Exceptional Service Award for Contributing to a Healthy Citizenry

Since the establishment of the Atomic Energy Commission (a predecessor to DOE) a half century ago, DOE's most fundamental health-research goal has been to understand the risks and exploit the benefits of energy technologies and their by-products.

As the BER program obtained definitive information in the 1940s and 1950s concerning the biological effects of relatively high levels of radiation exposure, attention turned to the potential effects of lower doses. The result was a comprehensive, long-term, multidisciplinary research program aimed at understanding the underlying mechanisms of biological damage from radiation and chemical exposures. BER studies have since revealed some of the underlying similarities of mechanisms at work in damage caused by exposure to radiation, X rays, ultraviolet light, and chemicals. These and other data obtained from the BER program have provided much of the scientific foundation for laws and standards that protect the population, including workers exposed to radiological sources.

Explorations into using radiation and radioisotopes in medical research and therapeutics led to the highly successful field of nuclear medicine, which began some 50 years ago when the U.S. Food and Drug Administration approved the first radiopharmaceutical for medical use—iodine-131, produced at Oak Ridge National Laboratory. DOE and its predecessors supported the further development and application of isotope generators, along with imaging devices to visualize the isotopes as they emit radiation in the body. These studies ultimately gave rise to many of today's tools that involve the use of radioisotopes, including imaging studies, therapeutic procedures, and diagnostic laboratory tests. Coupled with new discoveries in biology and genetics, these breakthroughs are stimulating novel ways to diagnose and treat cancer and other disorders, detect genes in action, and understand normal development and function of human organ systems.

In looking toward the next century of biological research, BER seeks to integrate human health research with information and technologies from genome, structural biology, and molecular biology research. BER's goal is to better understand the complex relationships among genes and the proteins they encode as well as the biological functions of proteins in the context of the whole organism.

To facilitate these explorations, the BER program develops and maintains DOE national user facilities housing synchrotron and neutron sources for scientists to determine the molecular structure of enzymes, antibodies, and other important biological molecules. Computational research combines computer science, structural biology, and genome research to predict the functions of biological molecules. Such understanding also is central to advancing DOE's biotechnological mission over a wide range of applications, including environmental bioremediation and energy production from biomass. These research programs will provide greatly improved molecular tools for assessing health risk and predicting and evaluating individual susceptibilities to low-level workplace and environmental exposures from energy-related activities.

BER Accomplishments

Advanced DNA-Based Tools for Medicine

- BER researchers developed fluorescent dyes to "paint" chromosomes, enabling diagnosis of some types of cancers, prediction of treatment outcomes, and quantification of DNA damage in cells.

Bioassays

- The Ames Salmonella Assay, developed with BER support, tests for potential mutagenicity and is one of the first hurdles a new compound must clear on its way to regulatory and public acceptance.
- BER-sponsored research led to the discovery and understanding of DNA repair enzymes. The enzymes were named Molecules of the Year in 1994 by *Science* magazine because of their central role in the maintenance of human health.

Radioactive Tracer Biology and Nuclear Medicine

- Research on the beneficial effects of radioisotopes in medicine gave rise to the field of nuclear medicine. An estimated 1 in 3 U.S. hospitalized patients undergoes a nuclear medical procedure, and nearly 100 million laboratory tests using radioisotopes are performed every year in the United States.
- Radioisotopes have been developed for use in detecting diseases in such organs as kidney, liver, heart, and brain.
- Radioisotopes are being used to treat thyroid diseases, pituitary tumors, and eye cancer, among other disorders.
- Development of advanced instrumentation technology, coupled with expertise in the use of radiation, led to the debut of such sophisticated imaging tools as positron emission tomography (PET), computerized tomography (CT) scans, and magnetic resonance imaging (MRI) that allow noninvasive diagnosis, monitoring, and exploration of human disorders and their treatments.
- Isotopes and other tracers of brain activity are being used to explore drug addiction, effects of smoking, Alzheimer's disease, Parkinson's disease, and schizophrenia. Research has been instrumental in linking dopamine deficiency with Parkinson's disease and in developing a treatment using the medication L-dopa.

Guidelines and Training

- BER studies provided the scientific foundation of guidelines for the safe use of diagnostic X rays and radiopharmaceuticals, safety standards used in the presence of radioisotopes in food and drinking water, and radiation-detection systems and dosimetry techniques.
- BER programs provide training and research experience for radiation biologists and health physicists, radioecologists, and nuclear medicine experts.

EXCEPTIONAL SERVICE AWARD
For Contributing to a Healthy Citizenry

Mina Bissell, Ph.D.
E.O. Lawrence Berkeley National Laboratory
Berkeley, California

Mina Bissell received a B.A. in chemistry from Radcliffe-Harvard College and an M.A. in bacteriology and biochemistry from Harvard University, where she earned a Ph.D. in microbiology and molecular genetics in 1969. She received a Milton fellowship from Harvard and was an American Cancer Society fellow at the Department of Molecular Biology, University of California, Berkeley. In 1972, she joined E.O. Lawrence Berkeley National Laboratory, where she became Director of Cell and Molecular Biology in 1988. She was named Director of the newly formed Life Sciences Division in 1992.

