysis, spectral display and data storage.

Surface-Enhanced Raman Gene Probe for HIV Detection. The Advanced Monitoring Development Group has reported for the first time the use of surface-enhanced Raman (SERS) active labels for primers used in polymerase chain reaction (PCR) of specific target DNA sequences. This method has the potential for combining the spectral selectivity and high sensivitity of the SERS technique with the inherent molecular specificity offered by DNA sequence hybridization. The effectiveness of the detection scheme is demonstrated using the *gag* gene sequence of the human immunodeficiency virus (HIV). The SERS gene probe technology, which can make use of multiple probes for simultaneous detection of multiple biological targets, is currently developed for improved DNA mapping using BAC close methods.

Antibody-Based Nanosensor for Single-Cell Measurement. Optical sensors with nanoscale dimensions are powerful tools that are capable of providing selective identification of biochemical compounds at ultra-trace levels in biological systems. Research staff in the Advanced Monitoring Development Group have recently developed an antibody-based nanosensor for measurement of benzo(a)pyrene tetrol (BPT), a metabolite of the carcinogen benzo(a)pyrene inside a single cell. The antibody has recognition/binding sites for specific molecular structures of the antigen

and “fit” the unique antigen such that hollows, protrusions, planes, and ridges of the antigen and antibody are complementary. One can then develop antibodies to recognize molecular structures of chemicals, biochemicals, and microorganism components. The inherent selectivity of these antibodies can be utilized as specific “detectors” to identify many analytes of interest that are present at ultra-trace levels in single cells for studying gene expression or for medical diagnostics. Combining the exquisite specificity of biological recognition probes (antibodies) and the excellent sensitivity of laser-based optical detection, optical biosensors are capable of detecting and differentiating bio-chemical constituents of complex systems in order to provide unambiguous identification of a variety of diseases.

Monoclonal Antibodies Developed in Life Sciences Laboratory. The integrins are a family of cell-surface proteins involved in cell attachment. Researchers in the Molecular Immunology Group developed monoclonal antibodies (MAb) which recognize two members of the family and can be used to identify these proteins and their role in cellular functions. Although not patented, a bailment transfer mechanism was developed to “sell” the antibodies to companies so that they can be made available commercially. Three companies have acquired a total of four of these MAbs. In the last several years previous to these agreements, the group's laboratory has supplied over 300 samples of these reagents to other scientists.

Protein Crystal Annealing. Cryocrystallography has become the method of choice for macromolecular crystallography because of the many advantages conferred by cryogenic data collection. The only significant disadvantage, in some cases, is increased mosaic spread as a result of flash cooling. In crystals containing large unit cells, increased mosaicity can make data reduction difficult to impossible due to reflection overlap. Scientists in the Physical Biosciences Group have developed a process that, when applied to a flash-cooled crystal, will often lower the mosaic spread. The process has been applied to a number of different macromolecular crystals. Refined values of mosaicity have been observed to improve by greater than a factor of two, and resolution may also improve. Experiments demonstrate that the molecular structure is unaffected by the annealing process. The process has been successfully applied to crystals grown using a number of precipitants. Crystals have been flash cooled using a variety of cryoprotectants and also by using Paratone N to remove surface solution from the crystal. The process is simple, reproducible, and promises to routinely improve data quality in flash-cooled crystals of biological macromolecules. It should also extend the application of cryogenic data collection to a wider range of challenging crystals and simplify the handling of flash-cooled crystals.

Enhanced Electron Attachment to Highly-Excited Molecules Using a Plasma Mixing Scheme. Researchers have developed a novel plasma mixing technique to achieve enhanced electron attachment to highly-excited states of a variety of molecules. In this scheme, long-lived metastable states of inert gases are produced in a glow discharge and are extracted into an adjoining discharge-free region (target region); a suitable molecular gas is fed into the target region where they

undergo excitation transfer from the inert gas metatstable states. The highly excited molecules thus produced attach slow electrons that are also extracted to the target region from the discharge region. Researchers observed negative ion formation in a variety of gases including methane, nitric oxide, and some fluorocarbons. In addition to the production of negative ions, this technique automatically leads to the formation of radicals (molecular fragments).

This technique may have a variety of applications including (1) an inexpensive negative ion (neutral beam) source, (2) the means to efficiently produce radicals for plasma processing of materials, and (3) the means to dissociate molecules in plasma remediation of volatile toxic compounds. Two patent disclosures have been filed regarding the last two applications.

A Novel Energy-Efficient Plasma Chemical Process for the Destruction of Volatile Toxic Compounds. Researchers have reported several achievements in developing a novel energy-efficient plasma chemical process for the destruction of volatile toxic compounds (VTC). The basic physics/chemistry involved in the dissociative electron attachment to highly excited molecules was unraveled in a plasma mixing apparatus. The researchers have developed a methodology for the evaluation of VTC destruction in a plasma mixing apparatus and completed a baseline study on the destruction of VTCs using a DC glow discharge apparatus.

Tumor Blood Vessels Targeted with Radioisotopes in Cancer Therapy. Therapy of metasteses from solid tumors remains as a major problem in curing carcinoma—the major cause of death from cancer in humans. Much current work has focused on tumor blood vessels as a target for directed therapy. Inhibition of the growth of new blood vessels has shown to keep tumors at bay, but does not actually cure the cancer. Working in a mouse model system, researchers from BABS and ATS have used radioisotopes targeted to tumor blood vessels to kill not only the cells lining the vessels, but also the tumor cells they serve. In the most recent experiments, the effects of an alpha-particle emitter, ^{213}Bi, and a beta-particle emitter ^{90}Y were compared. Alpha particles can travel only about 10 cell thicknesses in tissues but are extremely destructive in their short path length, whereas beta particles can travel 100 times farther, but are less destructive per unit path length.

The data show that mice bearing artificial metasteses in their lungs can be cured of the tumors with vascular targeting of either radioisotope; however, the beta-particle emitter causes more damage to the adjacent normal lung as well as nearby organs. These results indicate that for radioimmunotherapy by vascular targeting to small tumors, up to 2000 cells or so, the “surgical strike” of a vessel targeted alpha-particle emitter is a more focused and specific agent for therapy.

Cloning and Characterization of an Enzyme Integral Tophotosynthetic Assimilation of Atmospheric Carbon Dioxide. The seemingly trite bumper sticker, "have you hugged a plant today?", actually reflects the profound truth that the entire animal kingdom requires plants for survival. We depend on plants for oxygen that we breathe, food that we eat, shelter that protects us from the elements, and medicinals that ward off disease. Fossilized

plants fuel our automobiles, generate electricity, and provide innumerable consumer products and industrial materials. All of these benefits are consequences of the photosynthetic machinery by which plants capture and utilize the energy from sunlight to produce carbohydrates from atmospheric carbon dioxide (CO_2). Photosynthetic conversion of atmospheric CO_2 to carbohydrates, which is the only biospheric avenue for sequestration of this predominant greenhouse gas, is dependent on the concerted action of multiple enzymes that comprise the Calvin cycle. As inefficiency of this biosynthetic pathway severely curtails potential plant growth and yield, application of genetic engineering toward improved efficiency offers the prospect of enhanced biomass for energy, food, and global carbon management. Reaching such an ambitious, long-term goal is predicated on comprehensive understanding of mechanism and interplay of the requisite enzymes. Although some of the Calvin cycle enzymes are well-characterized, others have been glaringly neglected. For example, ribulose-5-phosphate epimerase, which is essential for the regeneration of the substrate for CO_2 fixation and also provides for critical linkage between distinct metabolic pathways, has never even been isolated from plants due to its extreme instability and low natural abundance. Scientists in the division have overcome these impediments by cloning the gene that encodes the spinach epimerase, expressing the gene in *Escherichia coli*, identifying conditions for stabilizing the epimerase, and isolating the overproduced enzyme. Structural, catalytic, and stability parameters of the purified, biologically active epimerase have been characterized, thereby paving the way for future mechanistic studies.

Laser Desorption Mass Spectrometry for Dynamic Mutation Analysis with Clinical Samples. Working with researchers at UT Medical Center, the Photophysics Group recently developed laser desorption mass spectrometry (LDMS) for dynamic mutation analysis with clinical samples, and gave the first demonstration for Huntington Disease (HD) and denatorubral-pallidoluysian atrophy (DRPLA), which are two major genetic neurodegenerative diseases. With LDMS, the number of trinucleotide repeats can be rapidly and reliably measured. The analysis time by LDMS per sample can be a few seconds per sample *versus* minutes to hours for conventional gel electrophoresis. With LDMS, no radioactive or dye tagging are required. Thus, the cost for analysis can be significantly lower. It has been found that trinucleotide expansion is associated with many other serious genetic diseases. Among those diseases are Spinobulbar muscular atrophy (Kennedy disease), spinocerebellar ataxias, Fragile X, myotonic dystrophy, and FRAZE. LDMS is expected to be able to detect any of the above diseases. Since the analysis time is shorter and the cost can be lower, LDMS has the potential for population screening for these diseases. In addition to the detection of dynamic mutation, the ORNL researchers also cooperated with staff from the FBI Laboratory the Academia Sinica in Taiwan to apply this technology for DNA fingerprinting for forensic applications. LDMS was successfully used for DNA typing of short tandem repeat (STR) for different loci from several human samples for person identification. These results indicate LDMS can become an important tool for DNA fingerprinting for forensic applications in the future.

Licensing Agreement with Graviton, Inc., for Research in Micromachined Sensors. Culminating progress in developing novel micromachined sensors, an agreement for a multiyear research effort has been reached between ORNL and Graviton, Inc. of San Diego, CA. Graviton's license of intellectual property will allow commercial development in a number of fields. The licensing agreement represents the largest commitment of funds by an outside firm for technology transfer. As a part of the agreement, funds in from Graviton will be used for research supporting advanced sensing techniques. The novel concepts for sensing by microcantilevers originated several years ago in a DOE-funded basic research program. A recent internally funded program involving Life Sciences, I&C, and CASD successfully demonstrated the world's first palm-sized, wireless, multiple-input sensor.

Life Sciences Division Part of Initiative for Superconducting Transformer. A Superconductivity Partnership Initiative was signed on September 1, 1998, by the DOE and Waukesha Electric Systems, Waukesha, Wisconson, that is a mega boost toward next-generation transformers that are vastly more efficient, reliable, and compact.

The goal of the three-year $6-million cooperative agreement is to design, build and test a prototype transformer rated at 5 mega-volt-ampere with a 10-mega-volt-ampere overload—or emergency—capability. One megawatt will light 10,000 100-watt light bulbs. The initiative pools the resources of ORNL, Intermagnetics General, and Rochester Gas and Electric with those of transformer manufacturer Waukesha.

The 5/10-mega-volt-ampere superconducting transformer will be a scaled-down version of the final product, a 30-mega-volt-ampere commercial unit that will weigh half that of a conventional transformer. Furthermore, the superconducting transformer will not contain the thousands of gallons of cooling and insulating oil, a potential fire and environmental hazard. Superconducting transformers could be in wide use in about 20 years. The goal of the project is to fund cutting-edge research on difficult but important engineering problems.

Tasks include helping to develop high-voltage bushings that operate at cryogenic temperatures and conducting studies on electrical insulation materials, geometries, and sub-scale testing to verify the transformer design.

