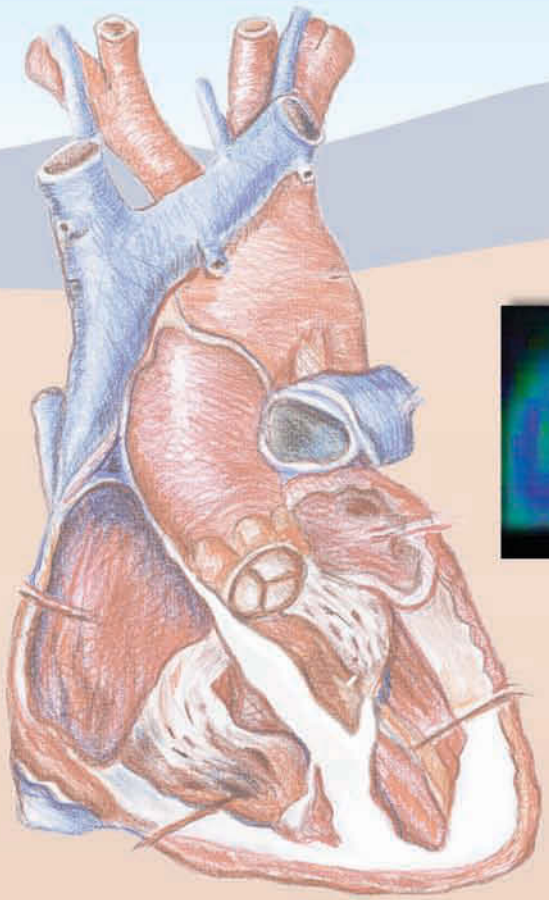
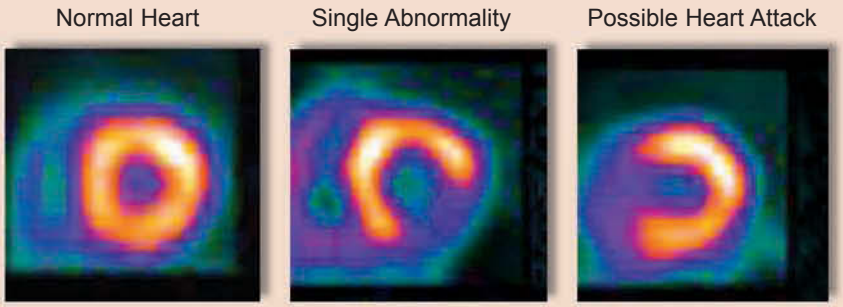