Dr. Bissell has published more than 100 articles and papers in peer-reviewed journals and more than 50 book chapters and reviews. She has submitted three patent applications and sits on the scientific advisory boards of several biotechnology companies. She has won numerous awards, including a Guggenheim fellowship in 1993. She was elected a fellow of the American Association for the Advancement of Science in 1995, and in 1996 she received the E.O. Lawrence Award, one of DOE's highest honors. In 1997 Dr. Bissell was President of the American Society for Cell Biology and was elected to the Institute of Medicine of the National Academy of Sciences. In 1998 she won the Mellon Award of the University of Pittsburgh and in 1999 the Eli Lilly/Clowes Award of the American Association for Cancer Research.

Mina Bissell

"In recognition of your . . . research in the area of molecular and cell biology, to understand how cell growth, differentiation, and survival are controlled in normal and cancerous breast cells."

Reversion of the Malignant Phenotype

Mina Bissell, with her team of scientists at Berkeley Lab, has taken several novel approaches to studying normal cell growth, differentiation, and carcinogenesis. Using human and mouse breast cells in a three-dimensional tissue culture model, Dr. Bissell has demonstrated that the extracellular cellular matrix (ECM), the mass of fibrous and globular proteins that surround the cell, plays a vital role in gene expression and thus bears significantly on cell growth, functional differentiation, apoptosis (programmed cell death), and cancer.

In 1981, Dr. Bissell formulated the concept of "dynamic reciprocity," in which she proposed that signals are transduced into the cell nucleus through ECM receptors (subsequently discovered by others and called integrins). These receptors would have attachments to the proteinaceous filamentous network (the cytoskeleton) that encompasses the cytoplasm, with connections to the nucleus and chromatin via the nuclear matrix. Her studies not only have confirmed the model but have revealed an unexpected role for ECM in gene expression. This research has demonstrated that ECM can trip switches deep within the nucleus and spur the genes themselves into action. Her group was the first to identify the molecular components of the ECM signal and to establish that ECM also is responsible for protecting against apoptosis. This discovery provides an important key in understanding how cell growth, survival, and differentiation are controlled in normal cells but become aberrant in tumors.

Reversion of the Malignant Phenotype. Mina Bissell's group demonstrated that the microenvironment surrounding cells plays a vital role in gene expression. After manipulation of the proteins surrounding the cell as well as the cell-surface molecules to which they bind, human breast cancer cells reverted to normal cell function in culture and tumors were reduced dramatically in immune-deficient mice. Postdoctoral fellow Dr. Valerie Weaver (left) and Dr. Bissell prepare tissue specimens for confocal fluorescence microscopy imaging of frozen sections of breast cell colonies. The inset images, captured by Dr. Carolyn Larabell of Lawrence Berkeley National Laboratory, depict this reversion: the well-organized rounded structures of normal cells (left), the haphazard arrangement of proliferating malignant cells (middle), and the return to a more normal arrangement after treatment (right). Labeled in green and red are the cytoskeletal protein actin and the cell nuclei, respectively.

In a profound insight with practical significance, Dr. Bissell and her colleagues put forward the notion that cancer is the result not only of genetic change, developmental regulation, or loss of tissue structure but is an interweaving of all these factors. Making important strides to reinforce this assertion, Dr. Bissell's group has demonstrated that, by manipulating the microenvironment and ECM receptors, overtly tumorigenic human breast cancer cells are reverted to normal cell function in culture and tumors are reduced dramatically in immune-deficient mice. These findings have vital implications for breast cancer diagnosis, prognosis, and treatment.

EXCEPTIONAL SERVICE AWARD
For Contributing to a Healthy Citizenry

Joanna Fowler, Ph.D.
Brookhaven National Laboratory
Upton, New York

Joanna Fowler is a Senior Chemist and Director of Brookhaven National Laboratory's (BNL) Positron Emission Tomography Program. After completing the B.A. in chemistry at the University of South Florida and Ph.D. in chemistry at the University of Colorado, she joined the BNL Chemistry Department in 1969. Dr. Fowler has received numerous awards, including the BNL R&D Award in 1995, Aebersold Award of the Society of Nuclear Medicine in 1997, Francis P. Garvan–John M. Olin Medal of the American Chemical Society in 1998, and the E.O. Lawrence Award in 1999.

