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Biotechnology
At Brookhaven National Laboratory

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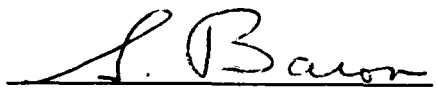
Biotechnology at Brookhaven National Laboratory

Brookhaven National Laboratory (BNL) is a multiprogram laboratory that carries out basic and applied research in the physical, biomedical and environmental sciences and in selected energy technologies. The Laboratory is supported by the U.S. Department of Energy and other federal agencies.

Biotechnology at BNL is an interdepartmental/interdisciplinary effort, drawing on the expertise of a large group of staff scientists and their laboratory facilities.

Currently, active programs which encompass applied and basic research activities address several key areas of biotechnology. These activities represent a broad base for continuity, expansion and development of biotechnology at BNL.

In this document a brief description of the various capabilities is given. Scientists associated with each program are also identified.



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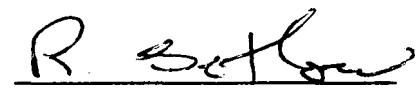

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Environmental Microbiology

The Environmental Microbiology Group is actively involved in both fundamental and applied research on microbial treatment of mixed wastes containing toxic metals, radionuclides and organic compounds; distribution and activities of denitrifying and iron-reducing microbes in deep subsurface; microbial mobilization and immobilization of toxic metals from coal waste and ash; microbial enhancement of low-rank coals by demineralization and its effect on ash fusion properties; effect of pollutants on soil microbial processes (organic matter decomposition, transformations of nitrogen, sulfur and pesticides; and anaerobic microbial production of organic acids for commercial use.

Current research emphasis is on anaerobic microbial processes involved in the transformation of toxic metals, radionuclides and chelating agents in mixed wastes. In particular, we are investigating the various anaerobic microbial processes involved in the dissolution and removal of toxic metals and radionuclides from industrial sludges, fossil- and nuclear-energy wastes as well as stabilization (immobilization) of the toxic metals and radionuclides in wastes by enhancing certain microbial processes.

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DAS technician monitors the activities of subsurface soil microorganisms.

Biochemistry of Microbial Processes in Extreme Environments: Biotechnological Applications

Selected groups of microorganisms capable of living in harsh environments are a subject of systematic studies in this laboratory. Some of these organisms are capable of solubilization of natural metal salts, while others can live in acidic, high temperature and high pressure environments. Such acidophilic and thermophilic organisms possess properties which make them suitable candidates for industrial processes. Specifically, studies in the area of detoxification and recovery of metals by means of acidophilic microorganisms are focusing on removal of metals from by-products and wastes produced by geothermal power plants. Feasibility of developing a detoxification biotechnology based on microbial processes has already been demonstrated. This new biotechnology is also applicable to other residues of geological origin with comparable geochemistry. Concurrent exploratory studies are aimed at concentration and the recovery of metals from dilute aqueous solutions. In this area, combinations of chemical and biochemical processes serve as the basis of new biotechnologies.

Some thermophilic microorganisms, i.e., those capable of living at high temperatures, are also capable of living at high pressures. The study of chemical, biochemical and physical properties of interactions between a number of thermophilic, acidophilic and barophilic microorganisms and crude oils are the subject of extensive studies at BNL.

In all cases, particular attention is paid to:

1. Biochemical observation and its process potential including the feasibility of new biotechnology development.

From flask to scaled up to pilot-plant studies

2. Studies of chemical mechanisms involved at the interface of inorganic and/or organic matrices and microorganisms.

3. Effects of microbial biochemical processes at high temperatures and pressures on different organic substrates (e.g., crude oils).

The best laboratory results serve as the basis for technical and economic feasibility studies. Results from these studies are used for scaling up of bioprocesses and pilot-plant design.

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Biotreatment

Application of biotechnology to waste water renovation has been studied at the Experimental Waste Treatment Facility (EWTF) at BNL. Biota are largely responsible for degradation of organic wastes with varying degrees of efficiency in the natural environment and play a significant role in regulating the chemical species and mobilities of metals and organics in the natural environment. Each organism has specific physical and checmical habitat requirements. Habitat diversity increases the abundance of different types of organisms and, therefore, the opportunities for biota to act on a particular material increases with habitat diversity.

Combination of biotechnology and wetland ecology has led to design engineered ecosystems at BNL. EWTF provides the types of habitats that favor diversity of organisms. Various types of ecosystems such as meadows, marshes and ponds are created and seeded with numerous types of plants and microbiota. These organisms may include strains selected from the biotechnology laboratory for specific enzymatic activity through batch culturing. Invasion of natural macro- and microflora also may be controlled or enhanced. Plans include construction of lined 20-m^3 soil block lysimeters for evaluation of soil microbial biotechnological processes. Further plans are underway to develop a system which will initiate and maintain biochemical processes viaa horizontal and vertical wells through a soil block.