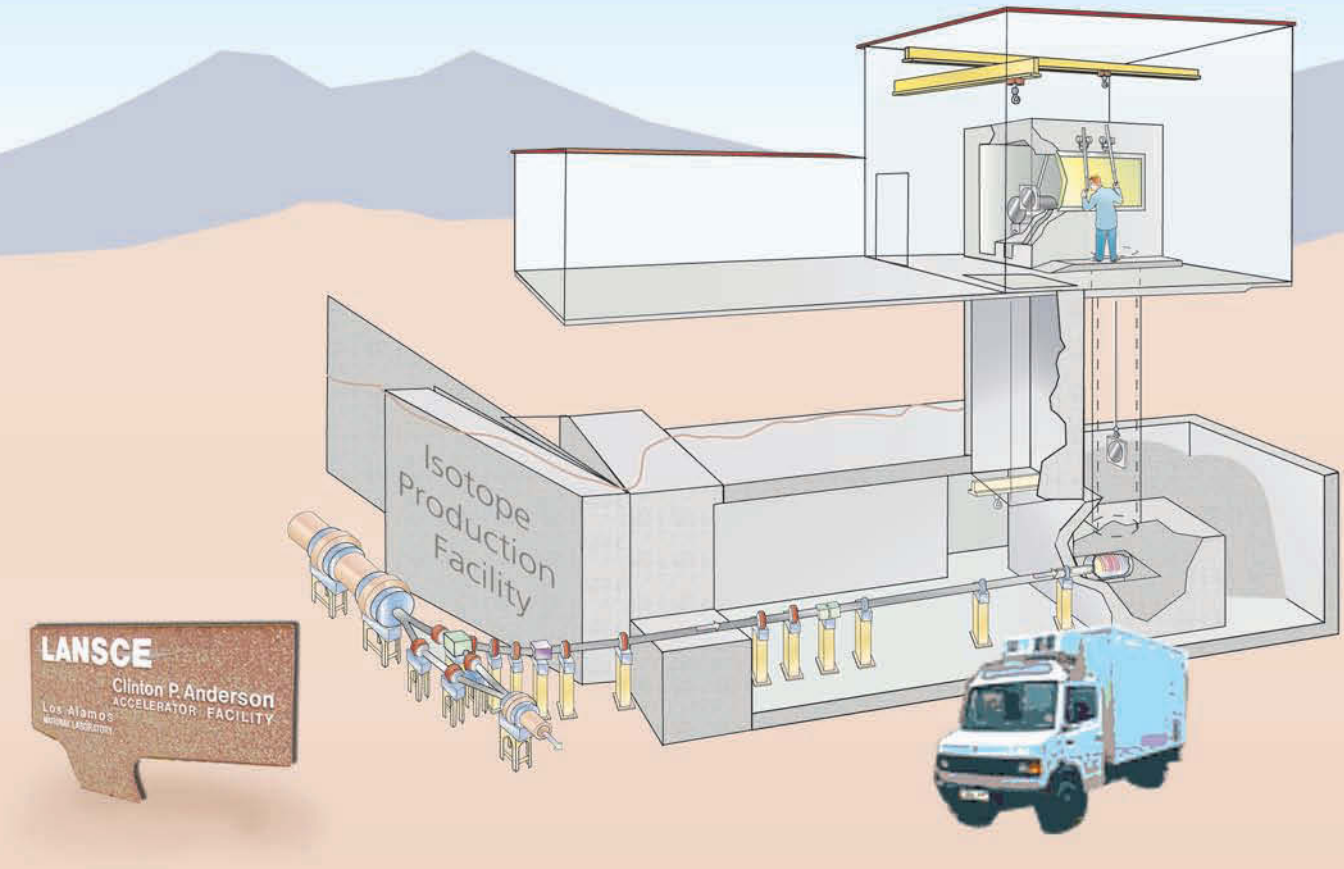


Accelerator Radioisotopes Save Lives

The Isotope Production Facility at Los Alamos

Eugene J. Peterson

On April 11, 2005, the new Isotope Production Facility (IPF) at the Los Alamos Neutron Science Center (LANSCE) delivered its first commercial product, 4.5 curies of the radioisotope strontium-82, to General Electric Healthcare. Strontium-82 is the source for an ideal tracer used in scanning the heart by positron emission tomography. Every month, a supply of 4.5 curies makes it possible for 6,000 patients to receive this potentially life-saving procedure. But strontium-82 is only one of many radioisotopes produced at LANSCE. A whole range of products has been made available by the scores of scientists, engineers, and technicians who have developed new radioisotopes and increasingly sophisticated ways of using them. They have designed the Los Alamos state-of-the-art irradiation facility for an entirely safe, perfectly orchestrated production process. Together with the isotope facility at Brookhaven National Laboratory, the IPF will ensure a steady year-round supply of radioisotopes for medicine, biomedical research, threat reduction, and research into nuclear weapons and fundamental science.



Isotopes of a given element are atoms whose nuclei contain the same number of protons (known as the atomic number, *Z*) but different numbers of neutrons. Therefore, they are chemically alike but have different atomic masses and different nuclear properties. Every chemical element has one or several isotopes, which can be stable or unstable. Whereas the nuclei of stable isotopes remain unchanged indefinitely, the nuclei of unstable, or radioactive, isotopes disintegrate spontaneously, emitting radiation as they transmute into other isotopes, often of different chemical elements. It is the radiation they emit that makes "radioisotopes" useful for medical applications—both for imaging specific organs for diagnostic purposes and for treatment of diseases such as cancer. Radium was the first isotope used for cancer treatment at the beginning of the 20th century, and its success was much publicized. However, at that time, radioactivity was still a novelty, and some thought that the healing powers of radium were unlimited. And so, radium was soon advanced as a miracle cure for every ailment and was used indiscriminately. Unfortunately, the long half-life (1600 years) of this radioisotope led to its silent accumulation in the body and, eventually, to numerous deaths. Since that time, it has been known that, to be suitable for medical treatment and imaging, radioisotopes must be short-lived. Short half-lives maximize the radioisotopes' effectiveness during the limited time of a medical procedure and minimize their side effects to nontargeted organs. Typical half-lives of medical radioisotopes are as long as weeks, days, hours, or even minutes, which means that an administered dose decays away in times of that order (see the box "Radioisotopes: Production, Decay, and Half-Life" on the next page). It is clear that, if the medical procedures they support are to be widely available, medical radioisotopes must be produced artificially on a more or less continuous basis. Today, the demand is increasing as about one in three hospitalized patients requires a medical procedure involving radioisotopes.