Joanna Fowler

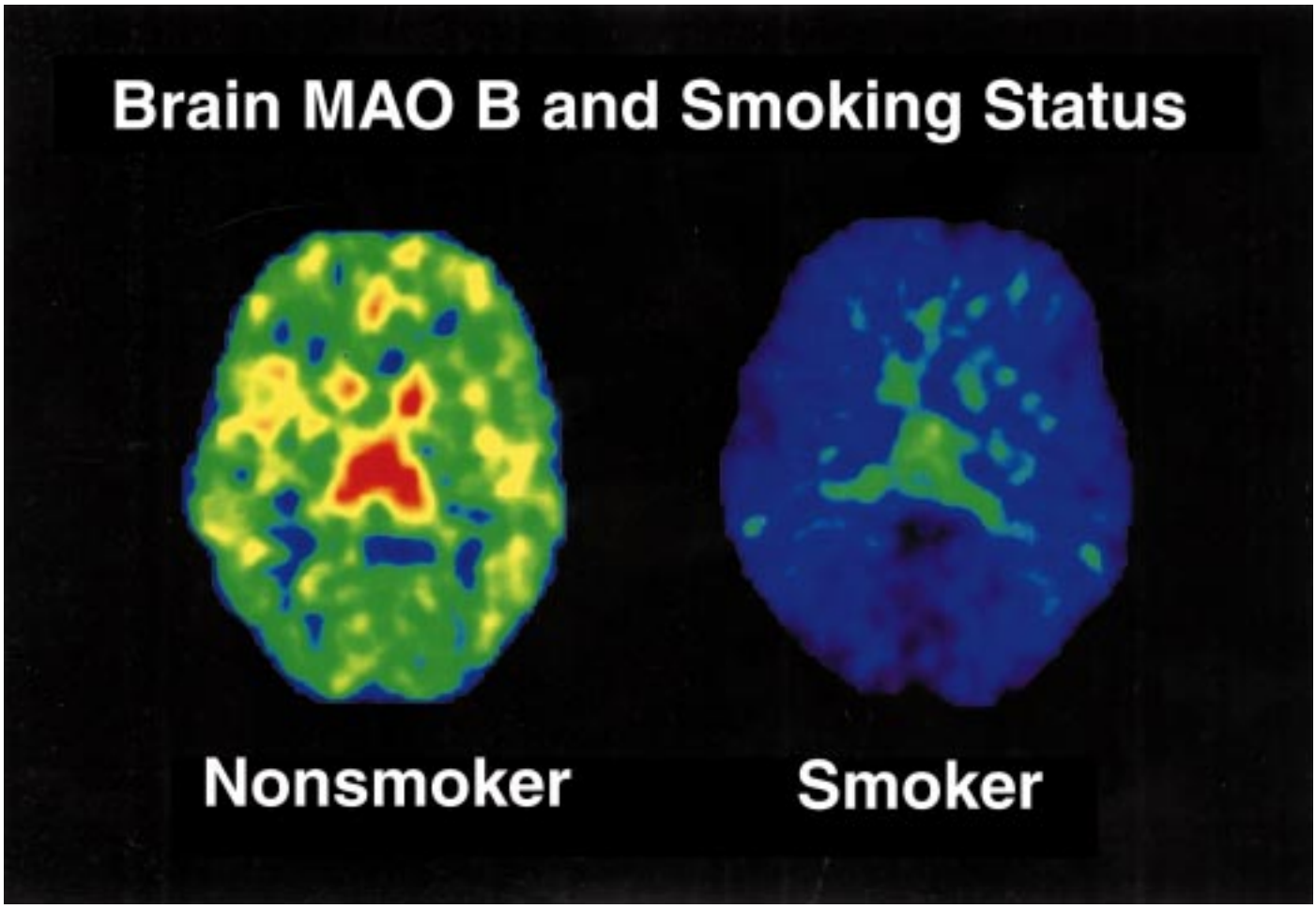
"In recognition of your . . . research for medical applications to create new concepts in medical imaging and to design, synthesize, and apply radiotracers to the study of the human brain in health and disease."

PET Technology

From her beginnings as a synthetic organic chemist, Joanna Fowler has played a seminal role in developing positron emission tomography (PET) technology, which allows researchers to monitor the brain activity of people afflicted with schizophrenia, Alzheimer's and Parkinson's diseases, brain tumors, drug addictions, and other substance abuse. The use of PET, which provides a time and space window into the function of vital organs and human biochemistry, depends on the availability of organic compounds labeled with short-lived positron-emitting radionuclides.

Dr. Fowler has made important contributions to the synthesis of labeled compounds for PET research and has opened new vistas in the study of human biochemistry and the mechanism of drug action. She made exceptional contributions to the design and synthesis of ^{18}F-fluorodeoxyglucose (FDG) in 1976, profoundly accelerating the growth of PET research. FDG, the most widely used PET tracer in the world, has played a pivotal role in understanding human brain function, in diagnosing and monitoring cancer patients, and in assessing cardiac viability.