Staff Scientists:

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Bioprocess Technology and Biochemical Engineering

BNL has the expertise and facilities designed to perform engineering scale experiments on biochemical processes. Its investigators have experience in the design of reactors for a variety of chemical and biochemical processes, and have constructed and operated engineering scale tests to verify the designs. Based upon the results from these studies, process flowsheets have been developed and economic estimates performed, sometimes as collaborative efforts with university or private sector groups.

The biochemical processing facility contains all of the equipment necessary to scale-up critical components or entire biochemical processes. For example, one of the principal components in the facility is a 5-ft diam x 10-ft long stainless steel reaction vessel (see Figure 1). A full diameter pneumatic-operated top closure provides full access to the vessel. The vessel is equipped with stirring devices and has an operating pressure of 75 psi to full vacuum and a coincident temperature range of 0 degree to 160 degrees C. Services available at the

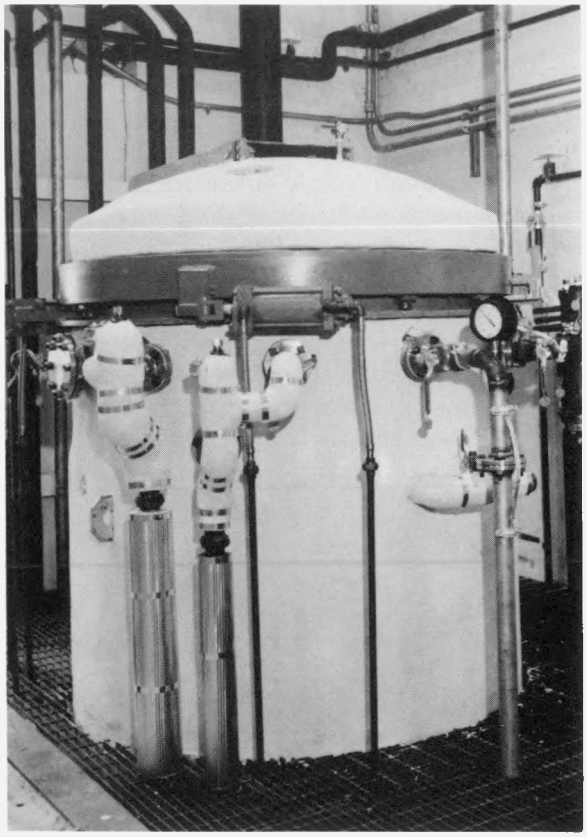

Figure 1. Large-scale reaction vessel for use in the evaluation and performance of biochemical processes.

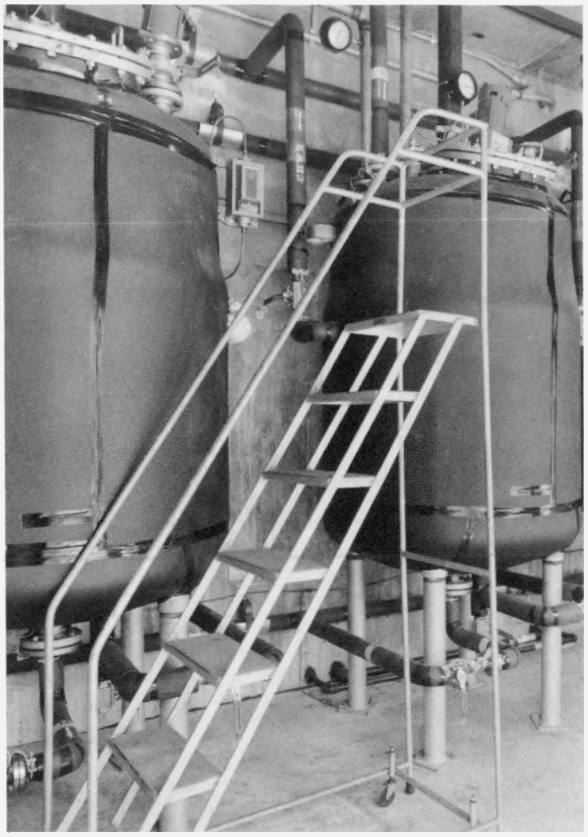

Figure 2. Intermediate size reaction vessels suitable for use with biochemical processes.

reactor include steam, hot and cold water, vacuum, and compressed gases.