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Advances in computational sciences have facilitated approaches based on modeling and simulation for the prediction of behavior in many biological systems. The Computational Biosciences Section represents an inter-disciplinary, multi-investigator program designed to integrate key elements of the biosciences with expertise computing, Internet tools, intelligent systems, and bioinformation systems. The section's research program covers several high-impact scientific areas including methods for gene discovery and the analysis of genomes, simulation and modeling of protein folding and functional and structural classification using artificial intelligence-based techniques, systems for computational forensics and video processing, medical applications of intelligent systems, and the development of bioinformatics tools and systems for use by the research community. The interpretation of sequenced genomes represents the next great challenge at the interface of computing and biology, providing knowledge which is of immeasurable value to medical research, biotechnology, the pharmaceutical industry and researchers in a host of fields ranging from microorganism metabolism, to structural biology, to bioremediation. The section is developing new ways of recognizing and understanding the many important features of genomes and defining the infrastructure necessary for high quality and comprehensive analysis and sequence annotation processes. A comprehensive framework for analysis and annotation is being constructed using a distributed interoperable system of analysis servers and biodatabases together in a project called the “Genome Annotation Consortium.” The section has designed and continues to develop major online analytical systems for genomics such as the GRAIL® and genQuest Internet servers. The generation of new genome sequence and functional data is also a focus of the

section, which has an emerging effort to develop high-throughput sequencing capabilities and advanced sequencing automation. Due to the flood of genome data, it is a high priority to improve the efficiency of protein characterization based on protein sequence. The section is developing new algorithms and tools for protein structure prediction and functional classification using a variety of techniques such as neural networks, protein threading, global optimization, genetic algorithms, and molecular dynamics. Also with the increased amount and complexity of biodata, an important emphasis is the architectural design and construction of integrated analysis systems, databases, and knowledge bases for such data. The section addresses fundamental research issues related to the design, development and maintenance of bioinformation databases, Internet tools, query systems, and other types of bioresources. Research issues include biodata representation, database and analysis system interoperation, data integration, automated agent-based data retrieval and update technologies, semantics, data mining, and knowledge discovery methods.

Selected Accomplishments

The GRAIL EXP High Performance Gene Modeling System. GRAIL® EXP is the world's most advanced and accurate sequence-based gene modeling code. It provides a unique capability to determine the structure of multiple genes in sequences using pattern recognition and ESTs. Significant changes in the structure of the GRAIL® EXP codes and advancements in the algorithms have made it possible to process the current 150 million base pairs of human genomic DNA for gene content. Most recently, the codes were restructured to improve accuracy and performance, and modularization into smaller logical units has enabled the system to be incorporated into a streamlined, client/server architecture. Tests of the code on the Paragon 150 and on workstation clusters have been completed with parallelization of the database search components of GRAIL® EXP facilitated using MPI (message passing interface) and PVM (parallel virtual machine) to allow execution on multiple processors. These scaling tests showed near-linear speedup and are a prerequisite to providing community-wide Internet access to Paragon-based GRAIL® EXP services by January 1, 1999.

Globally Optimal Protein Threading. Predicting the folded state of a protein sequence is essential to the understanding of the function of the protein. Protein threading, a technique for finding a globally optimal sequence-structure alignment, is considered to be one of the most promising computational techniques for protein tertiary structure predictions. Up till now there have been no computer algorithms that promise to solve the protein threading problem in its full complexity due to its overwhelming computational complexity and the lack of understanding about the problem. Researchers have recently, for the first time, developed a rigorous polynomial-time algorithm which can realistically solve the protein threading problem under a condition that is widely accepted by the protein threading community. This research has also lead to a number of discoveries about the computational properties of the protein threading problem, which potentially have significant theoretical implications. These algorithms, as top computational biologist Dr. Richard Lathrop commented, "are

innovative advances on the state of the art and represent much needed progress in the field." A summary of the initial research results were published in the *Journal of Computational Biology*, Fall 1998, as an invited paper.

The PROSPECT Protein Structure Prediction Toolkit. A suite of computational tools was recently developed for protein structure predictions by the Computational Protein Structure Group. These computational tools include a new polynomial-time protein threading program, a fast probabilistic protein threading program, an innovative protein secondary structure prediction program, and a number of new and effective methods for modeling and computing protein potential energies. A computer package called Protein Structure Prediction and Evaluation Computer Toolkit (PROSPECT), consisting of these tools, allows a user to predict a protein tertiary structure based on recognition of structures or partial structures in a large database of known protein structures that are potentially similar to the unknown. Using this package, the Computational Protein Structure Group has made predictions for all 43 target proteins in the recent community-wide protein structure prediction contest CASP-3. A number of research groups from organizations such as NIH, Lawrence Berkeley Laboratory, Amgen, and Boston University have expressed interest in utilizing the system in their research and in collaborative development related to the project.

Improvements in GRAIL® Spliced Message Prediction. A new approach to splice site recognition. Once genes have been located in sequences, predicting the detailed structure for the gene accurately using computation is still a considerable challenge. A major problem is false prediction of Donor and Acceptor splice sites because of the large number of false signals in DNA sequences. A new clustering technique was used to better separate real signals from noise based on a subpartitioning of splice sites (for example donors) into a number of clusters with similar properties, where the set of clusters reflects the diversity of donor classes. Two different strategies for cluster-initialization were tried: greedy algorithm and random selection. The greedy algorithm gave better results in terms of inter- and intra-cluster distances. The scoring function for evaluation of a candidate donor site is based on a linear combination of weighted distances between the candidate and each cluster. This approach outperforms the standard GRAIL® method and a combination of this clustering technique with the original GRAIL® donor prediction system provides even greater improvement in splice site accuracy.

Progress in Genome Annotation. ORNL and the Genome Annotation Consortium have made progress in building a computational resource that will help us understand the basic biology of humans, microbes, and other biological organisms. This resource will include a comprehensive genome-wide analysis of genome sequence data from different organisms and facilitate an integration of biological data around a genome-sequence framework. The need for a comprehensive genome analysis process is pressing. Several organisms already have complete sequence data available; other organisms will be completed soon. The human genome and a considerable portion of the mouse genome will likely be completed in a few years.

However, molecular biologists, medical researchers, environmental biologists, biotechnologists, and others will be unable to make best use of these sequences without a more organized and comprehensive computational analysis. ORNL and the Genome Annotation Consortium are building this needed genome analysis framework. The steps in this computational process are: (1) retrieving biological data and assembling genomes; (2) computing genes, proteins, and genome features from sequences and experimental data; (3) computing homology and function among genomes, genes, and gene products; (4) three-dimensional structure modeling of gene products; and (5) linking genes and gene products to biological pathways and systems. We have built infrastructure to keep up with the data flow in steps 1 and 2 and processes to add value to the sequence data, but the scale up to data flow in the next phase will require considerable enhancements. These computational analysis results, together with the relevant experimental results, need to be stored and accessed by researchers in several ways. We have made considerable progress in some data management, data storage, and data access issues. We have constructed one method of data access (Genome Channel) that is currently being used by the community and other data access methods will be released over the next fiscal year.

The Genome Channel Interface and Analysis Framework. The Genome Channel is a high-throughput distributed computational environment providing the genome community with various services, tools, and infrastructure for high-quality analysis and annotation of large-scale genome sequence data. The Genome Channel provides the only current and comprehensive assembled view of the human genome and attaches high-quality computational annotation to this data on a consistent basis. Users can access graphical and text-based interfaces for a comprehensive view of the genome information, including known genes and predicted gene structures, gene relatives in sequence databases, links to function information about new genes. The Genome Channel browser provides a highly intuitive view of the data at various levels of detail. An automated system has been constructed that provides and updates various kinds of computational analysis on genomes in the Genome Channel repository. It schedules the analysis of sequence contigs by the supported analysis tools in a concurrent, pipelined fashion. Software agents (search and update agents) perform automated data retrieval, collation, assembly, and fusion to link relevant function information from many databases to newly discovered genes. Computer-intensive analysis tools use distributed processing systems (namely, PVM or MPI) to achieve speedup by distributing the subtasks among a cluster of workstations or MPP machines such as the Intel Paragons.

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ORNL established a Mammalian Genetics program soon after World War II specifically to assess the genetic effects of ionizing radiations in mammals. Experiments were carried out to determine both rates of induction of germline mutations and differential sensitivities of germ cell stages to induced genetic and cytotoxic damage in mice. In more recent experiments, a wide variety of chemicals

have also been tested for germline mutagenicity. While this program generated the data upon which assessments of human risk following exposure are based, it also produced important findings in basic mammalian genetics and led to the establishment of the largest experimental mouse colony in the world. The current mission of the section is the mutagenesis, genetic mapping, and functional analysis of the mouse as proxy mammal for human genetic studies. New mutations are being made in various regions of the mouse genome using both chemical and molecular mutagenesis strategies. Testing is ongoing for subtle phenotypes that would not traditionally have been recognized, even by very experienced technicians who consistently recognize mutations that alter general health, size and morphology, and normal motor behavior. For example, both existing and newly generated mutants are being evaluated for behavioral and biochemical aberrations. Mice that show abnormalities during any of these tests are analyzed in more detail. Technology is being developed to increase the sophistication, efficiency, and throughput for these behavioral assessments. Various bioactive molecules or byproducts in blood and urine are also being measured to monitor mutations induced in biochemical pathways.

Selected Accomplishments

Program Restructuring. In response to both the announced Health Effects Research funding recompetition and to our own sense of the need for redirection of scientific aims, we have revised our programmatic focus. Historically, we have targeted seven specific mouse genes/genome regions for experimental mutagenesis, a strategy that has allowed the accumulation of massive data sets for understanding the mutagenic potential of agents in the mammalian germline and has provided hundreds of mutant stocks for analysis of gene function. In these mutagenesis experiments, emphasis was on the detection of visible and lethal phenotypes resulting from induced genetic alterations. Additional programmatic funding has been devoted to separate but interactive principal investigator/group leader-driven research projects investigating aspects of the functional biology of specific gene mutations.

Beginning in FY 1999, we will use new mutagenesis strategies to accomplish a genome-wide approach to the induction of mutations as tools for the analysis of gene function. Essential elements will be:

(1) Chemical mutagenesis within selected genome segments defined by chromosomal deletions and inversions, including development of methods for applying this approach genome-wide.
(2) Broad-based screening of potential mutants for a wide variety of biochemical, behavioral, and morphological phenotypes.
(3) Cryopreservation, archiving, and distribution of all mutant stocks, and live maintenance of only that subset of stocks necessary for funded projects.
(4) Development of *in vitro* mutagenesis strategies, with emphasis on methods especially useful for generating meaningful changes in complex biochemical pathways.
(5) Basic research into the biology of gene function; the training of young scientists in the design and execution of biological experimentation will be an important element.

(6) Close interaction with bioinformatics and structural molecular biology research teams, so that our joint, integrated programs form a comprehensive functional genomics effort.

Role of the Agouti Gene in Cancer. Scientists in MGDS have been involved in research directed at the agouti gene. The goal of this project was to determine if the mouse agouti gene has a primary role in promoting skin cancer. The mouse agouti gene normally regulates the production of pigments involved in hair coloration. However, dominant mutations in the agouti gene cause the normal agouti protein to be produced at high levels throughout the body, resulting in yellow-haired mice that are obese, diabetic, and have an increased susceptibility to cancer of the skin, liver, lung, mammary gland, and urinary bladder. It is unclear if the agouti protein has a direct role in causing cancer, or if the cancers develop as a secondary consequence of the agouti-induced obesity and diabetes. If the cancers develop secondary to the onset of obesity and diabetes, then the agouti gene is unlikely to provide any new insights into the development of cancer. On the other hand, if the cancers develop as a direct effect of the action of agouti, then the agouti gene can be used as a tool to elucidate aspects of the molecular genetic basis of tumor development. The agouti gene was cloned here at ORNL, making it possible to now resolve this issue.

To determine if agouti has a primary role in the development of skin cancer, transgenic mice expressing high levels of agouti in the skin under the regulatory control of the human keratin-14 promoter (K14-agouti) were used in two-stage skin carcinogenesis experiments. K14-agouti mice are not obese or diabetic, but responded to chemical initiation of the skin with a significant increase in skin tumor prevalence (number of mice with tumors) and multiplicity (number of tumors per mouse) compared to nontransgenic control mice. Additionally, agouti acted synergistically with the phorbol ester TPA (12-O-tetradecanoylphorbol-13-acetate) to increase the cumulative prevalence, multiplicity, and malignant conversion rate of skin tumors, and to decrease the latency period of tumor formation. These data demonstrate conclusively that the agouti gene acts as a tumor promoter in skin carcinogenesis, and does so independent of the confounding factors of obesity and diabetes. These findings raise the possibility that deregulation of human agouti, which is 85% similar to the mouse protein, may also be associated with some types of human cancers.