Dr. Fowler's development of ^{11}C-cocaine provided the tools for the first documentation that cocaine movement in the human brain parallels its subjective effects. Her approach to mapping human brain

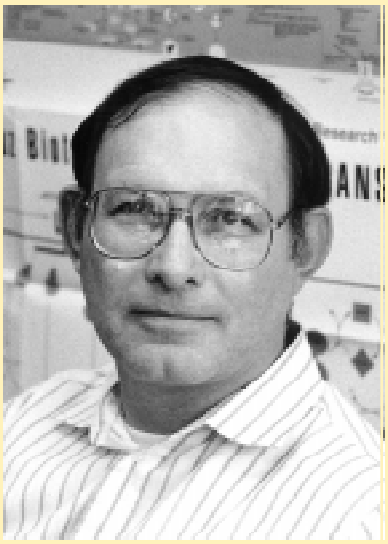


Positron Emission Tomography (PET) Technology Application to Brain Studies. Dopamine is a neurotransmitter involved in movement, motivation, and reward; monoamine oxidase B (MAO B) is a brain enzyme that breaks down neurotransmitters like dopamine. Using PET imaging and [11C]L-deprenyl-D2 (a radiotracer that maps brain MAO B), Joanna Fowler's group discovered that cigarette smokers have less brain MAO B than nonsmokers and former smokers. MAO B inhibition by smoke may account for some of smoking's epidemiological features, including the lower risk of Parkinson's disease in smokers and the high rate of smoking in individuals who are depressed or addicted to such other substances as alcohol and cocaine.

monoamine oxidase (MAO) made possible the direct measurement of the turnover rate of MAO B in the living human brain. Dr. Fowler recently used this strategy to provide the first documentation that cigarette smokers have reduced brain MAO, an observation that opens a new vista on the biological effects of cigarette smoke and offers alternative treatment strategies.

Dr. Fowler's research, coupled with pioneering research in radiotracer chemistry by Alfred Wolf and internationally recognized studies of addiction led by Nora Volkow, has pushed BNL to the forefront in the use of PET technology and led to BNL's selection as the site for a new National Institute on Drug Abuse (NIDA) Regional Neuroimaging Center. This center, funded jointly by DOE, NIDA, and the Office of National Drug Control Policy, features a new PET scanner to be used in studies to understand addiction and to develop drug-addiction treatments.

EXCEPTIONAL SERVICE AWARD
For Contributing to a Healthy Citizenry



Joe Gray, Ph.D.
University of California
San Francisco, California

Joe Gray did his undergraduate studies in physics at the Colorado School of Mines and received his Ph.D. in physics from Kansas State University in 1968. He then joined Lawrence Livermore National Laboratory as a biomedical scientist and served as leader of the Cytophysics Section from 1982 to 1991, when he accepted a position in the Department of Laboratory Medicine, University of California, San Francisco (UCSF). In 1992 Dr. Gray was appointed Senior Scientist at Lawrence Berkeley National Laboratory, and in 1993 he became Professor of Laboratory Medicine and Radiation Oncology at UCSF.

Dr. Gray has published some 170 peer-reviewed articles and 80 reviews, chapters, and other publications, and has edited 5 books. He currently holds 15 patents with 10 more pending.

Dr. Gray was President of the Cell Kinetics Society from 1983 to 1984 and was elected in 1996 to a 2-year term as President of the International Society of Analytical Cytology. He currently serves on the editorial boards of six professional journals. His honors include the 13th Research Award from the Radiation Research Society in 1985, Smith-Kline and French Distinguished Lectureship in 1986, DOE E.O. Lawrence Award in 1986, and appointment as a fellow by the American Association for the Advancement of Science in 1996 and to the Cell Proliferation Society Shiffer Lectureship in 1999.