Three 300 gal jacketed closed stainless steel reaction vessels and a transfer pump are also installed in the facility. These vessels, shown in Figure 2, have an operating pressure range from 50 psi to full vacuum. Chilled or heated fluids can be circulated through the vessel jackets to maintain the contents at the desired temperature. All of these components make the bioreactor facility a very versatile tool, particularly useful for process studies.

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Biochemistry and Genetic Selection of Microalgae Products

Microalgae are valuable sources of fine biochemicals, including β-carotene, phycobilisomes for fluorescent antibodies, lipids, polysaccharides, antioxidants and anticarcinogenic molecules. DAS has an active group examining biochemical pathways leading to these unique compounds in microalgae with a goal of genetically improving the yield of specific products in commercial mass culture systems.

Staff Scientists:

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High Energy X-Ray Microscopy

The new science of x-ray microscopy is focused on the imaging of materials with spatial resolutions that are of the order of micrometers (0.00004 inches). The image obtained may reflect either differences in the linear attenuation coefficient of x-rays in different parts of the sample or it may give the concentrations of particular elements.

The x-ray microscope is based on the use of very intense x-ray beams produced by the Brookhaven National Synchrotron Light Source. These beams are much more intense than those produced by an x-ray tube and their existence makes high quality x-ray microscopy possible.

The microscope can make measurements with lateral resolutions of less than 10 micrometers and with elemental sensitivities in the range of 10^7 to 10^{10} atoms. The instrument can be used to investigate wet samples at atmospheric pressure with elemental sensitivity. It is thus well suited to investigations in the fields related to Biotechnology.

Images of transverse sections of an object can be obtained using the methods of computed microtomography. The relatively weak attenuation of the x-ray beam makes it feasible to produce images of small animals, for example, an image of a section through the head of a live mouse can be obtained.

The x-ray microscope has already been used for experiments on many biomedical topics. One such use is the study of elemental distributions in bone where it is being used in two distinct experiments. One is the evaluation of the distribution of gallium in rat bone as part of a project to study the action of the therapeutic agent gallium nitrate for treatment of hypercalcemia in cancer cases. The second is the assessment of the distribution of bone lead in order to improve our understanding of the toxic effects of lead stored in the skeleton.

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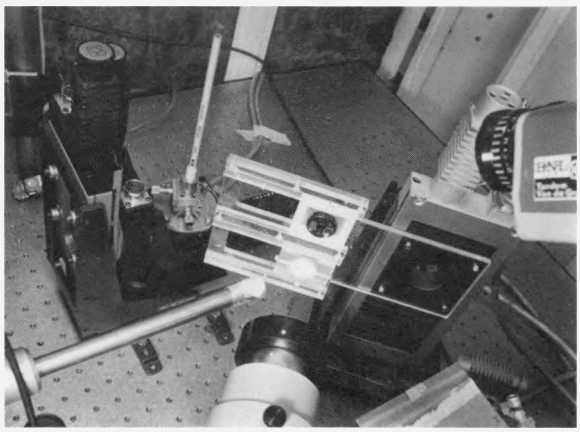

BNL's Department of Applied Science's first high energy x-ray microscope and tomography system.

Enzymes — Conducting Polymer Interactions

The development of enzyme electrodes has been a productive area of bioelectrochemistry. The devices combine the substrate specificity and affinity of biological catalysts with the analytical power of electrochemistry. The ongoing program involves studies of enzyme catalysis in a novel system where the enzyme is immobilized in a conducting polymer matrix. This allows direct electron transfer, or electronic communication, between the conducting polymer host and the enzymes, in particular oxido-reductase enzymes.

The field of biosensor research is expanding rapidly and important advances have been made during the last few years in developing amperometric, potentiometric and optical biosensors with high specificity and sensitivity. Coupled enzymes-antibody systems for example, can achieve picomolar and sub-picomolar sensitivity. The ability to switch enzyme reactions on and off reversibly opens the possibility of using enzyme electrodes for electroorganic synthesis of specialty chemicals and analogue signal processing in biomolecular electronics.

Staff Scientists:

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Biology Department

Research in the Biology Department includes the study of structures and functions of complex molecules and parts of cells, the organization of the genetic material of viruses and cells, environmental agents that change the genetic code, and the conversion of light energy to biomass.

The research program includes work in molecular biology and genetics, plant sciences, and structural biology. The latter is built around three unique facilities at Brookhaven that make up the Center for Structural Biology.

Neutron diffraction experiments are conducted at the High Flux Beam Reactor, the only facility in the country with experimental stations devoted exclusively to the study of biological structure. Neutrons are useful probes because they are able to locate the positions of hydrogen atoms in biological systems, such as digestive enzymes, cell organelles, membranes, and blood proteins. In such studies, neutrons strike a sample and are scattered off at different angles and intensities. By closely monitoring the deflected neutrons, a picture can be made of a sample's molecular and atomic structure.