A Mouse Model for the Human Angelman Syndrome. Children born with Angelman syndrome (AS), also known as the “happy puppet syndrome,” suffer from severe mental retardation, motor delay, seizures, and behavioral manifestations such as absence of speech, sleep disorders, unbalanced gait, stiff and puppet-like limb movements, and inappropriate laughter. Mutations in a gene, ubiquitin ligase enzyme 3A (*Ube3A*), found in human chromosome 15q, have been implicated in causing AS.

Among the radiation-induced mutations generated in MGDS’s program is a deletion (p^{30PUb}) in mouse chromosome 7 that includes the mouse version of the AS gene, *Ube3A*. Since large deletions in human 15q cause 70% of known cases of AS, this similar deletion in a strain of mice allows us to determine which of the physical, mental, and behavioral symptoms characteristic of AS can be studied in mice

as well. To date, tests have proven that AS mice are quite below normal in their ability to maintain position on a rotating rod; this test measures balance and coordination. AS mice are also much less active than normal mice in a test for exploratory behavior in an activity-test chamber. Interestingly, the performance of mice on these tests improves somewhat with age, mirroring the gradually improving (up to a point) clinical picture seen in AS children as they mature. Further tests are under way to measure the ability of AS mice to remember and try to avoid an unpleasant stimulus as a model for mental retardation, and to assess their 24-hour biorhythms as a model for sleep disturbance.

We have used dissected mouse brains to show which specific brain regions express the AS gene, an experiment obviously not possible in humans. *Ube3a* is normally expressed in the cerebellum, the center for motor control, and in the hippocampus, thought to control some kinds of learning and memory. Importantly, in both humans and mice, AS occurs only when the mutant gene is inherited maternally. This genetic phenomenon, known as genomic imprinting, is poorly understood and we hope to gather crucial information not only about the functional causes of AS but also about the mechanisms that control imprinting.

A Novel Gene in The Mouse P Region, Expressed Exclusively in the Central Nervous System, Maps to a Human Chromosomal Region Associated with Mental Retardation. One of the Oak Ridge radiation-induced chromosomal deletions, p^{8FDFoD}, at the pink-eyed dilution (*p)* locus in mouse chromosome 7, disrupts a gene expressed only in the brain and spinal cord. This gene, named *Ihw* (included in the human WAGR region) encodes two transcripts that we have cloned and sequenced; the DNA sequences show no similarity to other known genes.

WAGR is a human clinical syndrome, consisting of Wilms' tumor (a lethal kidney cancer), aniridia (absence of the iris of the eye), genito-urinary abnormalities, and mental retardation, caused by the deletion of a group of genes in human chromosome 15. The W, A, and G components map as a group to mouse chromosome 2, but the gene grouping has been separated in the mouse so that the R component is in the *p* region on mouse chromosome 7. *Ihw* is one of a small cluster of brain-specific genes that may determine the mental retardation in WAGR patients.

Researchers in MGDS have engineered a transgenic knockout of the *Ihw* gene, and are breeding mice that will have both copies of *Ihw* disabled. Those mice will go through our behavior-testing center to determine if the absence of the *Ihw* gene product causes abnormalites in mice that may mimic the mental retardation associated with WAGR in humans.

Major Cryopreservation Effort for Mutant Mouse Stocks. MGDS has launched a major cryopreservation effort for mutant mouse stocks. By freezing sperm and/or embryos, we propose to become a major archiving and distribution center for experimentally induced mouse mutations that have significant phenotypes of interest to the functional genomics and wider biological communities. Sperm freezing will provide a facile means for distributing any mouse mutation that is not male-lethal or male-sterile to the scientific community, and thawed embryos can very

reliably be used to reconstitute many stocks, especially inbred strains, via transfer into recipient females.

Cryopreservation will also provide a logistically feasible means for rederiving the conventional (not pathogen-free) ORNL colony into a new, specific-pathogen-free (SPF) facility, when that facility becomes available within three years. We are endeavoring to freeze down mutant stocks now so that only those stocks that will be actively used upon opening of the new facility need be reconstituted. In the interim before our move into the clean facility, we will cryopreserve many stocks not used in active investigations in order to free our genetics staff for new experimental work.

Since the effort has been running five to seven days a week, we have frozen 3000 embryos; this is more than were frozen in the entire previous year. We have also frozen sperm from 39 mutant stocks, and are collecting mice from an additional 80 stocks into the freezing queue. The effort has included the quality-control measures necessary to ensure that our recovered embryos are fully viable and our thawed sperm competent for fertilization either by artificial insemination or *in vitro* fertilization. We are also in active collaboration to test the efficacy of freezing whole ovaries for subdivision and transplantation into recipient females; this method would be invaluable for male-sterile and female-subfertile stocks. This collaboration includes testing to determine if embryos, sperm, and ovaries from non-SPF stocks still transmit any potential pathogens when used to reconstitute live stocks.

Identification of Gene Associated with Deafness, Gastritis And Gastric Lymphoma. Researchers in MGDS have determined that the disruption of the mouse mucin 2 (*muc2*) gene in a unique Oak Ridge mutation called *14Gso* produces gastritis and gastric cancer and may also be involved in hereditary deafness.

14Gso is an X-ray induced mutation. Mutant mice were easily identified because they exhibit a persistent circling and head-bobbing behavior, indicative of defects in the inner ear, the organ where balance and hearing are controlled. Direct examination of the inner ear structures of *14Gso* mice revealed severe degeneration such as a collapse of membrane structures in the cochlea and vestibular apparatus at birth, progressive deterioration of hair cells, nerve and supporting cells. Culiat and Stubbs conducted research directed toward the identification of the gene(s) responsible for these defects and further biological characterization of the *14Gso* mutation.

Cytogenetic analysis showed that *14Gso* is a mutation due to the breakage and exchange of the tips of mouse chromosome 7 and 10. Further cytogenetic and physical mapping data of the mutation indicated that the breakpoint region in chromosome 7 is located at the regulatory region of *muc2* (intestinal mucin 2), gene coding for a major protein in the mucus lining of the intestine. Since a region of the human *muc2* gene was very similar to the gene associated with deafness in man (Norrie Disease Protein), the expression of this gene in *14Gso* was investigated. The *muc2* gene expression is abnormal in mutant mice, indicating a loss of regulation of the normal levels and tissue specificity. The gene is normally expressed in the intestine and in mutant mice it is found at very high levels in the stomach and also misexpressed in the kidney and lungs. In

man, the overexpression of *muc2* (could be induced due to infection by the bacterium causing ulcer, Helicobacter pylori) in the stomach is associated with chronic gastritis leading to gastric lymphomas and adenocarcinomas. When stomachs of mutant mice were examined, these same defects were discovered. *14Gso* is therefore a good mouse model for studying the progression of gastric cancer from chronic gastritis.

Abnormal expression of *muc2* in *14Gso* in the inner ear has not been demonstrated; however, it is well known that mucin-like proteins are found in the mammalian inner ear, though their functions are not known. *Muc2* is very large and so far only pieces of the mouse gene have been cloned and are useful as probes for expression in the inner ear. The region of mouse *muc2* with highest homology to the Norrie Disease protein has been difficult to clone. Cloning and sequencing of the entire gene is currently being done at Lawrence Livermore National Laboratory. The cloning and characterization of the mutated regions in *14Gso* (both translocation breakpoints in 10 and 7) will be completed as a collaborative project between LLNL and ORNL.

Technology Applications

Assessment Technology Section

Environmental Technology Section

Toxicology and Risk Analysis Section

Assessment Technology Section

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The focus of this section is to conduct research and technological applications aimed at solving problems of national and international importance in areas concerning human health and the environment. Environmental programs are aimed at detecting, characterizing, and assessing the impacts of all classes of radiological and chemical environmental pollutants. These efforts include

performing site characterizations at potentially contaminated facilities across the country, developing and testing new instruments and techniques for detecting chemical and radiological pollutants, and ensuring the quality of data obtained from field measurements and laboratory analyses. In addition to pollutant characterization programs, life cycle analysis studies are also conducted in areas concerning waste minimization, remedial action determination, and decontamination and decommissioning to optimize regulatory, economic, social, and environmental concerns in the decision-making process. Human health studies include nuclear medicine programs aimed at applying radiopharmaceuticals to the diagnosis and therapy of neural, cardiac, and cancer diseases; and biokinetic and metabolic computer modeling for calculating the effects of radiological and chemical insults on humans. In support of these efforts, state-of-the-art data management, training, information analysis, and communication programs are maintained.

Selected Accomplishments

F. F. Knapp Appointed to Corporate Fellow at ORNL. The Lockheed Martin Energy Research Corporation appointed Dr. F. F. "Russ" Knapp to the position of Corporate Fellow at ORNL. Dr. Knapp is currently the leader of the Nuclear Medicine Group and is an internationally recognized authority in the development and application of radioisotopes to diagnosis and therapy of cancer, heart disease, and neurological diseases. This recognizes his accomplishments and contributions to the field of nuclear medicine.

Dosimetry Research Group Publishes Federal Guidance Report 13 on Environmental Dose Conversion Factors. The Dosimetry Research Group prepared and published Federal Guidance Report 13 which provides nationally recommended radiation dose conversion factors for environmental radionuclides. Senior staff led the effort to develop exposure scenarios, perform radiation transport calculations using computer codes and nuclear data developed by the Dosimetry Research Group for radionuclides of interest, and prepare the summary report which was issued as an EPA document. Federal Guidance Report 13 will provide the basis for exposure estimates for a variety of applications in the United States.

ORNL Awarded Contract to Perform Major Environmental Pollutant Assessment for the U.S. Postal Service. Staff of the Assessment Technology Section successfully completed a pilot study which led to receipt of a major contract to perform a multi-year environmental pollutant assessment at facilities in the midwest United States for the U. S. Postal Service. This effort required development of field measurement and assessment capabilities for lead, asbestos, and radon pollutants; development of remote and local data processing and evaluation systems; implementation of comprehensive measurement and quality assurance programs; and development of report preparation systems. The successful completion of the pilot program resulted in the awarding of the full multi-year, 4,000-site project which will enable ORNL to showcase its human health assessment expertise, measurement and analytical capabilities, and data management capabilities.

Nuclear Medicine Group Develops Method to Prevent Coronary Restenosis Following Balloon Angioplasty. Investigators in the Nuclear Medicine Group developed a method to prevent coronary restenosis following balloon angioplasty. The Group developed a method to apply rhenium-188 to prevent arterial blockage by coating a stent which allows irradiation during angioplasty. This effort resulted in an invention licensed by the Mallinkrodt Medical Corporation which consists of a special ion exchange system developed at ORNL that provides the highly concentrated form of rhenium required for this procedure. In addition, a cooperative research and development agreement (CRADA) was awarded with Innerdyne, Inc., to evaluate the effectiveness of this technology with international collaborators.

DOE Certifies M-100 Radwaste Boxes Made from Recycled Metal. DOE awarded a type 7A certification for the M-100 class of boxes which are to be fabricated from recycled metal and used to contain low-level radioactive waste during transport. The effort was championed by DOE's Office of Environmental Restoration and was aimed at developing containers that would reduce fabrication and disposal costs, maximize worker and public safety, and facilitate inspection and quality control functions. The M-100 containers should be ASTM certified in the near future, and the containers should be available to DOE and contractors in November 1998.

NCRP Publishes Report on Radionuclide Exposure to the Embryo/Fetus. On September 25, 1998, the National Council on Radiation Protection and Measurements (NCRP) published NCRP Report No. 128 titled “Radionuclide Exposure of the Embryo/Fetus. The leader of the Dosimetry Research Group was instrumental in the publication of this document in his role as consultant. The report describes effects of radionuclide exposure on the embryo/fetus, concerns of radiation exposure during pregnancy, dose estimation methods, and exposure limits. Primary contributions to this effort involved developing biokinetic and metabolic models and performing associated dose calculations for the embryo/fetus and mother following exposure to a wide variety of radionuclides.

ORNL Nuclear Medicine Programs Highlighted in DOE International Collaboration Effort. In an address the International Atomic Energy Agency in Vienna, Austria, Secretary of Energy Bill Richardson announced DOE participation in an international collaboration on research and development into the diagnosis and treatment of life-threatening illnesses using radioisotopes. In particular, the United States will provide surplus radioisotopes for nuclear medicine applications to heart disease, cancer, and bone pain diagnosis and therapies. The Nuclear Medicine Program at ORNL was highlighted in Richardson's presentation as being the key supplier of reactor-produced radioisotopes and rhenium-188 produced using a clinical generator developed at ORNL. Particular projects being conducted by the Nuclear Medicine Group were also highlighted including labeling of antibodies for cancer therapy, experimental procedures that prevent or retard

restenosis following coronary angioplasty, and cancer bone pain relief.