Artificial production of radioisotopes for medicine first began at Berkeley Lab in the 1930s, soon after the invention of the cyclotron. Iodine-131, for example, was produced in small quantities by bombarding tellurium with deuterons, 8 million–electron volts (MeV) in energy, at Berkeley's 37-inch cyclotron. This radioisotope was used to treat small numbers of thyroid cancer patients. The first large-scale radioisotope production was a spinoff from the development of nuclear energy and nuclear weapons during World War II. In the 1940s, radioisotopes were produced at both nuclear reactors and cyclotrons. Beginning in the 1950s, increasingly high-energy particle accelerators, built by the Department of Energy (DOE) primarily for studies of the fundamental makeup of matter, have also been used to produce radioisotopes for clinical medicine, as well as for research and development. Indeed, since the 1940s, the widespread availability of

medical isotopes and the growth of the radiopharmaceutical industry have been largely a result of successful technology transfer from the DOE and its predecessors, the Atomic Energy Commission and the Energy Research and Development Administration.

Radioisotope Production at Los Alamos

Los Alamos National Laboratory has had a long and prominent tradition in radioisotope production for medicine, biology, and nuclear physics. Beginning in 1974 and up until November 1998, the isotope production station was located at the very end of the proton beam line of what was once the Los Alamos Meson Physics Facility (LAMPF) and later became the Los Alamos Neutron Science Center (LANSCE). There, medium-energy protons—with energies of 800 MeV—were used to irradiate specially designed targets. Following irradiation, the highly radioactive targets were sent to the Laboratory's Chemistry Division, where a special hot-cell facility enables remote handling of the radioactive target materials during chemical separation, processing, and packaging of the radioisotopes of interest. The most important radioisotopes for medicine being produced at Los Alamos were germanium-68, used for calibrating positron emission tomography (PET) scanners; strontium-82, the parent of the very short-lived rubidium-82, used for PET scans of the heart; and the short-lived copper-67, used for research on cancer detection and therapy.

In 1998, as a result of changing programmatic requirements, delivery of the H^+ beam at LANSCE stopped. The Los Alamos Isotope Program would have come to a halt but for the enterprising spirit of the scientists. Through international collaborations, the program continued to be a supplier of germanium-68, strontium-82, and other isotopes with half-lives greater than 15 days in spite of not having its own irradiation facility. Targets were irradiated abroad and returned to the Los Alamos hot cell facility in the Chemistry Division building for chemical separations, purity checks, and delivery of final products to industrial partners.

In the meantime, a proposal for a new target irradiation facility was put forward and was soon approved for LANSCE. Its construction, funded by the DOE Office of Nuclear Energy, Science, and Technology, was started in 1999 and completed in 2003 at a cost of $23.5 million. Having been successfully commissioned—all the

Medical Radioistopes: Production, Decay, Source, and Half-Life

Production. An isotope with atomic mass A and atomic number Z, ${}^{A}N_{Z}$, has a nucleus consisting of Z protons and $A–Z$ neutrons held together by the strong force. That isotope can be transmuted to another isotope by bombardment with either protons or neutrons. The nuclear reactions that occur depend on the identity and energy of the incident particle.

A proton with an energy of up to 100 MeV will typically cause the target nucleus to emit one or more neutrons, producing an isotope of the next higher element (atomic number $Z + 1$) with an atomic mass equal to or lower than that of the original nucleus. The general form of the reaction for one proton absorbed and x neutrons released is

$$p + {}^{A}N_{Z} \rightarrow {}^{A-x+1}N_{Z+1} + xn \quad . \qquad (1)$$

The shorthand for this reaction is ${}^{A}N_{Z}(p,xn){}^{A-x+1}N_{Z+1}$. This reaction indicates that protons tend to produce neutron-deficient isotopes.

At higher energies, the protons cause nuclear spallation, in which lighter nuclides break off from the nucleus or from large numbers of neutrons and protons evaporate from the surface.