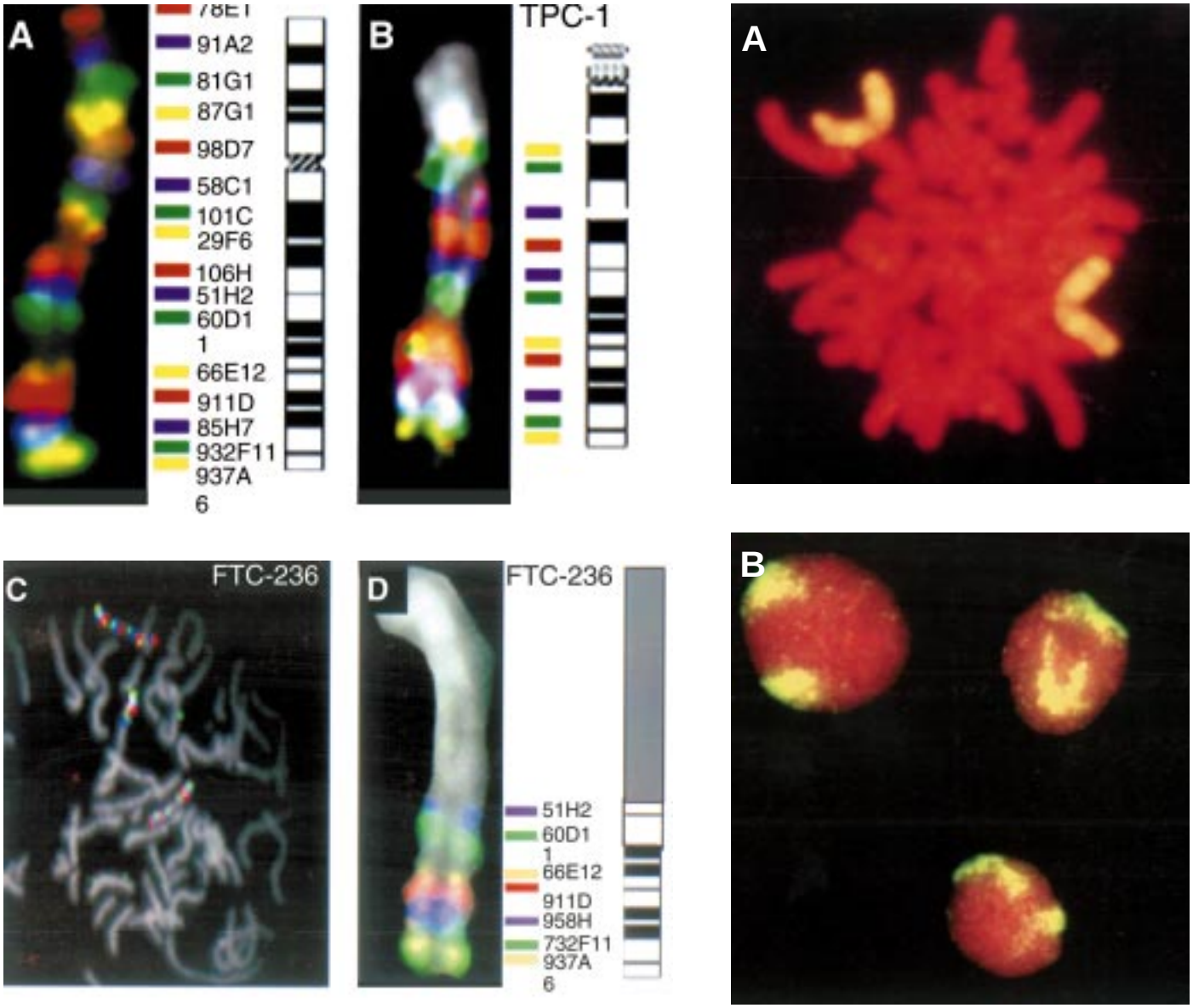
Joe Gray

"In recognition of your . . . research in the area of health effects to develop molecular cytogenetic tools such as 'chromosome paints,' so valuable for clinical and research applications."

Molecular Cytogenetics

Joe Gray's research goals are to gain a better understanding of the mechanisms by which genomic abnormalities form in solid tumors, identify and determine the function of genes associated with consistent regions of abnormality that contribute to solid tumor progression, and develop therapeutic agents to attack tumors carrying aberrations involving these genes. Molecular cytogenetic techniques such as fluorescent in situ hybridization and comparative genomic hybridization provide key information in these investigations.

Dr. Gray is well known for his work in molecular cytogenetics. One of his contributions in this area was the development of chromosome painting in collaboration with Dr. Dan Pinkel while at Lawrence Livermore National Laboratory. This technique, in which whole human chromosomes or portions are uniformly stained with fluorescent dyes for easy recognition under fluorescence microscopy, allows analysis of both interphase nuclei and metaphase chromosomes. Several dyes can be used so that different chromosomes can be recognized. Work in other laboratories has extended this capability to allow distinctive staining of all 24 human chromosomes for scoring in one preparation. Complementing and sometimes replacing expensive and time-consuming chromosome banding, painting has proved useful in identifying genetic aberrations associated with birth defects, aging, exposure to radiation, and cancer. More recently, at the University of California, San Francisco, and Lawrence Berkeley National Laboratory,



Application of Fluorescent In Situ Hybridization (FISH) in Mapping the Sites of Rearrangement After a Translocation Between Chromosomes 10 and 22 (Images: Dr. H.-U. Weier, Lawrence Berkeley National Laboratory). The four panels at left show (A) normal chromosome 10 stained with 16 different probes; (B) rearranged chromosome with parts of chromosomes 10, 21, and 22 from a thyroid cancer cell; (C) one chromosome 22 containing material from chromosome 10; and (D) closeup of chromosome 22 showing the translocated piece of chromosome 10 stained using FISH with probes from chromosome 10. Probes used in these analyses were derived from yeast artificial chromosomes.

Early Images of Whole-Chromosome Painting. The panels at right show (A) hybridization to a metaphase spread using a probe for chromosome 3 and (B) hybridization to three interphase nuclei using the same probe. Nuclei are counterstained with propidium iodide so they appear red. Hybridization signals are in yellow.

Drs. Gray and Pinkel collaborated with Drs. Anne and Olli Kallioniemi and Dr. Frederic Waldman to develop comparative genomic hybridization. In allowing regions of gene dosage imbalance to be mapped onto normal metaphase chromosomes, this technique can be applied using DNA extracted from archived tumor samples. It greatly facilitates identification of regions of recurrent abnormality.