The National Synchrotron Light Source represents the strongest source of ultraviolet light and x-rays in the United States. It is used to detect changes in conformation of DNA, the repository of genetic information, and also to obtain information rapidly on the structures of proteins and cellular organelles. Such x-ray diffraction experiments can be done several thousand times more rapidly than in a conventional laboratory x-ray setup.

A Scanning Transmission Electron Microscope is used to image biological molecules without staining or shadowing. The biology microscope can magnify objects ten million times. It is unique in being able to observe and to determine the masses of proteins and DNA in biological specimens.

The three unique facilities are used not only by Brookhaven scientists but are also open free of charge for use by scientific investigators in universities, industries, and other government laboratories.

Genetic Engineering, Special Facilities and Macromolecules

Molecular biologists investigate properties of DNA, the molecule that transmits genetic information from one generation to the next. A number of different systems are investigated, including bacterial and animal viruses and high plants. The bacterial virus T7 contains only about 50 genes and is used as a simple model system to study the organization, control, and expression of the genes, as well as the molecular details of the development and replication of viruses in general. The complete sequence of the 39,936 base pairs of the DNA has been determined at Brookhaven.

A detailed map of the maize genome is being prepared as a basis for improvement in the efficiency of plant breeding through use of modern genetic technologies. Studies on the role of regulatory genes are a natural corollary of this work.

Photosynthetic bacteria and plants are studied to understand how these utilize solar energy to convert carbon dioxide and water into biomass. Not all forms of solar radiation are beneficial, however ultraviolet radiation in sunlight is a harmful environmental agent, which can be directly related to human skin cancer. Continuing research in this area analyzes DNA damage in cells exposed to sunlight and the molecular mechanisms by which such cells are converted to cancer-related ones.

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Genetics, Biochemistry and Biophysics

Inasmuch as biotechnology requires a thorough grounding in the fundamental of biology, investigators in various fields can contribute both ideas and materials for initiatives in this area. The following programs, which study the genetics, biochemistry and biophysics of particular biological systems — mainly in higher plants and animals, including man — are a pertinent resource for any such initiatives. These programs, also, make use of forefront technology and are equipped with requisite instrumentation.

1. Algal/higher plant photosynthesis; protein phosphorylation; gene expression
2. Higher plant molecular genetics
3. Mechanisms of energy conversion in photosynthesis
4. Damage to DNA by radiation and chemical carcinogens and its repair
5. Plant biochemistry and physiology
6. Molecular origins of sunlight-induced human skin cancers
7. Chromosomal DNA replication of higher plants.

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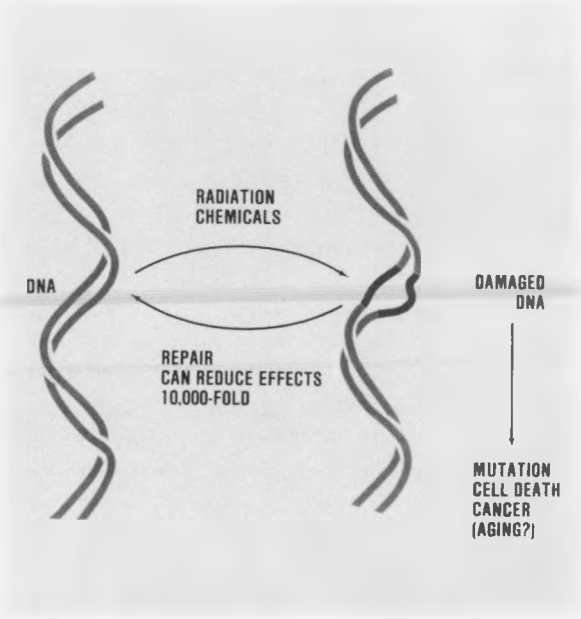
Patterns of DNA sequencing gels used to obtain the sequence of all the nucleotides of the DNA of T7 virus. Each vertical track shows a portion of the analysis used to determine the location of one of the four bases: A, G, T, or C. With practice, one can read these patterns to obtain directly the DNA sequence.