Assessment Technology Staff Receives Contract to Evaluate Ink for the U.S. Postal Service. The Environmental Management and Policy Office of the U.S. Postal Service has contracted with the Assessment Technology Section to evaluate ink used in mail processing systems. This effort involves determining the chemical composition of the ink, determining how it interacts with processing equipment, investigating the waste characteristics and disposal impacts, evaluating health concerns, and developing optimum specifications for ink from commercial suppliers. Specifications which take into account operational, health, waste, and processing costs should result in significant savings for the Postal Service.

Radon Mitigation Effort Completed on Guam. A major effort to conduct mitigation of radon hazard in facilities on Guam was completed in March 1998. This effort was funded by the U.S. Navy. A total of 119 facilities with initially measured radon levels greater than 20 pCi/L were mitigated over a five-week period beginning in February. This effort is the largest radon mitigation program conducted at one time to date.

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The necessity for the Department of Energy and the Department of Defense to remedy pollution caused by past environmental practices has resulted in the mission of the Environmental Technology Section. Environmental Technology staff are involved in characterizing and assessing the extent of environmental contamination, developing and demonstrating technologies to remedy contamination, and assuring that sites being cleaned by other organizations are adequately planned, conducted, and documented. The majority of the section's projects concentrate on developing new techniques, processes, and equipment to detect or remedy a wide variety of environmental pollutant, both radioactive and chemical. These activities are complemented by strong environmental statistical and technical programming support. Devices, technologies, and software created by section staff are transferred to private sector or other federal agencies whenever possible.

Selected Accomplishments

In Situ Chemical Oxidant Recirculation (ISCOR) Pilot Project. ETS staff designed, constructed, and operated the *In Situ* Chemical Oxidant Recirculation (ISCOR) pilot project in the 5-Unit Investigative Area of Quadrant I, Portsmouth Gaseous Diffusion Plant (PORTS). The project was developed based on an agreement between DOE and the Ohio Environmental Protection Agency (EPA) to gather additional technology information to assist in the development of Corrective Measures Study (CMS) alternatives at PORTS. The ISCOR approach involves injection through a

central well and extraction from a network of perimeter wells located at fixed distances from the injection well. The extracted groundwater is dosed with oxidant, $NaMnO_4$, and re-injected to the aquifer where it degrades organic compounds (present as either dissolved phase or free phase) on contact. This oxidant delivery technique is applicable to relatively permeable, saturated subsurface media contaminated with ganglia and/or pools of DNAPLs with an underlying aquitard. Results from the pilot project conducted during July through September 1999 indicated promise of the "5-spot" ISCOR approach as a remedial technology in an area of concern at PORTS while applying an aggressive remediation technology to a known area of groundwater contamination. The work was directed and funded by DOE and implemented by Bechtel Jacobs Company and ORNL. ORNL is currently overseeing the installation of additional injection/extraction well networks in the 5-Unit Investigative Area that will be implemented and deployed in FY 1999 by Bechtel Jacobs and ORNL.

Confirmatory Radiological Survey of the National Conversion Pilot Project Buildings 883 and 865 at the Rocky Flats Environmental Technology Site. ETS staff performed an independent verification radiological survey of interior walls, floors, and machinery in Buildings 883 and 865 at the Rocky Flats Environmental Technology Site (RFETS) for DOE Rocky Flats Field Office (DOE-RFFO). The verification included reviews of pertinent project documents, field measurements for beryllium, beta and alpha radiations, and gamma exposure rate ranges. The purpose of the independent verification was to verify the accuracy and completeness of measurements and the credibility of procedures used, resulting in an independent assessment of resulting site conditions versus project plans prior to project closeout. ETS's data indicated that removable contamination of lower walls and floors had been mitigated to levels below regulatory concern. Fixed radiological contamination, primarily depleted uranium, remained on equipment and floor surfaces. The original purpose of the verification was to determine if radiation and beryllium levels were reduced to acceptable concentrations for radiation workers. However, DOE-RFFO decided to transition the buildings for decontamination and decommissioning (D&D) rather than use the building for recycling of scrap metal as originally planned. Therefore, the level of characterization requested by DOE-RFFO was determined to be inadequate for D&D purposes and ETS recommended additional characterization in its final report issued June 1998.

Final Analysis Report of a Qualitative Radiological Survey of the CS-10 BOMARC Facility at the Otis Air National Guard Base, Massachusetts Military Reservation, Falmouth, Massachusetts. ETS staff performed a radiological scoping survey at the CS-10 BOMARC missile site on the Otis Air National Guard Base Massachusetts Military Reservation for the Air Force Center for Environmental Excellence (AFCEE) and the Hazardous Waste Remedial Action Program (HAZWRAP). This project had high public visibility and regulatory oversight (U. S. EPA and Massachusetts Department of Environmental Protection) due to CS-10's proximity to the town of Sandwich. The objective of the survey was to determine if

radioactivity was present at the BOMARC facility in concentrations exceeding natural background levels. There was no historical evidence to indicate that nuclear warheads were actually present or, if they were, that radioactivity escaped into the surrounding facilities and environment. Therefore, the purpose of this survey and associated soil sampling was to provide reasonable assurance of the absence of weapons-related radionuclide concentrations. The assumption for this analysis was that concentrations of radionuclides in soil and building materials did not exceed concentrations of nearby background sites. A statistical sampling procedure using the Visual Sampling Plan was developed to assess gross radiation levels in 56 abandoned missile shelters and 3 buildings (used for missile maintenance). Random locations were also selected for soil sampling in surrounding areas. Over 2500 radiation measurements and 150 soil samples were statistically analyzed. This analysis revealed that weapons-related radioactive contamination was not present at the BOMARC facility and surrounding areas and that additional characterization was not justified. More importantly, the results showed that the CS-10 BOMARC facility does not pose a radiological hazard to the environment, workers, visitors, or the public living in nearby residential areas. The sampling, statistical, and analytical techniques used held up under close public and regulatory scrutiny. A report discussing the findings was published in January 1999.

Independent Verification for Monticello Vicinity Properties Project (MVP) and Monticello Remedial Action Project (MRAP). ETS is designated the Independent Verification Contractor (IVC) for the Department of Energy Grand Junction Office (DOE-GJO) for the Monticello Projects based on a tri-party agreement between the DOE and the EPA, Region 8, and the Utah Department of Environmental Quality (UDEQ). The major scope of work for ETS staff on the MVP Project was to work with the Remedial Action Contractor (RAC) and the DOE to finalize the accelerated schedule for the delistment of the Monticello, Utah, vicinity properties. Staff conducted reviews of property completion reports and wrote a corresponding independent verification report recommending the certification status for individual properties to the DOE. ETS staff worked with the EPA to conduct investigative review and field survey on properties with suspect remedial action documentation. Independent verification funding was cut on the MRAP Project for the Monticello Mill Site (Operable Unit - I) and associated Peripheral Properties (Operable Unit - II) during the first half of 1998. In April, the DOE requested re-evaluation for independent verification for Monticello. In May, additional funds were approved by the DOE. The Independent Verification of the Monticello Remedial Action (OU- I) Work Plan Addendum report was submitted in June. ETS staff conducted on-site field survey throughout the field season on 10% of the verified Mill Site and Peripheral Properties area. Gamma surveys coupled with Global Positioning System (GPS) were completed. Contour maps were generated at the time of the survey using Surfer software. This provided for “in the field” identification of elevated gamma which exceeded 30% of the background and which required further investigation to document that the verified

area was remediated to EPA standards in 40CFR192.12 and the SFMP Hot-Spot Guideline. Site remedial action protocol is guided by analysis of all soil samples for Ra-226. ETS staff provided preliminary Ra-226 analysis using their mobile Opposed Crystal Gamma Spectroscopy (OCS) van or the ETS gamma spectroscopy lab. Independent soil samples were collected to document Th-230 and total U in the area of the final Montezuma Creek alignment and soil samples were collected to document metals concentrations associated with the remediated portions of the four on-site tailings piles. Document review for MRAP included a quarterly evaluation of the RAC database for split sample selection and validation that Ra-226 as a field excavation control guide is adequate to meet site standards for Th-230 and total U.

In Situ Remediation of DNAPL Compounds in Low Permeability Media. Dense non-aqueous phase liquid (DNAPL) compounds present in low permeability media (LPM) pose major challenges with assessment of their behavior and implementation of effective in situ remediation technologies. In situ remediation technology development has largely overlooked treatment of DNAPLs in LPM. Poor accessibility to the contaminants and the difficulty in delivery of treatment reagents have rendered conventional bioremediation, vapor extraction, and pump-and-treat ineffective for this type of contaminated media. As a result of the need for solutions and the gap in the current knowledge and technology base, a project was initiated to evaluate in situ remediation technologies for both enhanced mass removal and in place destruction of DNAPL compounds in LPM, specifically chlorinated solvents (e.g., trichloroethene [TCE] and perchloroethene [PCE]). This project was sponsored by the DOE Office of Science and Technology (OST) and the DOE Portsmouth Gaseous Diffusion Plant (PORTS) Site Office with significant leveraging with the American Petroleum Institute and private industry.

Since the initiation of the project in 1993, several *in situ* technologies for mass recovery and in situ degradation have been demonstrated at three sites in the United States and Canada for remediation of DNAPLs in both the vadose and saturated zones of LPM. The work during the past four years has focused on *in situ* remediation by either (1) thermally enhanced mass recovery using hydraulic fractures and soil vapor extraction, (2*) in situ* destruction involving redox treatment agents (permanganate solutions and solids (oxidative particle mixtures [OPM]) and/or iron metal solids) delivered by horizontal hydraulic fractures, (3*) in situ* destruction involving permanganate OPM delivered by vertical coreholes, or (4) *in situ* destruction involving redox treatment agents (peroxide or permanganate solutions and/or iron metal solids) delivered by vertical permeation lances. In addition, numerical and experimental analyses of the mobility of residual NAPLs versus varying degrees of remediation have been conducted. Based on these efforts, a promising *in situ* remediation approach selected for deployment includes enhanced delivery of reactive agents through soil fracturing and/or permeation for in-place destruction. The current goal of the ongoing project is to advance the technologies developed and demonstrated through transfer of the knowledge and experience gained into a standard of practice. This will be accomplished through multiple

deployments at multiple sites over several years.

During calendar year 1997, ETS staff were responsible for oversight and field execution of the continuing comparative demonstration of in situ remediation of low permeable media at the X-231A site at PORTS. The significant activities included pre- and post characterization, operation, and reporting. The field demonstration consisted of four systems:

- Hydraulic fracture enhanced steam flushing for 45 days.
- Hydraulic fracture enhance hot air flushing for 45 days,
- Evaluation of forced advection operation of reactive horizontal barriers with zero valence iron and oxidative particle mixtures (OPMs).
- Evaluation of passive operation of reactive horizontal barriers with zero valence iron and oxidative particle mixtures.

During calendar year 1998, ETS staff provided oversight and execution of a field scale implementation of OPM propped hydraulic fractures. While several problems were encountered, valuable insight was gained into OPM handling and delivery which has lead to additional development work.

Comparison of Groundwater Alternatives (CGA) Study. ETS staff conducted Phase I of a Comparison of Groundwater Alternatives (CGA) study at Naval Air Station (NAS), Fallon, Nevada. The purpose of Phase I was to develop potential alternatives for remediating dissolved-phase groundwater contaminant plumes at six NAS Fallon sites. Primary groundwater contaminants at the sites are jet fuel and chlorinated solvents. Potential groundwater remedial alternatives developed for the sites during Phase I included long-term monitoring, intrinsic remediation (natural attenuation), enhanced *in situ* bioremediation (both aerobic and anaerobic), hydraulic containment with aboveground treatment, and groundwater extraction with aboveground treatment. Potential groundwater containment and extraction technologies evaluated were pumping wells, interceptor drains, and slurry walls with pumping wells. The potential aboveground treatment technologies evaluated were aerobic bioreactor systems and air stripping with activated carbon polishing.