EXCEPTIONAL SERVICE AWARD
For Contributing to a Healthy Citizenry

Tuan Vo-Dinh, Ph.D.
Oak Ridge National Laboratory
Oak Ridge, Tennessee

Tuan Vo-Dinh, who received his Ph.D. in biophysical chemistry in 1975, is a pioneer and world leader in laser-excited luminescence spectroscopy, room-temperature phosphorimetry, synchronous luminescence spectroscopy, surface-enhanced Raman spectroscopy (SERS), field environmental instrumentation, fiberoptic biosensors, and optical data storage (ODS). A corporate fellow at Oak Ridge National Laboratory, Dr. Vo-Dinh has received numerous other honors, including five R&D 100 Awards and the Gold Medal Award from the Society for Applied Spectroscopy, French Languedoc-Roussillon Award, Martin Marietta Thomas Jefferson Award, and Inventor of the Year awards from the Inventors Club of America and the Tennessee Inventors Association.

Dr. Vo-Dinh has published some 220 articles and papers in scientific journals in the areas of analytical chemistry, molecular spectroscopy, environmental monitoring, and biomedical diagnostics. He is author and editor of 8 books and holds 19 patents, 5 of which have been licensed for commercial development (Luminoscope for pollutant screening, SERS Toxic Analyzer, SERODS optical data-storage technology, synchronous luminescence technology, and optical biopsy technology for cancer diagnosis).

Tuan Vo-Dinh

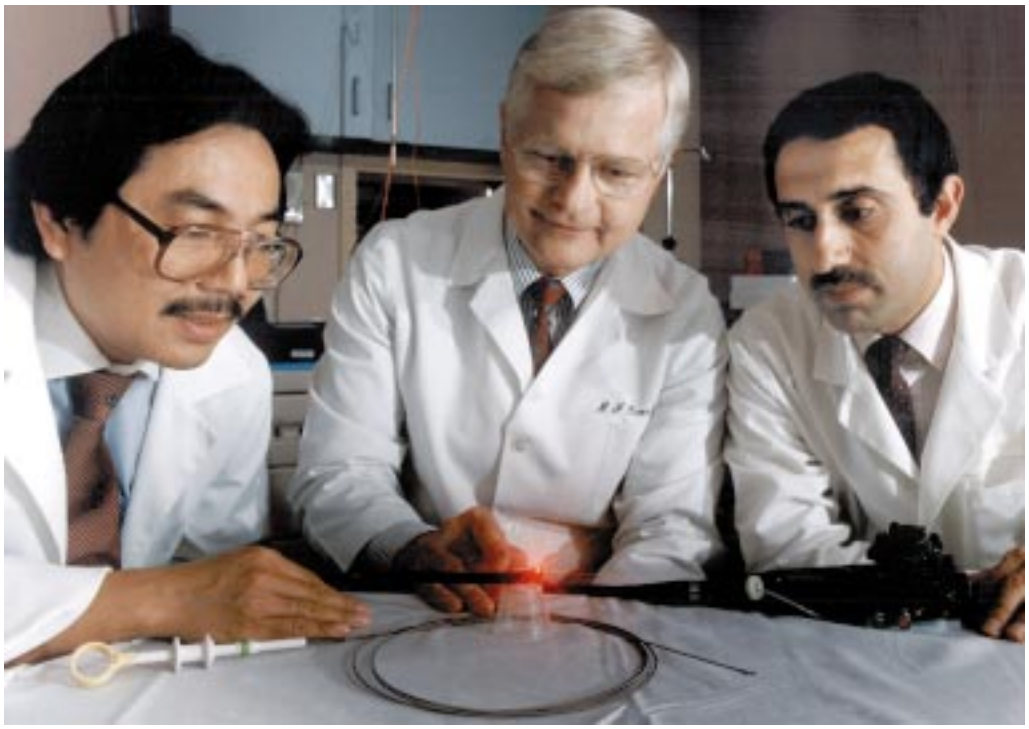
"In recognition of your . . . research . . . to discover new concepts in analytical chemistry and to invent and transfer to the private sector technologies applicable to medical and environmental monitoring."

Molecular Spectroscopy, Lasers, and Fiberoptics

Tuan Vo-Dinh has established a distinguished record of accomplishments in the field of applied spectroscopy, the science that uses the interaction of light and molecules to probe and analyze matter. His fundamental research on synchronous luminescence (SL) has set the foundations of the technique and has led to numerous applications. In the environmental and biological fields, for example, use of SL decreases the cost of environmental monitoring at petroleum plants and detects DNA damage following chemical exposure. Most spectrometer companies have incorporated SL as a standard feature in luminescence instruments.

Dr. Vo-Dinh was one of the first U.S. scientists to develop and effectively use the room-temperature phosphorescence technique for rapid and cost-effective analysis of trace organic compounds adsorbed on filter paper. He has expanded the technique for use in a passive personnel dosimeter to detect potentially toxic organic chemicals in occupational and residential environments.