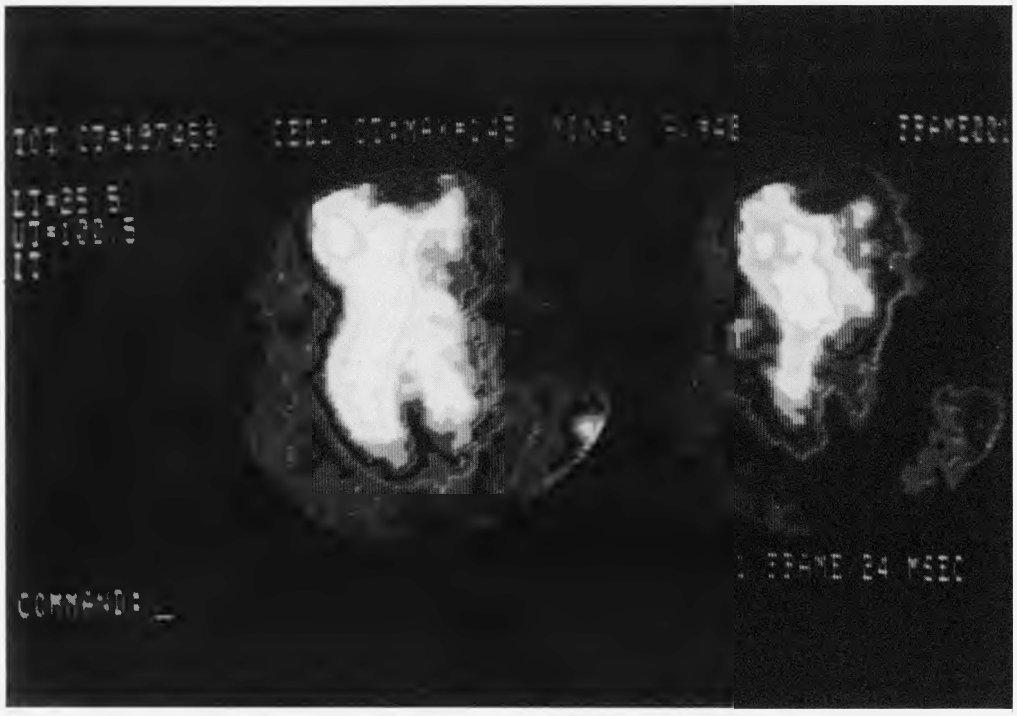
DNA is the most sensitive molecule of the cell and changes in it, as a result of external and internal agents, can result in a variety of biological effects. Cells contain many repair systems that reverse these damages and so mitigate the biological effects. Cells deficient in repair systems are much more sensitive to the deleterious effects of environmental agents.

Medical Department

Research on Radiolabeled Cellular Blood Elements

Various blood cells labeled with radionuclides such as ^{99m}Tc and ^{111}In have become important clinical and research tools for diagnostic imaging and for the study of cell physiology in health and disease. An ongoing effort at BNL has involved the development of precise and convenient methods for labeling red blood cells (RBC, leukocytes, (white blood cells, WBC) and platelets with ^{99m}Tc, the most desirable imaging radionuclide. This research has required extensive mechanistic work and has resulted in the development of a clear understanding of the chemistry and biochemistry of the cell labeling process thus leading to many practical and reproducible "kit" methods that give precise and quantitative diagnostic information.

For blood pool imaging, especially as required to diagnose heart disease, technetium-99m-labeled RBC are usually routinely in hundred of thousands of patients each year. Existing labeling methods are cumbersome, require prior cell separation by centrifugation, extensive washing of cells, and the absence of plasma for satisfactory labeling. The new BNL kit method developed recently in our program offers a number of advantages: (i) Small whole blood samples can be used and there is no need for RBC separation by centrifugation and cell washing; (ii) One-container operation allows



Left anterior oblique (LAO) projection images of the heart blood pool in end diastole (left) and end systole (right), obtained in a patient following the injection of technetium-99m-labeled red blood cells. The cells were labeled using a 1 ml sample of the patient's whole blood with the new BNL kit method. Images such as these provide important diagnostic information (e.g., left ventricular function, wall motion abnormalities, etc.) to the physician. This study was done in collaboration with the State University of New York Hospital at Stony Brook.

better maintenance of aseptic conditions; and (iii) since the cells stay in their native plasma environment, technique-related damage is virtually eliminated.

A Phase I clinical investigation sponsored by Mallinckrodt, Inc. was recently completed at BNL. This company was earlier granted an exclusive license to further develop and market this kit. Blood pool images (including list modes and multiple gated acquisition studies of the heart), quantitative whole body scans, and regional organ counting for kinetics and dosimetry, were obtained. No adverse reactions or toxicological effects were evident. The images were of excellent quality and allowed good quantification for radiation dose estimates.

Since the new BNL kit method offers greater convenience, simplicity, high labeling efficiency, and greater *in vivo* stability of the label, and is expected to potentially replace all other existing methods for technetium-99m-RBC labeling. Mallinckrodt, Inc. who have supported further research on this method are now sponsoring widespread Phase II and III clinical trials.The kit is expected to become commercially available following FDA approval in late 1989.