The CGA study (Phase II) is ongoing and will include a comparative evaluation of the potential remedial alternatives for each site based on effectiveness, implementability, and cost. Phase II will conclude with a recommendation of a preferred remedial alternative for each site.

Grand Junction Office Remedial Action Project (GJORAP). ETS was assigned as the IV contractor for DOE's GJORAP by the DOE D&D Branch Division of the Office of Environmental Restoration and Waste Management. The purpose of the GJORAP is to characterize, remediate, and verify cleanup of chemical and radiological contamination from past activities at the DOE-GJO facilities. Included in the D&D efforts are the buildings, exterior land area, and the underlying aquifer at the facility. The ETS role in this effort is to verify that all radioactively and chemically contaminated material is removed to levels that are consistent with the DOE limits of release and the Record of Decision for the site. During 1997 and 1998, ETS

performed verifications on nine buildings (released for occupancy), quarterly groundwater sampling, verification of outdoor areas of the GJO facility (including USRADS surveys and soil sampling), groundwater modeling, verifications of footprints of demolished buildings (31A, 33, and 35), scans and soil sampling, and verifications of release surveys of demo debris going to municipal landfill from demolition of buildings.

Toxicology and Risk Analysis Section

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[1]Retired or terminated employment with Life Sciences Division in 1997 or 1998
[2]Part-time

The major goal of this section is to apply scientific and regulatory analysis expertise to develop methods and provide information which will enhance the decision-making process. Objectives in this process are (1) assessing the impact of toxic and hazardous chemicals and other agents on human health and environmental quality, such as the development of acute exposure guideline levels, reference doses/concentrations and slope factors, and review of pesticide registrants' submissions; (2) analyzing federal and state environmental and radiation protection

policies, decommissioning and decontamination activities, and energy and utilization; (3) developing computerized toxicological and risk-assessment databases and analysis systems, such as the Genetic Toxicology Database (GeneTox) and the Risk Assessment Information System (RAIS), for predictive toxicity, fate transport modeling, and design of new chemicals; (4) developing PC-based knowledge systems for environmental, safety, and health (ES&H) compliance applications and decision-making systems; these support tools include the Intelligent Materials and Environmental Lifecycle Design Advisor (IMELDA), which facilitates new product design; and the Spatial Analysis and Decision Assistance (SADA), which combines ES&H risk factors with geospatial information and cost-benefit analysis; (5) providing "value-added" information analysis for projects such as the AIDS/Cancer registries, which elucidate the mechanism of disease progression and treatment; providing support to the Nuclear Regulatory Commission's (NRC) Materials Licensing Program by identifying and tracking over 30,000 closed sites requiring remediation as well as accountability for sealed sources; and tracking and follow-up on General Licenses tracking registration; (6) preparing technical communication products for nationally significant programs, such as the technical newsletters *Human Genome News*, *CFCC News*, and *Energy Crops Forum*; and (7) providing responses to queries on toxicological, regulatory, and remedial activities through the use of Toxicology Information Response Center (TIRC) and Remedial Action Program Information Center (RAPIC) resources, which include some 1,200 health and ecological risk documents, a registry dictionary of over 30,000 chemicals and agents, and 200,000 printed references. In all efforts, section staff emphasize the application of new and more efficient methods to the processes of conducting risk assessment, regulatory analysis, and data/information management and dissemination, such as those offered through use of Web-based applications.

The new M&O contractor, Bechtel-Jacobs LLC, now manages the local cleanup activities for the DOE Oak Ridge Operations (DOE-ORO). Due to this transition, work previously performed by TARA has been drastically reduced in this area.

Selected Accomplishments

Assessment Reports for National Program of Acute Exposure Guidance Levels (AEGLs). Under the Federal Advisory Committee Act, the U.S EPA established a National Advisory Committee (NAC) to develop AEGLs for hazardous substances. The committee is comprised of individuals of federal/state agencies and the private sector representing industry and non-profit organizations. In a concerted effort, TARA's toxicologists and NAC members identify, review, and interpret relevant toxicological and other scientific data and develop AEGL's for high-priority, acutely toxic chemicals. AEGLs represent ceiling exposure values for the general public and are applicable for emergency exposure periods ranging from less than 1 hour to 8 hours. Three AEGL values are developed for each of four exposure periods (30 min., 1-, 4-, and 8 hrs). Each value is distinguished by varying degrees of severity of toxic effects as defined by AEGL-1, -2, and -3,. These toxicity values will be used for the Clean Air Act risk management planning and emergency

evacuation determinations. To date, we have developed 19 chemicals for NAS review, 38 chemicals are in proposed status, 11 chemicals are in draft status, and 8 chemicals are awaiting new data.

Office of Pesticide Programs, Document Evaluation Reviews (EPA). Prior to the registration or re-registration of a pesticide, the U.S EPA, Office of Pesticide Programs (OPP), must determine whether the chemical will cause reasonable adverse effects on humans and the environment under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In the process of making this determination, EPA reviews all data submitted by the registrant to support the effectiveness and safety of the chemical, published reports or studies from the open literature, unpublished reports or studies which bear on the issues at hand, and the chemical's general and environmental chemistry relationship to possible human and domestic animal exposure. TARA assists the OPP in this mission by performing technical and critical evaluations of the data submitted for the registration and re-registration process.

Progress of the Environmental Genome Project (EGP). TARA's Human Genome and Toxicology (HG&T) Group has recently teamed with staff of the Computational Biosciences Section on a project for NIEHS to develop a gene identification resource and database. Specifically, the work involves (1) providing National Institute of Environmental Health Sciences (NIEHS) with a list of known genes that are involved in responses to environmental agents that may, in turn, influence human susceptibility to disease, and (2) providing additional information for use in selecting a subset of the candidate gene listing for resequencing. This project contributes to the EGP goal of identifying environmental agents—particularly chemicals— that may cause a genetic-based disease and place the population at risk. Achieving this goal may lead to more effective disease prevention and improved public health.

Management of the Human Genome Management Information System (HGMIS). HGMIS functions as primary communication resource for the Human Genome Program (HGP). HGMIS produces the quarterly *Human Genome News* (HGN), and the DOE *Primer on Molecular Genetics*, as well as progress reports on contractor-grantee workshop proceedings. In its role as an information clearinghouse, HGMIS responds to numerous inquiries annually for information about the HGP and requests for copies of DOE- or HGMIS-generated publications. A text-based World Wide Web server is maintained that provides excellent coverage of topics relevant to the HGP for scientists and non-scientists. The work of HGMIS contributes to the increased use of HGP-generated resources, the reduction of duplicative research efforts, and the fostering of collaborations and contributions from other disciplines that benefit the HGP and DOE-OBER's research interests. As more research results and discoveries become available from the HGP each year, the role of HGMIS increases in importance.

DOE-ORO Risk Assessment Program. During this report period, TARA staff

continued to provide support to the DOE-ORO Risk Assessment Program by managing the integration activities for all risk assessments conducted at ORO Sites. As part of this effort we developed improved risk assessment methods such as statistical applications for the identification of site-related contamination and revised ORO-specific risk assessment guidance. This work also included the maintenance of the Environmental Management Risk Ranking System, a critical tool employed in the determination of project sequencing for all ORO-EM projects.

Interaction with DOE Center for Risk Excellence. The section provided technical support to the DOE Center for Risk Excellence (CRE). This included the development of Web sites and links to available risk information, improvements to the Risk Assessment Information System (RAIS); demonstrated the RAIS system to various field offices (the use of the RAIS has increased by 400% since this effort began); participated on a team of CRE and Operations Office representatives to develop risk guidance for the DOE Paths to Closure document, and completed the OR Risk Profile.

Environmental Technology Verification of Environmental Decision Support Software (EPA). The Environmental Technology Verification (ETV) Program was created by the EPA to facilitate the deployment of innovative technologies by substantially accelerating the acceptance and use of improved and cost-effective technologies. The goal of the ETV Program is to promote environmental protection. TARA provides support to ETV by designing and conducting performance evaluations of environmental decision support software. The evaluations focus on the utility of decision support software in addressing environmental problems. Three endpoints were selected for technical evaluation: (1) Visualization, (2) Sample Optimization, and (3) Cost/Benefit Analysis. In CY 1998, evaluations were conducted on six environmental decision support softwares to verify their performance.

Impact of Deregulation on Electric Utility Industry (NRC). TARA assisted NRC in evaluating the impact of deregulation on the long-term ability of power reactor licensees to adequately finance safe operation and decommissioning of nuclear power plants, whether the plant is operated to the end of its licensed term or is shut down prematurely. TARA provided evaluations of state deregulation and restructuring initiatives which affect the traditional cost of service regulation of NRC power reactor licensees in California, Illinois, Massachusetts, New Hampshire, New York, Rhode Island, and Pennsylvania. Each state's restructuring initiative was analyzed with particular attention paid to issues of stranded costs, going-forward costs and decommissioning costs as they applied to nuclear power plants and their safe operation.

Facilities, Infrastructure and Support

Laboratory Animal Resources

Operations and Support Section

Mouse Genetics Research Facility (DOE User Facility)

DNA Sequencing Laboratory

Gene Expression Chip Laboratory

Center for Dosimetry and Biokinetic Modeling

Center for Life Cycle Analysis

Center for Independent Environmental Assessment

Laboratory Animal Resources Section

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[1]Retired or terminated employment with Life Sciences Division in 1997 or 1998

The section is dedicated to maintaining the highest standard of animal care and welfare, ensuring the best quality of animals for research activities and support of divisional research initiatives utilizing animals. The animal resource program is responsible for ensuring continued accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care, International, compliance with federal regulations of the Animal Welfare Act and the Public Health Service Policy on Humane Care and Use of Laboratory Animals, and maintaining standards in accordance with the National Research Council's "Guide for the Care and Use of Laboratory Animals." Efforts provided by the section support care for the large experimental mouse colony utilized by the Mammalian Genetics and Development Section as well as animals utilized by the Assessment Technology and the Biochemistry and Biophysics Sections. The section is headed by a veterinarian who is a Diplomate of the American College of Laboratory Animal Medicine. Support staff includes a supervisor and 19 full-time bargaining unit animal care technicians. The section provides husbandry requirements for approximately 70,000 laboratory mice and a minimal number of rats and oversees maintenance of the animal facilities' physical plant and equipment to assure provision of acceptable operations standards. In addition, veterinary care is provided to ensure the health and well-being of the division's research animals. Research support is provided through training and guidance of animal care technicians and investigative staff in the care and use of research animals procedures for proper performance of surgery, anesthesia, analgesia, and related non-surgical procedures, and protocol development. Research is additionally supported through cooperative efforts with investigative staff to recognize and characterize phenotypic expression of genetic mutations.

Operations and Support Section

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[1]Retired or terminated employment with Life Sciences Division in 1997 or 1998
[2]Matrix assignment from Office of Safety and Health Protection
[3]Dual capacity; also staff in Biochemistry and Biophysics Section

The Operations and Support Section was formed in May 1997. Staffed with subject specialists, the section goal is to provide resources and assistance in the day-to-day activities of the division within the general areas of Resource Management (RM); ESH&Q; and Support Services (SS). Utilizing both full- and part-time appointees, the section focuses on Integrated Safety Management Systems (ISMS) and provides aid and direction to the line organization as they define work and its hazards, analyze the imbedded hazards, develop and implement controls, and perform the work utilizing the determined controls. Section personnel also provide and receive feedback from the ongoing work processes. Section personnel serve as resources and provide guidance/direction in the following representative activities throughout the division structure: *RM* – facility management, property and hazardous material(s) management, space allocation, and management/disposal of both radiological and RCRA/TSCA waste streams; *ESH&Q* – provide biological and division safety officers, promote and assist in up-front evaluations and plans to assure adherence to environmental and radiological codes and regulations, furnish resources guidance in the areas of chemical hygiene and laser safety, and lead a graded approach to the Laboratory's Quality

Assurance Program; *SS* – serve as resources in the areas of educational assistance, network and computer support, and required/optional training opportunities. Members of the section are charged with providing assistance to the division office, laboratory, and field personnel in all areas of compliance and safety and to utilize ISMS principles and core values to promote line involvement in preliminary analyses and formulation of needed safety plans. In specific areas of expertise, they provide leadership and maximum assistance while striving for minimal disruption of ongoing research activities.