Recognizing the potential of lasers in vibrational spectroscopy, Dr. Vo-Dinh demonstrated the analytical potential and general applicability of the surface-enhanced Raman scattering (SERS) effect by developing solid nanoparticle-based active substrates for use in



Minimally Invasive Optical Techniques for Rapid Cancer Diagnosis. From left, Dr. Vo-Dinh and his research colleagues, Dr. Bergein F. Overholt and Dr. Masoud Panjehpour (both of the Thompson Cancer Survival Center), have developed optical techniques for rapid diagnosis without surgery. The photograph shows the probe that directs light along optical fibers through an endoscope to the suspected tissue. Malignant tumors can be detected and differentiated by laser-induced fluorescence in less than one second.

trace organic analysis. This important technology demonstrates that practical, simple-to-prepare, and cost-effective metal-covered nanoparticle materials can provide efficient SERS substrates to detect chemical and biological compounds.

Dr. Vo-Dinh invented a technology for large-memory optical data storage (ODS) based on the SERS effect. SERODS could be useful in applications such as supercomputer memories and medical databases and imaging.

Dr. Vo-Dinh also has focused on integrating biotechnology, fiberoptics, laser techniques, and spectroscopy to develop unique antibody-based fiberoptic fluoroimmunosensors (FIS). FIS is a breakthrough in such chemical applications as assessing an individual's exposure to chemical carcinogens and response to drug therapy as well as in characterizing naturally occurring, biologically active substances. FIS also will open new horizons to the fundamental technology of a "smart catheter-sensor" for in vivo analysis of trace compounds of environmental and biomedical interest.

To address the critical need for lower costs in environmental remediation, Dr. Vo-Dinh has invented a simple method to test for polychlorinated biphenyls. The new test, which uses photoactivated fluorescence, allows for onsite sampling to avoid time-consuming laboratory analysis.

Detecting multiple sequence-specific DNA fragments from infectious human pathogens will be one of the first steps in diagnosing disease or developing a new drug. Dr. Vo-Dinh recently developed the SERGen gene probe and the biochip technology for clinical and field applications to detect DNA biotargets rapidly, simply, and without the use of radioactive labels.

Recent collaborations with scientists from the Thompson Cancer Survival Center in Knoxville, Tennessee, have resulted in development of a laser-based, nonsurgical method of detecting cancer. The technique is called "optical biopsy" because laser light is directed along optical fibers through an endoscope to excite the questionable tissue and collect the fluorescent light emitted from the tissue. This technology has proven nearly 100% accurate in diagnosing esophageal tumors in more than 500 tests on more than 100 patients. It is being developed further for diagnosing tumors in such other organs as the colon, cervix, and lungs.

EXCEPTIONAL SERVICE AWARD
For Contributing to a Healthy Citizenry

Edwin Westbrook, M.D., Ph.D.
Argonne National Laboratory
Argonne, Illinois

Born in San Juan, Puerto Rico, Edwin Westbrook received an A.B. with highest honors from the University of California, Berkeley, and both an M.D. and a Ph.D. in biophysics from the University of Chicago in 1981. From 1981 to 1983, he was a National Institutes of Health (NIH) postdoctoral fellow at the Molecular Biology Institute of the University of California, Los Angeles. In 1983, Dr. Westbrook joined the staff of Argonne National Laboratory (ANL) and in 1991 became Director of its Structural Biology Center. He was an assistant professor at the University of Chicago from 1983 to 1988 and has been an associate professor at Northwestern University since 1988.

Author of more than 60 journal articles, Dr. Westbrook has received many honors, including the Pacesetter and Exceptional Performance awards from ANL. He has been a member or chair of numerous committees for ANL, the American Physical Society, the American Crystallography Association, NIH, the National Science Foundation, and DOE.