Previous attempts to label WBC and platelets with ^{99m}Tc have had limited success particularly with regard to labeling efficiency and/or in-vivo stability of the labeled cells. Our detailed mechanistic investigations have led to a new kit method which allows convenient and efficient labeling of WBC and platelets. The method that utilizes stannous glucoheptonate for cell "tinning" is effective using small (4 ml) blood samples, works well with mixed WBC, or separated polymorphonuclear leukocytes, lymphocytes, or platelets, and is equally effective for human, dog, rabbit, and rat cells. The in-vitro and in-vivo stability of the label are higher than previously achieved. Although some improvements are still necessary, preliminary experiments in animals have shown sufficient promise to warrant future evaluation in patients with abscesses, inflammation, and platelet-active lesions, including blood clots.

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Radiolabeled Monoclonal Antibody Immunoconjugates for Imaging and Therapy

There has recently been a large surge of research activity in the area of radiolabeled monoclonal antibodies because of their potential as specific carriers of diagnostic and therapeutic radionuclides to tumors in vivo. The potential extends to non-neoplastic lesions as well. For example, we have recently demonstrated the effectiveness of a radiolabeled antiplatelet antibody for prompt localization by imaging of venous and arterial clots including coronary thrombi in dogs.

Even though the progress has been impressive, several problems remain to be solved. A main issue relates to the influence of chemical manipulations required for radiolabeling on the specificity, in-vivo stability, and tumor uptake of the labeled immunoconjugates. To date most imaging studies with antibodies have used iodine or indium radionuclides. However, radioiodinated antibodies often lose their iodine label in the body leading to non-specific uptake, while there is a high liver and whole body retention of indium when indium labels are used. We are evaluating ^{203}Pb as a better alternative to iodine and indium for imaging. We have demonstrated that ^{203}Pb conjugated via various polyaminocarboxylates to an anticolon carcinoma antibody has much faster liver and whole body clearance than compar-

able ^{111}In preparations. A new series of chelating agents based on cyclohexyl polyaminocarboxylates is being synthesized to provide stronger complexing ability for lead (and other radiometals) and greater in-vivo stability. The new agents will undergo preclinical and clinical evaluation using the in-house SPECT and other facilities.

In order to better determine radiation dose for radioimmunotherapy, we have begun a systematic investigation of positron labeled monoclonal antibodies. Since PET has advantages in the areas of resolution, quantification, and sensitivity over conventional single photon imaging, it is expected that development of positron labeled antibodies will lead to promising new agents not only for quantitative dose assessment and imaging of tumors, but also for studies to better understand the biochemistry of these disease states. These studies have continued in collaboration with the PET group of the Chemistry Department.

Antibodies labeled with therapeutic nuclides would allow the selective delivery of a tumoricidal radiation dose. Since many antibodies required 1-3 days to reach maximum tumor uptake, it isa advantageous to use a radionuclide which has a half-life that matches the antibody uptake kinetics. Unfortunately, because of an inverse relationship between half-

Brookhaven scientists controlling the processing of radioisotopes produced by the Brookhaven Linac Isotope Producer (BLIP). Isotopes for radiodiagnostic and radiotherapy research are produced and developed at Brookhaven. Where commercial facilities for the production of isotopes are not available, they are produced by the BLIP facility for distribution by pharmaceutical companies. Many of these radionuclides have spatial characteristics of properties that make them attractive for use as agents for labeling monoclonal antibodies for both imaging as well as therapy applications.

life and beta decay energy there are not many attractive candidates which have both a high energy beta emission dose useful for therapy and the appropriate half-life. Our recently developed in-vivo generator concept involves the labeling of an antibody with an intermediate half-life radionuclide which decays in vivo to a much shorter lived radioactive daughter. Since the daughter will be in equilibrium with the parent in-situ, it is a localized source of high energy beta emission — essentially an in-vivo generator. This approach circumvents the limitation of the straightforward method used to date. Theoretical modeling has demonstrated the feasibility of the concept and will be used to guide experimental work in this area. The modeling has shown that an improvement in the ratio of tumor dose to background dose, extremely important for successful therapy, may be achieved with this method.