Mouse Genetics Research Facility

ORNL established a Mammalian Genetics program soon after World War II specifically to assess the biological effects of ionizing radiations in mammals. Experiments were carried out to determine both rates of induction of germline mutations and differential sensitivities of germ cell stages to induced damage in mice. In more recent experiments, mutagenesis has also been carried out using a wide variety of chemicals, in particular with N-ethyl-N-nitrosourea (ENU), a mouse supermutagen discovered here at ORNL. A new animal facility, now in design stage, will house the ORNL mice in a specific pathogen-free, rather than the current conventional, colony. This colony currently houses about 70,000 live mice that represent about 400 mutant strains; a variety of other strains are being or have been cryopreserved. Most of these mutations, many of them radiation-induced deletions, encompass the seven visible genetic loci that were targets for the risk assessment studies. These loci are agouti (*a*, mouse chromosome 2), brown (*b*, now tyrosinase-related protein 1, mouse chromosome 4), albino (*c*, now tyrosinase, mouse chromosome 7), pink-eyed dilution (*p*, mouse chromosome 7), dilute (*d*, now myosin Va, mouse chromosome 9), short-ear (*se*, now bone-morphogenetic protein 5, mouse chromosome 9), and piebald spotting (*s*, now endothelin receptor B, mouse chromosome 14). We also keep many various inbred and hybrid parental stocks used for experimentation, many other strains that carry coat-color markers for mapping and allelism-testing, and dominant mutations and chromosomal translocations scattered throughout the genome. Ongoing mutagenesis projects involve transgenic technology, including gene knockouts, creation of specifically-targeted deletions, and ectopic or overexpression of transgenes; expertise with these technologies allows us to preselect our gene or chromosomal region chosen for mutation. A database that details available strains and phenotypes is accessible though the Life Sciences Division WWW homepage. Many of the deletion complexes that surround these seven marker loci have been characterized both molecularly and by genetic complementation to determine visible and lethal phenotypes that neighbor the marker locus. In addition, three of the deletion complexes (*p*, *c*, and *b*) have undergone additional mutagenesis studies, using chemicals that induce point mutations, to create other mutant phenotypes within the deleted regions. Any phenotype can be quickly submapped by crosses to mouse stocks that carry other, overlapping deletions that may or may not complement the mutation. We are testing all these mutants for subtle phenotypes that would not traditionally have been recognized, even by our very experienced technicians who consistently recognize mutations that alter general health, size and morphology, and normal motor behavior. For example, both existing and newly generated mutants are being evaluated for behavioral and biochemical aberrations; we are screening all potential mutants for levels of activity, anxiety, and reaction to novelty, for behavioral despair, for neuromuscular coordination, for learning and memory, and for acoustic startle response. Mice that show abnormalities during any of these tests are analyzed in more detail. We are developing technology to increase the sophistication, efficiency, and throughput for these behavioral assessments. We are also measuring various bioactive molecules or byproducts in blood and urine to monitor mutations induced in biochemical pathways. We welcome other investigators to come to Oak Ridge to screen potential mutants for their phenotype of interest, or to

identify phenotypic changes in their mouse of interest. The MGRF is a Department of Energy User Facility.

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DNA Sequencing Lab

A DNA sequencing and automated genotyping laboratory has been established at ORNL. This laboratory can provide researchers in Life Sciences and other Laboratory divisions with state-of-the-art DNA sequencing and automated fluorescence genotyping. The current facility is housed in approximately 1395 sq. ft. of lab and office space. Sequencing equipment currently consists of 1 ABI 377 sequencing machine (modified for 96 lanes) and 1 ABI 373 sequencing machine (modified for 64 lanes). For template preparation the lab has a Qiagen template robot capable of producing 96 sequence-ready DNA templates in less than 2 hours. Recently, in collaboration with the Robotics and Process Systems Division, we have constructed a robotic line for carrying out DNA sequencing reactions. This line integrates a CRS A465 robotic arm with a Robbins Hydra pipettor (96 well), MJR quad PCR machine, and a refrigerator (with actuator door). Associated with the DNA sequencing facility is a standard molecular biology lab which includes a Beckman Ultra centrifuge L8-80M, BioRad electroporater, 2 New Brunswick air shakers, microfuges, various gel electrophoresis equipment, etc. Computer needs of the facility are taken care of by a group of networked computers including 3 PowerPCs, 7 PCs, and 1 SGI O2 machine.

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Gene Expression Chip Laboratory

A genosensor laboratory has been established at ORNL. This laboratory is dedicated to the development of technology for genome analysis, the support of various applications, and the support of ORNL's functional genomics program. Genosensors take advantage of the specific hybridization properties of nucleic acids to assess the expression level of particular gene sequences or changes in gene coding regions. Such measurements are key to learning gene function. Extensive libraries of DNA sequences can be arrayed to probe test samples in a miniaturized, parallel fashion. The resulting test device is called a genosensor. A cornerstone of our genosensor technology has been an advanced configuration in which the hybridization reactions occur on high surface area substrates, such as channel glass or porous silicon, rather than on conventional flat substrates. The porous substrates provide a unique "flowthrough" architecture that lead to an increased surface area and faster reaction kinetics. A customized robotic spotting system, based on ink jet dispensing, has been developed to position DNA probes onto the genosensor. Individual probe can be placed at pitches as small as 200 microns. Additionally, instrumentation and protocols for sample preparation, fluid handling,

and hybridization detection have been developed. Currently, genosensors are being generated and analyzed for monitoring gene expression profiles in mammalian and bacterial systems, for analyzing polymorphic markers in the human genome, and for bacterial typing of environmental samples.

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Center for Dosimetric Modeling and Computation

In recognition of the Life Sciences Division's capabilities and scientific contributions in the area of human metabolic and biokinetic computational modeling, federal agencies concerned with occupational and public radiation protection formally recognized a "Center for Dosimetric Modeling and Computation" (CDMC) at ORNL. The primary mandate of the CDMC, which consists of staff from the Dosimetry Research Group in the Assessment Technology Section, is to centralize and coordinate computational human modeling capabilities and associated medical information in the United States. Dr. Keith Eckerman, Director of the Center, and the staff of the Dosimetry Research Group have been recognized leaders in the field of human computational modeling for radionuclides and recently served as the International Center for the Development of the ICRP Reference Man, which provided the calculational basis for dosimetric computation.

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Center for Life Cycle Analysis

The Center for Life Cycle Analysis (CLCA) formally opened at ORNL on October 1, 1998. A formal announcement and description of the CLCA appeared in the September 28, 1998, issue of the "Weapons Complex Monitor" and described the mission, history, and objectives of the Center. Dr. Kathy L. Yuracko, Technical Program Leader for Life Cycle Analysis in the Assessment Technology Section, is the Director of the Center. Other key staff of the CLCA include senior technical staff members from other sections with the Life Sciences, Energy, and Environmental Sciences Divisions at ORNL.

The mission of the CLCA is to provide environmentally conscious and cost-effective solutions to environmental concerns such as reindustrialization, recycling, pollution prevention, and decommissioning. Each problem is approached with multi-attribute decision analysis considering the uncertainties and socio-economic impacts as part of the criteria used to facilitate decision-making and determine conclusions. The ORNL life cycle analysis approach

leads to the most appropriate selection of a solution that is both understandable and defensible. Details of the CLCA, current activities, and life cycle analysis methods can be found on the Internet at http://ats.ornl.gov/clca.

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Center for Independent Environmental Assessment

In May 1998, the Center for Independent Environmental Assessment (CIEA) was established in the Life Sciences Division at ORNL. The mission of the CIEA is to apply Life Sciences Division resources and experience to provide independent, consistent, and state-of-the-art technical assessments in support of environmental pollutant remedial action. Technical support activities of the Center are aimed at independent designation/inclusion of potentially contaminated sites for remedial action, independent confirmation of cleanup following remedial action, and independent technical oversight and evaluation of all aspects of remedial action operations. The Center consists of staff from the Assessment Technology and Environmental Technology Sections in the Life Sciences Division and has capabilities and experience in hydrology, risk assessment, pollutant detection, geology, indoor air quality, toxicology, pollutant modeling and transport, and regulations. The CIEA also has a full complement of analytical, field survey, and pollutant assessment capabilities to detect, sample, and analyze any type of radiological and non-radiological environmental pollutant.

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Partnerships

Joint Institute for Biological Sciences

UT/ORNL Graduate Program in Genome Science and Technology

Tennessee Mouse Genome Consortium

Joint Institute for Biological Sciences

Much of the progress in biological sciences during the past 20 years can be traced to (1) understanding the structure and function of genes and (2) applying biological processes to engineer organisms, treat disease, and manufacture pharmaceuticals and other materials. During that time, the contributions to these areas of research made by ORNL and UT have benefited people locally, nationally, and worldwide. Also during that time, ORNL and UT have enjoyed a relationship of cooperation. In keeping with that longstanding tradition, ORNL and UT have agreed to establish the Joint Institute for Biological Sciences to promote collaborative R&D.

The Institute will address the biological needs of the future by meeting the following objectives:

- obtain public and private funding;
- combine the areas of strength and merge the R&D currently under way at both institutions;
- help and advise state, regional, and national organizations;
- offer R&D support for private industry;
- offer education, training, and on-the-job experience for students, medical personnel, and policymakers; and;
- devise strategies to finance
    - construction of needed research facilities,
    - acquisition of state-of-the art equipment, and
    - appointments of collaborating-scientist positions;

The Joint Institute will be developed in phases. The first phase will involve programs already in existence at ORNL and UT, which include a graduate program in biological sciences as well as programs in functional genomics, computational biology, and bioinformatics. The second phase will involve developing areas of research that include forensic sciences, biomimetics and biomaterials, and biomedical technologies.

Phase 1

Graduate and Postdoctoral Education:
ORNL and UT have a 30-year history of working cooperatively on graduate education through the UT-ORNL Graduate School of Biomedical Sciences. That program is undergoing a major revision that will culminate in a shift in focus toward the disciplines of functional genomics, structural biology, and bioinformatics/computational biology. Educational activities will also involve undergraduate students, who will be encouraged to pursue advanced studies.

Functional Genomics:

Until recently, genetic research has been limited to studying the function of individual genes. Developments within multiple disciplines have enabled researchers to begin pursuing functional genomics, in which gene function is studied on the genome scale. The ORNL Laboratory for Comparative and Functional Genomics will be the focal point for multidisciplinary functional genomics research within the Institute.

Bioinformatics and Computational Biology:
Mathematics and computational science will play a key role in biological and environmental research at the Institute. Emphasis will be placed on education and training. In addition, researchers and engineers from a number of disciplines will collaborate at to meet the following challenges:

- computational infrastructure,
- prediction of macromolecular structure and function
- cell biology
- genomic computation,
- biomechanics, and
- neuroscience.

Phase 2
As first-phase goals are met, new areas of research will be pursued at the Institute. The following disciplines have been identified as phase-2 goals:

- forensic sciences
- biomimetics and biomaterials
- biomedical technologies

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UT/ORNL Graduate Program in Genome Science and Technology

The University of Tennessee and Oak Ridge National Laboratory have teamed during 1998 to restructure the former Oak Ridge Graduate School of Biomedical Sciences to form a graduate program with emphases in mammalian genomics, structural biology, proteomics, computational biology and bioinformatics, and bioanalytical technologies. Students will be trained in emerging areas of the genomic sciences and upon completion of the program will be qualified to join the competitive work force in academics, government laboratories, and private industry such as pharmaceuticals or other technologies. To this end, the program will provide a firm foundation in genetics, molecular and cellular biology, biochemistry and computing, and specialty training in applications of these sciences to functional genomics.

The program takes advantage of interactivity and collaboration among scientists and faculty from both the University of Tennessee Knoxville and Oak Ridge National Laboratory in conjunction with the Joint Institute of Biological Sciences. Faculty from both campuses will offer courses. Research opportunities are available on both campuses; research projects will be mentored by a faculty member from each campus. Students are encouraged to develop research projects at the interfaces of the emphasis areas.