A neutron with an energy of up to a few million electron volts will typically be captured, producing a heavier isotope of the original element:

$$n + {}^{A}N_{Z} \rightarrow {}^{A+1}N_{Z} + \gamma s \quad . \qquad (2)$$

This reaction indicates that neutron capture reactions tend to produce neutron-rich isotopes.

Radioactive Decay. Often the isotopes produced by bombardment with neutrons or protons are radioactive; that is, they are unstable and spontaneously decay, or transmute, to a new isotope through the emission of radiation. Typical radiation emitted in radioactive decay includes alpha particles, which are just helium nuclei (${}^{4}He_{2}{}^{++}$), beta particles, which are either electrons or positrons; gamma rays, which are very high energy x-rays; and neutrinos, which pass through most materials without interacting with them. The energies of alphas, betas, and gammas are typically quite high, and they cause ionization as they pass through matter, which may result in permanent damage, especially to live cells. As shown in Figure A, the two most common decay reactions are alpha and beta decay:

α-decay: ${}^{A}N_{Z} \rightarrow {}^{A-4}N_{Z-2} + {}^{4}\mathrm{He}_{2}^{++}$. (3)

β-decay: ${}^{A}N_{Z} \rightarrow {}^{A}N_{Z+1} + e^{-} + \bar{\nu}_{e}$, or (4)

${}^{A}N_{Z} \rightarrow {}^{A}N_{Z-1} + e^{+} + \nu_{e}$.

Each radioisotope has a characteristic decay mode and thus emits a particular type of radiation. Radioisotopes that emit alpha particles or electrons are used for cancer treatment because those particles deposit their energy in very short distances. Radioisotopes that emit positrons or gamma rays are used for imaging specific organs and physiological processes. [The positron does not travel far because it annihilates with a nearby electron (its antiparticle), producing two gamma rays that go off in opposite directions and are easily detected by detectors used in PET scanners.]

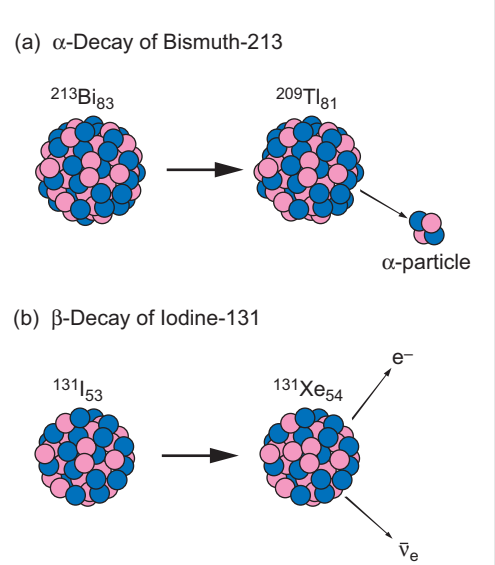


Figure A. Examples of α- and β-Decay

Radioactivity of a Source. The activity of a radioactive source is a measure of its intensity and is equal to the number of atoms decaying each second. Radioactivity is measured in curies. A curie is the number of decays per second in 1 gram of radium and is equal to 3.7×10^{10} decays per second. The more atoms in the source and the shorter the half-life of the source, the higher its radioactivity.

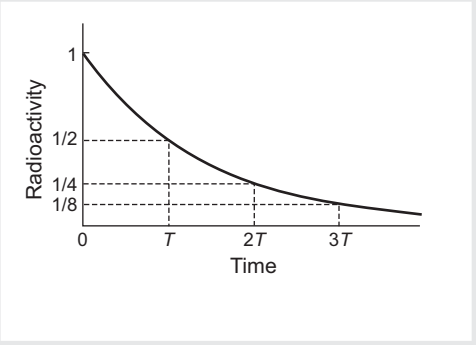


Figure B. Exponential Decay of Radioactivity

Radioactive Half-Life. Radioactive decay is a quantum mechanical process; one cannot therefore predict when a particular atom will decay. What can be known is the decay rate, or probability for decay per unit time. That probability is intrinsic to the radioisotope and remains constant in time. Rather than specifying the decay rate of a radioisotope, it is customary to give its half-life T—the time during which an individual atom has a 50 percent chance of decaying. Thus, as shown in Figure B, if there is a collection of identical radioactive atoms, then after one half-life, half of the atoms will have decayed; during the second half-life, half of the remaining half will have decayed, leaving only 25 percent of the original number, and so forth. This exponential fall-off in the number of atoms continues, and after seven half-lives, about 98.8 percent of the original number will have decayed away and become another isotope. Radioisotopes used in medicine are chosen, in part, because they have short half-lives and decay to stable, benign isotopes.