Another novel approach to radioimmunotherapy is currently being investigated in collaboration with the Biology Department. The method involves covalently linking stable clusters of gold atoms to antibodies and antibody fragments in such a way that full antigenic specificity and capacity are preserved [Hainfeld, et al., Science, 236: 450 (1987)]. With existing methods only a small number of radioactive atoms can be attached before antibody specificity is reduced or lost. This limits the radioactive dose which can be delivered to tumor cells for radioimmunotherapy. By using cluster chemistry, 11 (and perhaps 55) gold atoms can be covalently attached as an entity at a site on the antibody which is at the opposite end from the antigen combining region. Gold-199 is an attractive therapeutic radionuclide because of its 3.1 day half-life, intermediate energy β-emission, and an imageable gamma ray. It can be made at BNL with high specific activity for more effective radioimmunotherapy. Preliminary work, using an anticolon carcinoma antibody conjugated with an 11-gold atom cluster showed good preservation of antigen binding specificity. Studies in animal tumor models are presently underway.

There are many unique facilities and areas of scientific expertise at BNL that constitute a very fertile environment for carrying out research on radiolabeled antibody immunoconjugates for both diagnosis and therapy. Unique isotope production facilities include the Brookhaven Linac Isotope Producer (BLIP), the High Flux Beam Reactor (HFBR), and various cyclotrons. High radiation processing hot cells, well equiipped radiochemical and radiopharmaceutical laboratories, extensive animal testing and clinical facilities complement the isotope production capabilities and the scientific expertise that exist in the BNL Medical Department to carry out research on radiolabeled monoclonal antibodies.

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Chemistry Department

The Protein Data Bank

The Protein Data Bank (PDB) was established in 1971 as a computerized archive for three-dimensional structures of biological macromolecules. The PDB collects and distributes atomic coordinates, structure factors, bibliographic citations and other information related to structural studies. The format adopted by the PDB has been accepted in the field as a standard for interchange of atomic coordinates. A notable advantage of this format is that users need not be familiar with the details of crystal coordinate systems because data is transformed to a conventional orthogonal coordinate frame. Nomenclature standards adopted by the IUPAC-IUB have been followed through the entries. A detailed description of the Data Bank's format and operations may be found in the document, "Protein Data Bank Atomic Coordinate and Bibliographic Entry Format Description".

The impact of this detailed structural information in chemistry and biology has been enormous; it has been essential in the development of an understanding of many biological

Protein Data Bank staff.

processes on the molecular level. As the number of known protein, nucleic acid, virus and polysaccharide structures has increased, the computer-based file has become indispensable and provides the only practical means to ensure that the structural data are preserved and made available to the scientific community.

At present some 2400 biological macromolecules are reported to have been crystallized, of which approximately 600 have structures determined to sufficient resolution that an atomic model has been generated. The PDB currently holds over 400 coordinate entries, with bibliographic entries for many of the remaining structures. Most of the information in the PDB is derived from crystal structure determinations but, in addition, several structures based on solution NMR studies are included, as are coordinates for a number of model structures predicted from theoretical studies.

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BNL Cyclotron-PET Center

The Cyclotron-PET Center is a regional center established and dedicated to the development and application of positron emitter labeled radiotracers to problems in biology, biochemistry and medicine. Major areas of focus include (1) basic research on production of the positron emitters ^{11}C, ^{13}N, ^{15}O and ^{18}F and on new methods for rapid radiotracer synthesis; (2) the design and validation of new highly selective radiotracers for probing biochemical transformations in vivo and (3) basic and clinical PET (Positron Emission Tomography) studies to further the understanding of human biochemistry and physiology and therapeutic drug mechanism and to enhance diagnostic capability in Schizophrenia, and other psychotic disorders, Parkinson's Disease, Alzheimer's Disease, tumors of the brain and drug dependency.

The Center is composed of two units, the Cyclotron Facility and the PET Facility. The Cyclotron Facility consists of the following components, (a) the BNL 60-inch Cyclotron, (b) the JSW 168 Small Medical Cyclotron and (c) adjoining laboratories for target processing, radionuclide analysis, radiotracer and radiopharmaceutical development and production.

The 60-inch Cyclotron is a four particle, variable energy machine which can accelerate protons, deuterons, helium-3 and helium-4(alpha) particles. The characteristic beams are: protons, 10-34 MeV, 40μA; deutrons, 17-23 MeV, 40μA; helium-3, 30-65 MeV, 10μA and helium-4, 34-46 MeV, 10μA. This machine is used for the production of isotopes which cannot be produced by the smaller machine such as ^{211}At, ^{123}I and ^{75}Br and for non-production quantities of the positron emitters, carbon-11, fluorine-18, nitrogen-13 and oxygen-15.

The JSW 168 Medical Cyclotron is a two particle fixed energy machine with characteristic beams of 17 MeV protons and 10 MeV deuterons at an external current of)50μA. This machine is used primarily for the production of large quantities of positron emitters which can be incorporated into radiotracers and radiopharmaceuticals to probe biological and physiological processes in human and animal studies withPET.