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Tennessee Mouse Genome Consortium

On December 3, 1998, ORNL signed a memorandum of cooperation with a number of the state's medical institutions. The memorandum, called Tennessee Mouse Genome Consortium, is designed to help medical researchers collaborate in applying ORNL's mouse colony resources to their studies. Participants with ORNL in the venture are the University of Tennessee (Knoxville and Memphis), Meharry Medical College, Vanderbilt University Medical Center, and St. Jude Children's Research Hospital. The signing was part of a conference in Knoxville, "The Impact of Emerging Technologies on Health Care in the 21st Century," that included a presentation by MGDS's Dabney Johnson and featured Tennessee Senator Bill Frist as the keynote speaker. The increased research collaboration throughout the state, using the mutations in the Lab's mouse colony, will bring important findings in genetic medical research

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Initiatives

Center for Biological Sciences

Functional Genomics and Proteomics

Structural Biology

Biomedical Engineering

Technology Applications

Center for Biological Sciences

DOE-OBER is planning for a significant investment in a new Center for Biological Sciences (CBS) at ORNL during the FY 2001–FY 2004 period. The CBS is planned as a modular complex of buildings, equipment, and infrastructure that will house current and future research programs in the areas of functional genomics, structural biology, proteomics, and systems biology. It will provide the environment for the ORNL biological research program to make significant contributions to biology during the next decade and beyond, with a special focus on complex biological systems research. Development of the CBS will enhance the advantages gained from the program's recent restructuring to embrace not only the biological sciences but also allied disciplines in information science and computing, analytical methodologies, and chemistry. The table below provides funding projections for the CBS.

The first phase in the development of the CBS is the construction of a Laboratory for Comparative and Functional Genomics (LCFG), at an estimated cost of $12 million, to house the MGRF. The LCFG will replace an aging building at the Oak Ridge Y-12 Plant that is no longer adequate to house one of ORNL's premier research facilities. In addition to housing the mouse colony, the LCFG will include laboratories with special phenotype screening and cryopreservation capabilities.

The CBS will also encompass a proposed Center for Structural Molecular Biology (CSMB), a user facility that will integrate ORNL's unique capabilities in neutron science, as represented by the HFIR and the Spallation Neutron Source (SNS), with strong programs in mass spectrometry and computational biology. The SNS beam line identified in the table is the principal new capital resource needed to support the CSMB beyond 2003.

Capital Funding Projections for ORNL Center for Biological Sciences by fiscal year
(in millions of dollars)

	2001	2002	2003	2004
Laboratory for Comparative and Functional Genomics	8	4	0	0
Structural biology beam line for the Spallation Neutron Source	0	0	3	3
Computational biology and bioinformatics	2	3	0	0
Proteomics	3	5	2	0
Instrumentation	2	1	1	1
Total	15	13	6	4

Laboratory resources in bioinformatics and computational biology will add to the scientific stature of the CBS. Efforts in these areas link the functional and structural biology components and also support the development of new efforts in systems biology envisioned as part of the CBS. The CBS will provide space and "connectivity" (computing and information technology infrastructure) for both the bioinformatics and computational biology researchers

and the experimental biologists. The leverage gained through this combination of expertise and infrastructure will also provide the tools for use of the CBS facilities as a virtual laboratory by research partners at other institutions.

Research programs at the CBS will encompass ORNL's important efforts in protein biochemistry, which were recognized in 1998 with the election of a senior staff member to the National Academy of Sciences. The CBS will provide the physical environment for integrating these efforts into ORNL's biological research program and bringing them to bear them on the broader charge of proteomics.

Future biological research at ORNL will be aggressively directed to take advantage of advances not only in computational biology but also in instrumentation and measurement sciences and technology. Facilities at the CBS will co-locate bioinstrumentation and bioengineering R&D efforts with the new biological research programs. These programs will build strong alliances with other biological and medical research centers, building on the resources of the Joint Institute for Biological Sciences.

Functional Genomics and Proteomics

Recently announced plans for accelerating the sequencing of the human genome call for a first draft of the reference human genome to be completed within the next year. This 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 the human chromosomes. Given the rate at which sequence data are being produced, there is the potential for discovering hundreds of new human genes every day. In addition, intensive efforts are under way to sequence the genomes of important pathogenic and environmentally and commercially significant microorganisms. Increasing focus is also being placed on sequencing plant genomes, with obvious implications for agricultural crops. Several of these smaller genomes have been completely sequenced.

As these various genomes are completed, significant advances in the ability to determine the function of genes, within and across genomes, will be required to unlock the information contained 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 this situation. In the new era of biomedical research that has just begun, it will be possible to perform experiments in functional genomics—that is, to determine the function of genes and systems of genes on a genome-wide scale.

Gene function is determined (1) by analyzing the effects of DNA mutations in genes on normal development and health in the whole organism; (2) by analyzing a variety of signals encoded in the DNA sequence; and (3) by studying the proteins produced by a gene or system of related genes. Researchers are able to study functional genomics in humans by using genome information from other model organisms that provide rich scenarios for experimental research. The mouse, with 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. In addition, the availability of completed DNA sequences for plants and microbes opens opportunities to work on gene networks and gene interactions in systems where all the genes are known. Work on other model organisms also opens related research areas that are important to DOE, such as the identification of organisms in the environment and the genetic manipulation of organisms to help mitigate environmental problems.

The availability of complete DNA sequences for many organisms in the near future will enable whole new lines of scientific inquiry into the nature of the proteome, the proteins encoded by the genome. Thus, an important aspect of determining gene function is the characterization of the vast number of proteins expressed by the genome, including establishing both the structure of a particular protein and its role organism. Proteomics research programs are being planned by the DOE and other agencies. Efforts are under way to perform high-throughput assays to determine the structures of proteins and study protein complexes using x-ray crystallography,

NMR spectroscopy, mass spectrometry, neutron scattering techniques, and computational tools.

At ORNL, we have initiated a program that combines unique strengths of existing research programs in mouse mutagenesis with analytical technologies and computational biology/bioinformatics to address critical issues in Functional Genomics and Proteomics. Our approach is based on the conviction that genetics and protein studies should be viewed as integral components of an overall strategy to understand protein function in the context of the whole organism and to define this function at the molecular level. The ORNL effort builds on synergism between the existing Mouse Genetics and Mutagenesis Core effort, the Computational Biology/Bioinformatics Program, and the proposed Center for Structural Molecular Biology. This approach will maximize our ability (1) to assign both biochemical and organismal function to genes and proteins, (2) to define interacting protein pathways at the molecular level, and (3) to establish the role of proteins in the whole organism. The investment of Laboratory Directed R&D (LDRD) funds in this program from FY 1997 through FY 1999 has served to catalyze cross-disciplinary research projects involving biologists, chemists, engineers, physicists, and computer scientists, to develop tools required for mounting a highly efficient, comprehensive system for functional genomics and proteomics. This team brings new approaches to bear on the scientific issues of enriching raw DNA sequence generated at the DOE Joint Genome Institute (JGI) and elsewhere, with functional information derived from gene expression and protein studies of mutations in the mouse. Specifically, we are combining advanced methods in mouse mutagenesis with the development of new functional genomics and proteomics technologies, both analytical and computational, to dissect and understand how gene expression impacts specific biological systems. This program also applies these new technologies to study important bacterial and plant systems.

A key component of our Functional Genomics and Proteomics Program is the MGRF, a DOE national user facility, which is an unparalleled resource for functional genomics. The MGRF represents one of the largest facilities in the world for carrying out experimental research in functional genomics using the mouse as a model organism. Mouse geneticists can “target” a specific gene to eliminate or alter its function in the whole animal or only in a specific cell population, or they can add normal genes back to a mutant mouse to correct an abnormality. They can engineer rearrangements in large regions of the genome and then create gene-by-gene mutations in these regions using the chemical mutagen ethylnitrosourea (ENU) to make single-base changes in DNA. ENU is useful for making multiple different 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.

Outlined below are examples of how we are melding our advanced technologies and computational biology capabilities with our mouse mutation resource for the purpose of establishing highly efficient techniques for defining specific functions of proteins in mutation models.

1. **Gene expression and protein analysis techniques for augmenting primary phenotype screening and secondary/tertiary analyses of mutant phenotypes.** Phenotype screening is both a huge undertaking and a commitment that is well suited for a national laboratory resource. The Mouse Genetics and Mutagenesis Core effort is focused on recovering phenotype-defined mutations in selected regions of the genome. Using chemically induced mutations (e.g., ENU), a sufficient number of potentially mutant animals (and carrier siblings) will be produced, allowing us to identify mutations affecting a wide variety of biological pathways. These mutants will be identified with our in-house phenotype-screening protocols (the "Screenotype" system). Additional screens will be provided by distribution of these animals to our collaborators in the Tennessee Mouse Genome Consortium, which at present includes Vanderbilt University Medical Center, Meharry Medical College, St. Jude Children's Research Hospital, and the University of Tennessee (Knoxville and Memphis). As part of this effort, we will incorporate automated, high throughput phenotype screening techniques to expand our phenotype-screening net to identify subtle physiological phenotypes. For example, we have developed a micro CAT (computerized aided tomography) device for rapidly screening mice for organ and skeletal changes. We have also developed microfluidic devices ("lab-on-a-chip") for a number of analytical processes employed in the molecular biology laboratory, such as sample purification, PCR amplification reactions, electrophoretic separations, and others. We are developing mass spectrometry-based techniques for monitoring targeted proteins, such as expression of cytokines as sentinels for mutations leading to chronic inflammatory disorders. These new technologies, as well as others being developed at ORNL and in other laboratories, represent a vital component in our strategy to meet the requirements of a large-scale proteomics effort.

2. **Technologies that facilitate genetic linkage analyses in large-scale mouse crosses for genetic dissection of complex biological pathways.** Currently, we have the capability to induce and discover modifiable mutations, as well as their modifiers; however, to conduct whole-genome screening for linkage using simple-sequence repeat (SSR) markers to identify the involved genes and proteins requires new, efficient analytical tools. We will apply our established methods in mass spectrometry (based on matrix-assisted laser desorption techniques) to accomplish rapid, gel-less analyses of SSR PCR products for high-throughput linkage analyses required in studies of modifier mutations and of meiotic recombination. Other complementary technologies are also being developed, including novel hybridization chips and "lab-on-a-chip" microfluidic devices for combined PCR/electrophoresis/detection of DNA fragments.

3. ***In vitro* and whole-animal approaches for complex pathway analysis.** In a current LDRD project, we are focusing on how to best approach the global analysis of a complex system, which promotes organ-directed, whole-organism phenotyping of genes/proteins/mutations. We are investigating a new means for screening for recessive mutations *in vitro* in embryonic stem (ES) cells that will allow us to focus on genes affecting complex pathways and which are likely to affect phenotypes of target organs. As an initial test system, we are examining skin differentiation in ES cells. Skin has been

selected as a target organ because it is involved in developmental, cancer, aging, and exposure biology, and ES cells can be induced to differentiate into skin *in vitro*. As part of this endeavor, we will incorporate chip-based mRNA expression profiling technologies (which can screen for expression of genes involved in skin development, as well as other cellular processes, i.e., cell cycle, apoptosis, and others to define skin pathway perturbations induced by both existing and newly induced mutations. Technologies developed as part of this work will be readily applied to other test systems.