Edwin Westbrook

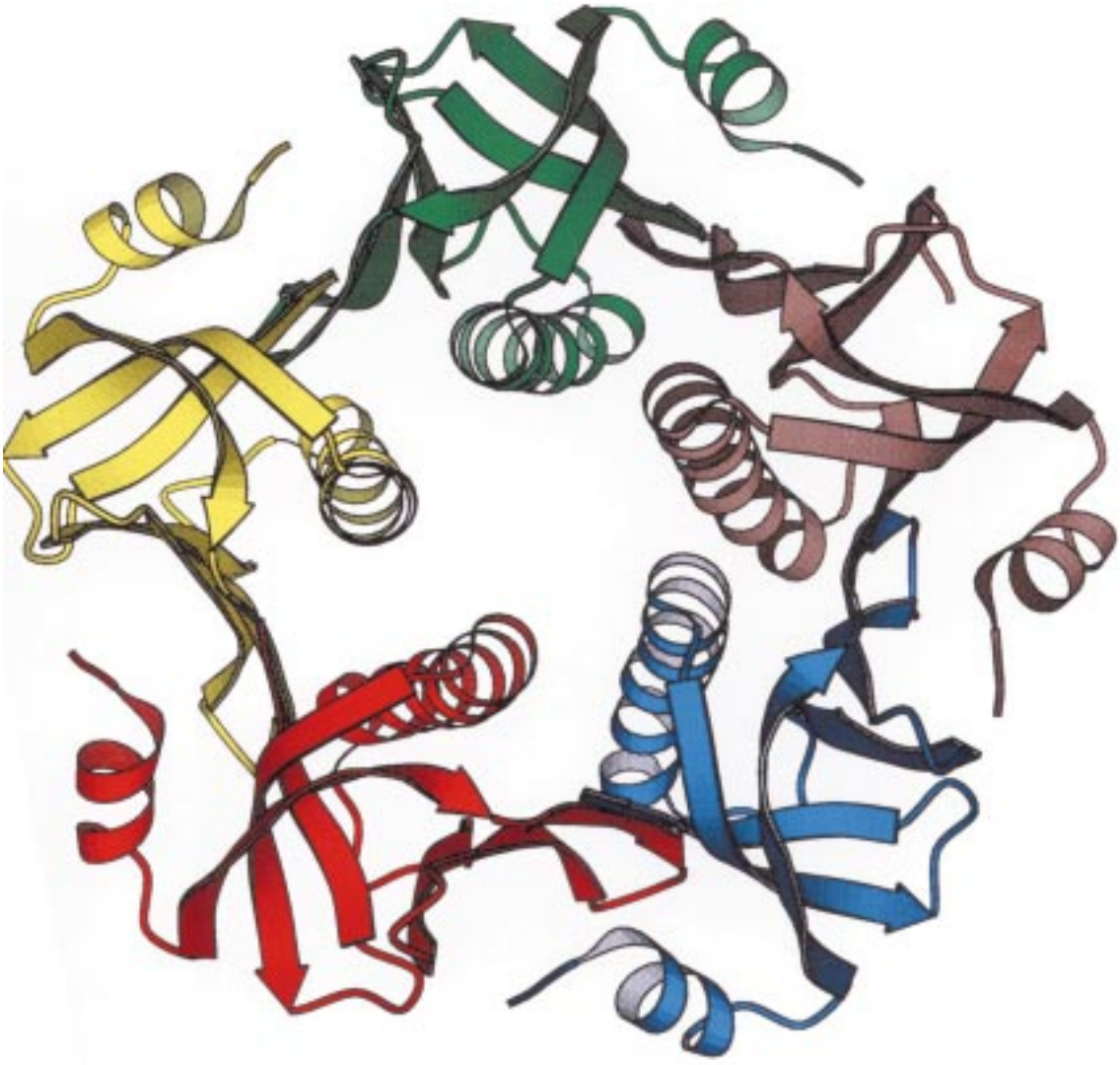
"In recognition of your . . . research . . . to develop advanced detectors for crystallography while providing leadership to establish user facilities for structural molecular biology at the Advanced Photon Source."

Protein Crystallography

The Argonne Structural Biology Center (SBC) is responsible for the design, fabrication, installation, and operation of instruments and systems for the application of synchrotron radiation to protein crystallography. SBC has built two X-ray beamlines at Argonne National Laboratory's Advanced Photon Source (APS), the nation's only third-generation high-energy synchrotron source. With its high intensity, low angular divergence, and small size, APS provides X-ray beams that are ideal for protein crystallography. The SBC beamlines can be focused onto crystals smaller than 50 microns while remaining almost parallel, and the flux densities of these beamlines are far greater than at any previous synchrotron source.

The power of the two SBC beamlines, coupled with the application of the latest electronic X-ray detectors, computer system design, and optimized software, contributes to an experimental facility that is extremely useful to protein crystallographers. The beamlines can work on structures of very large molecules and obtain accurate data quickly and efficiently.

SBC is a national user facility for structural biologists who need its unique capabilities. Access to SBC is through open peer-reviewed proposals that are



Cholera Toxin. The cholera toxin protein is made by the organism Vibrio cholerae. *When swallowed (e.g., in contaminated water), the bacterium survives transit through the human stomach and produces this toxin in the small intestine. Determining the molecular structure of cholera toxin by X-ray crystallographic methods permits rational design of vaccines against the disease.*

prioritized on the basis of scientific excellence and the need for SBC power. Users can collect extremely high quality data at the highest possible speed, while choosing any X-ray wavelength for their experiments. Applying the latest methods for structure determination, crystallographers can use the SBC facility for rapidly and accurately determining new structures of large biological molecules, refining and improving the accuracy of existing structures, and exploring the functional effects of structural modifications to known molecules. Such research is now of great importance in basic and applied research at the molecular level of biological sciences.

A large team has worked over the years to conceive, design, and build SBC. Now that the construction phase is finished, the user program is ramping up.

In addition to the Argonne beamlines, new BER-supported beamlines for structural biology are coming online at Stanford University and at the Berkeley and Brookhaven national laboratories. BER also continues to support several existing synchrotron beamlines at Stanford and Brookhaven.