The PET facility located adjacent to the cyclotrons, has two tomographs (scanners), the PETT VI and the CTI 931. The PETT VI is a four ring seven slice instrument with 0.95 cm transverse and 1.4 cm axial resolution and uses cesium fluoride crystals in its detectors. This tomograph is used for scanning the head only.

The CTI 931 is a whole body scanner with eight crystal rings providing 15 slices with 6 mm transverse and 6.5 mm axial resolution. The PET facility has a small laboratory for blood sample analysis and counting and a patient preparation room.

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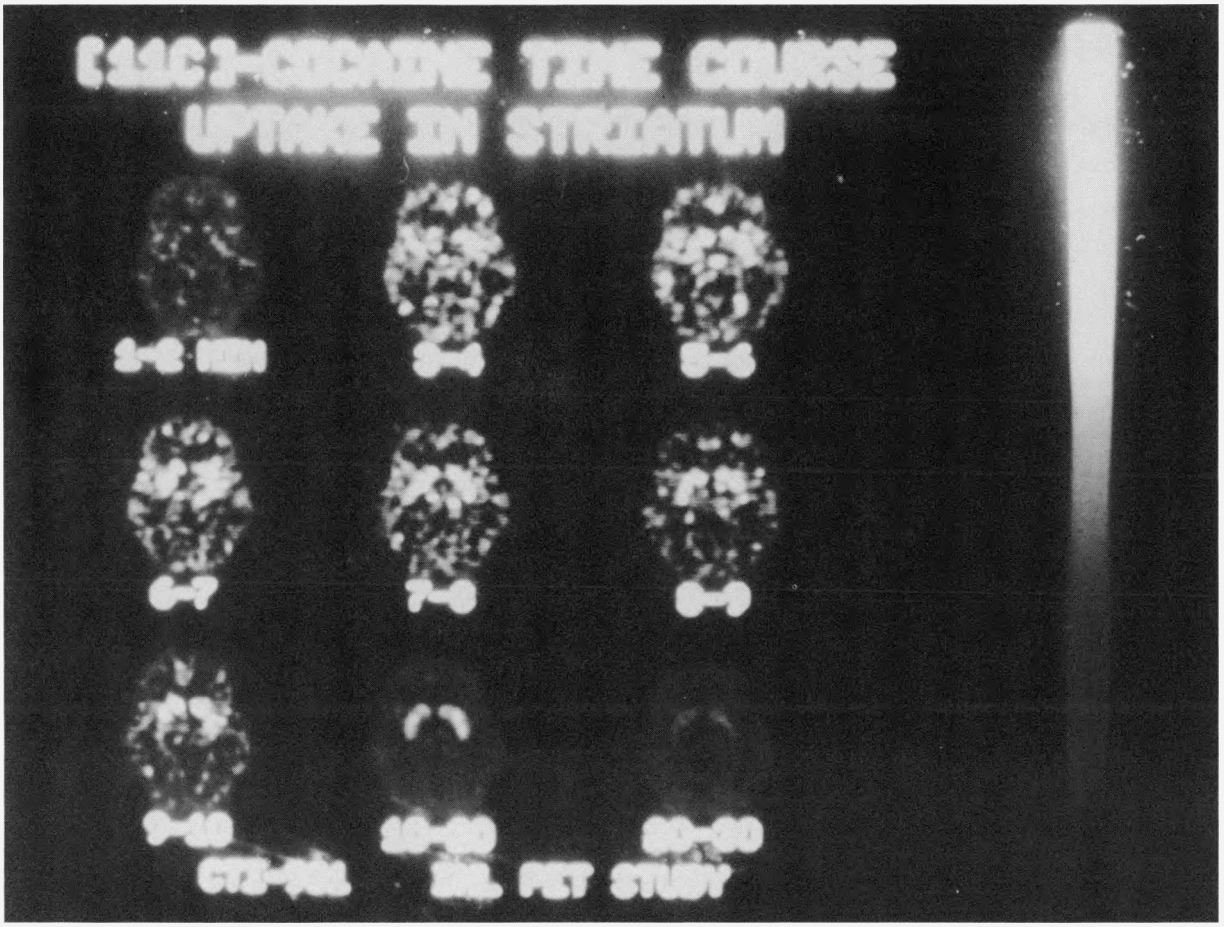
PET Studies of Cocaine Abuse



PET scan images represent the localization of tracer doses of carbon-11 cocaine in the human brain at the level of the striatum. Maximum concentration of the radioactive cocaine in the striatum occurred between 4-6 minutes after administration, the same time at which the most intensive behavioral effects of intravenous cocaine are observed.