4. **New techniques for high-throughput detection of variants of specific proteins that can then be funneled into both genetic (organismal) and structural (biophysical) analyses.** We will develop high-throughput mass spectrometry-based procedures to detect, in one-generation chemical mutagenesis screens, partially functional variants of proteins. The mutant protein identified from this "Protein Variant Screen (PVS)" would then direct the matings of variant mice to reveal both dominant and recessive whole-organism, functional phenotype(s). Such new technologies should have the sensitivity to detect heritable mutations in protein processing, as well as abnormalities in protein primary and secondary structure. Such a simple, one-generation test could easily be piggybacked onto ongoing ethylnitrosourea experiments with little additional mouse costs, in contrast to the rather substantial costs that might be incurred if one were to modify protein structure blindly, one residue at a time, by modifying loci *in vitro* in ES cells. Furthermore, we would specifically assay for protein polymorphisms, not knockouts; indeed, the knock-out mutation leaves the structural biologist no material to study. As one example, the MLH1 protein, involved in DNA repair, is required for recombination and the successful completion of meiosis. Male animals homozygous for knockout mutations in this gene are sterile because meiosis is arrested; thus, an allelic series of mutations would be highly desirable to ascertain whether variants (not nulls) of this protein have an effect on sterility, nondisjunction, DNA repair, and mutation rate. The developed technologies would be broadly applicable to other biological issues. For instance, it may be possible to induce a series of slightly malformed estrogen receptors in whole animals that could then be tested for interaction with xenobiotic estrogens *in vitro* while at the same time tested for cancer susceptibility in the whole animal. We feel that the uses for this particular marriage between classical germline chemical mutagenesis and mass spectrometry are far-ranging.

5. **Structural characterization of mutant proteins with phenotypic ramifications and comparison with wild type for determination of structure/function relationship**. Using techniques of structural biology, we will analyze protein variants from a phenotypically characterized allelic series of chemically induced mutations. An important issue in functional genomics/proteomics is establishing the structure and effects of the many types of post-translational modifications that can occur in expressed proteins. State-of-the-art structural techniques will be used to characterize modified proteins at the molecular level and identify differences in their interactions with other key biomolecules. We will employ techniques such as existing resources at ORNL in mass spectrometry and the proposed CSMB facility for small angle neutron scattering, as well as structural techniques available at our collaborating national laboratories, including synchrotron-

based protein crystallography and nuclear magnetic resonance. We will also draw upon ORNL's expertise in computational biology to help establish protein structure via threading and other techniques.

6. **Validating predictions of protein structure and function through mouse genetics and mutagenesis.** Computational techniques in genomics and molecular biology generate predictions of gene and protein structure and function that may, in turn, generate hypotheses that can be tested both *in vitro* and *in vivo*. For example, bioinformatics techniques might suggest a function for a newly identified protein by assigning it to a family of proteins that share similar motifs and functional domains. Starting from this prediction, one would like to understand the function(s) of this protein both at the level of molecular mechanisms and its role(s) in the organism. As more and more genomic DNA sequence becomes available from the JGI and other sequencing centers, mouse genetics and mutagenesis, combined with computational analysis, will become a powerful tool for understanding the bases of gene and protein function. There are a number of levels where this can occur. In regions being targeted for mutagenesis, computational analysis of the DNA sequence of the region will suggest possible correlations between genes identified in the region and the phenotypes observed. Computational analysis can also help in identifying candidate genes in regions with known mutations by making structural and functional predictions. These predictions can then be tested by targeted mutagenesis methods. Another role for computational sequence analysis will be to determine the gene content of regions covered by "draft" sequencing to aid in the selections of regions as targets for various mutagenesis approaches. The results of mouse mutagenesis will also provide useful feedback for refining the techniques and approaches used in computational biology to predict gene and protein structure and function.

In summary, our goal is to understand protein function in the context of the whole animal and to define this function at the molecular level by combining advanced methods in mouse mutagenesis with the development of new concepts for functional genomics and proteomics technologies. Although the focus of this effort is not related to the field of drug discovery, the developed tools would certainly be applicable to this area as well. We will work with other national laboratories, in particular, to complement their related Functional Genomics/ Proteomics programs, making ORNL resources and technologies available to them. We will also form new collaborations and strengthen existing collaborations with and serve as a resource to laboratories at other national laboratories and in academia and industry. An April 1998 conference, "Partnering for Functional Genomics Research," attracted representatives from 14 pharmaceutical and biotechnology companies. All participating companies expressed interest in further interactions, and several new projects are being discussed. The Merck Genome Research Institute initiated a research project through the Joint Institute for Biological Sciences. Other follow-on activities are under way to establish collaborative efforts and to pursue the development of an R&D consortium involving several industry partners. As with all actively growing research programs, new directions become apparent which require change; however the general models outlined above give an overview of the type of program we are building and the types of important and relevant information that will be obtained.

Structural Biology

The proposed Center for Structural Molecular Biology (CSMB) is intended to bring together the existing strengths at ORNL in neutron sciences, mass spectrometry, and computational biology and make them available to a broad user community in the biological sciences. The cornerstone of the CSMB is a small angle neutron scattering (SANS) facility to be constructed at the HFIR at ORNL. SANS is an important tool for studying molecular conformations and molecular interactions. It provides insight into the molecular basis of communication pathways that achieve coordinated function by identifying specific chemical groups that interact with the environment and with molecular networks involved in binding and activation sequences. It provides information on the dynamics of a biomolecule in solution and complements the high-resolution structural x-ray crystallographic data obtained from a static, crystalline molecule. SANS will be a key tool for understanding the cellular level communication that is the basis for protein and, thus, gene function.

Establishing the CSMB at this time is particularly critical because we can take advantage of a recently initiated upgrade at the HFIR. As part of this upgrade, the "brightest" long-wavelength neutron source in the U.S. is being constructed. During this upgrade, we have the opportunity to design and build a SANS instrument (and associated resources) specifically designed for the study of biological systems. This instrument will incorporate both high flux and a large area ($1m^2$) detector to collect data over a wider solid angle to enhance the study of biological molecules. The resulting facility will provide the biological community in the U.S. with state-of-the-art capabilities in SANS**,** which will rival the world's best biological facilities at the Institut Laue Langevin (ILL) in France.

In addition to the SANS facility, we will incorporate well-established biological mass spectrometry and computational resources into the CSMB, providing the biological community with additional tools that would complement structural information obtained from SANS. As an example, it has been shown that modifications to proteins can effect both the structure and function of these biomolecules (e.g., Trewhella and co-workers, *Biochem.* **28**, 2220-2228, 1989). Mass spectrometry can provide information on both the extent of these modifications and the sites of attachment. Computational modeling can support conformational changes observed in SANS data. In addition, for uncharacterized proteins, computational methods can be used to identify fold families and build models from related known proteins prior to SANS analysis. Capabilities within the CSMB would also complement resources at other structural biology facilities, such as synchrotron x-ray crystallography centers, to provide a more thorough picture of the structure of biological molecules and their interactions in complex systems. The proposed CSMB would provide structural capabilities to programs within the DOE community, and to other government, academic, and industrial laboratories. An advisory panel of distinguished scientists has been established to provide guidance to the Director and staff of the CSMB in the establishment of the center. A CSMB User Group consisting of potential users of the center will be created to give advice on equipment and capabilities to be included in the CSMB and to establish guidelines for the operation of the Center. An important aspect of the CSMB will be the

training and education of students and scientists in the technologies within the CSMB. A wide range of opportunities for scientists and students working in the field of structural biology will be provided, including extended visits for experimental work, short courses, workshops, and scientific meetings.

Specific Features of the CSMB

- SANS facilities to be built at the upgraded HFIR will be specifically designed for high flux and located as far away as possible from other instruments to achieve the low background required for biological studies. Adjacent laboratory facilities will be available for final preparation of samples. Data acquisition/reduction capabilities will be integrated into instrument. ORNL staff will be available to support users.
- Additional existing neutron-based tools at HFIR will also be made available to the CSMB users, including another SANS instrument designed for studying materials with higher resolution and a reflectometer that can be used to study biomolecular monolayers and thin films. A small angle x-ray scattering (SAXS) instrument is also available at ORNL, which can be used to evaluate biological samples prior to SANS experiments.
- Existing resources in biological mass spectrometry will be made available to the users of the CSMB, including two Fourier transform in cyclotron resonance mass spectrometers and a number of other instruments equipped with electrospray and matrix assisted laser desorption sources. Dedicated staff will support users.
- Existing resources in computational biology/informatics will be made accessible to the users of the CSMB for modeling, prediction, and data base use, with dedicated staff to support users.
- Sample preparation facilities to support SANS and MS experiments will be maintained with dedicated staff.
- CSMB users will have access to the Joint Institute for Neutron Sciences (JINS) facility being built at ORNL during their visits. The JINS will include overnight accommodations, food facilities, offices, meeting space, etc.

Benefits to Structural Biology User Community

The proposed Center fills an important niche in the spectrum of scientific tools required to perform comprehensive structure – function experiments. It is designed with specific interfaces to the neutron crystallography center at LANL so as to jointly serve and grow the structural biology community that takes advantage of the unique features of neutron sources. It is unique in its combination of high-flux cold neutrons for SANS with a world-class computational biology resource, and pioneering mass spectrometry facility.

Biomedical Engineering

Biomedical science and technology is a vitally important R&D area for the nation, involving immense human, sociological, and economic consequences. Although this broad subject could encompass a vast array of disciplines and topics, we have focussed our efforts on the more narrow description used by the Medical Sciences Division at DOE-OBER as follows: "Medical devices, instrumentation, technology (including computational), or new methodologies that have a medical application. These could be used in medical diagnostics, monitoring, treatment, or patient rehabilitation."

The Life Sciences Division has core expertise in several emerging biotechnology areas including biomedical mass spectrometry, biosensors, nuclear medecine, medical telesensors, biochips, and bioinformatics. Complementary efforts in other divisions include medical imaging (I&C), biomaterials (Metals and Ceramics), and various bioanalytical techniques (CASD). Medical expertise is added by teaming with clinical researchers in collaboration with the UT Medical Center, Vanderbilt Medical Center and The Meharry Medical Center. All of these focus areas are extremely multidisciplinary and require a team approach including biologists, chemists, physicists, engineers, and medical doctors.

Building on these core, interdisciplinary competencies and our alliances within and outside ORNL, we have developed an intitiative in Biomedical Science and Technology that is expected to expand our current effort of about $4 million to over $10 million in the next five years. This initiative is designed to meet the growing needs of federal sponsors such as DOE, NIH, and DOD. It also is synergistically related to other division priorities such as functional genomics, proteomics, and instrument development.

In the current reporting period the following accomplishments have provided the framework for the initiative:

- Summary of current capabilities and projects; development of strategic plan for the future.
- Contacts/collaborations with neighboring medical centers—UT, Vanderbilt, Meharry, etc.
- Contacts/collaborations with neighboring Biomedical Engineering Departments—UT, Virginia Commonwealth University, Vanderbilt, Duke, etc.
- Participation in and founding member of the Tennessee Biotechnology Association.
- Sponsor, Planning Committee Member, and participation in the Annual Tennessee Conference on Biomedical Engineering (Vanderbilt, 1999 ; Knoxville, 2000).
- Sponsor, Planning Committee Member, and participation in the symposium on "The Impact of Emerging Technologies on Health Care in the 21st Century" (Knoxville, 1998).
- Planning Committee and participation in the "Wireless Medical Conference" (Nashville, 1999).

Technology Applications

The role that the Life Sciences Division plays in applying Laboratory-developed methods to solve problems of national concern is well recognized throughout the environmental and medical communities. For many years, the Division (or its predecessors) has been a leader in applying technologies, developing instruments, and formulating new approahes for dealing with environmental and medical problems that were beyond the technical scope of those that could be addressed by other federal or private organizations. To more effectively focus the Division's efforts in applying technologies, marketing capabilities, and ensuring cost-effective methods to solve national problems in these areas, a Technology Applications Program (TAP) has been initiated. The TAP consists of a "virtual" organization which includes the Assessment Technology, Environmental Technology, and Toxicology and Risk Assessment Sections and a Program Development Group that consists of recognized technical leaders in each section charged with determining programmatic needs and directions, marketing focus and methods, and long-range planning strategies. Initial efforts of the TAP will be aimed at environmental problems and will encompass pollutant detection and measurement, human health and ecological risk assessment, dosimetry and transport modeling, toxicology, life cycle analysis, laboratory analysis of samples, data management and computer applications, systems integration, and project management. This broad scope of capabilities covers the entire range of technical needs that could be required to address any environmental problem. Cooperative program development efforts are currently being conducted by the Program Development Group, and TAP management is evaluating financial structures and options to ensure cost-effective and efficient operation. The objective of this effort is to provide a model for structuring and strengthening applied programs at ORNL.