design goals were met or exceeded—the new facility became fully operational in the spring of 2004, and the Los Alamos Isotope Program returned to being a self-contained source of radioisotopes, ready to meet the needs of clinical medicine, as well as those of the biomedical, environmental, biological, nuclear physics, nuclear weapons, and homeland security communities.

Design of the New Isotope Production Facility

The Los Alamos state-of-the-art Isotope Production Facility (IPF) was designed to make isotope production more efficient, as well as completely reliable and safe. The new IPF is located near the beginning of the linear accelerator (Figure 1), where 100-MeV protons are diverted to the facility. This lowering of the incident-proton energy from 800 MeV at the old facility to 100 MeV at the new one has resulted in a more efficient process for isotope production.

Bombardment with 800-MeV protons causes nuclear spallation reactions that leave behind a very wide array of isotopes, as protons smash

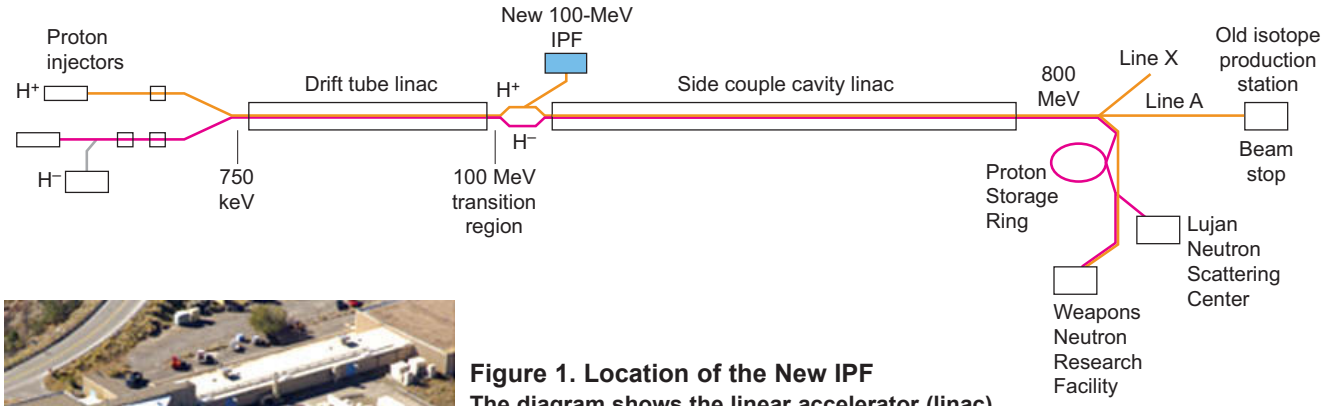


Figure 1. Location of the New IPF
The diagram shows the linear accelerator (linac) at LANSCE and the locations of both the old isotope production station at the end of the proton beam line and the new IPF, located alongside the accelerator between the Drift Tube Linac and the Side-coupled Cavity Linac. At that point, protons, which have been accelerated to energies of 100 MeV, are diverted to the IPF. The photo shows the exterior of the new IPF.

into target nuclei, sometimes causing chunks of a nucleus to break off and sometimes causing large numbers of neutrons and smaller numbers of protons to evaporate from the nuclear surface. Separating the desired isotopes from the unwanted ones is chemically challenging and time consuming. Only small quantities of the desired isotopes are produced; the radioactive waste, on the other hand, is considerable and must be carefully disposed of. By contrast, when 100-MeV protons hit target nuclei, they release primarily neutrons and occasionally protons and alpha particles, yielding much greater amounts of the desired isotope and lesser amounts of byproduct isotopes and involving a much easier chemical-separation task. Figure 2 illustrates the nuclear reaction processes occurring at 800 MeV and 100 MeV.

Designing for Safety. The IPF is a radiological facility in which irradiation with protons causes not only the targets but also the environment around the targets to become radioactive. Therefore, our first priority throughout the design and construction phases was to create an environment where workers would be safe during all operations. Ease of pre-

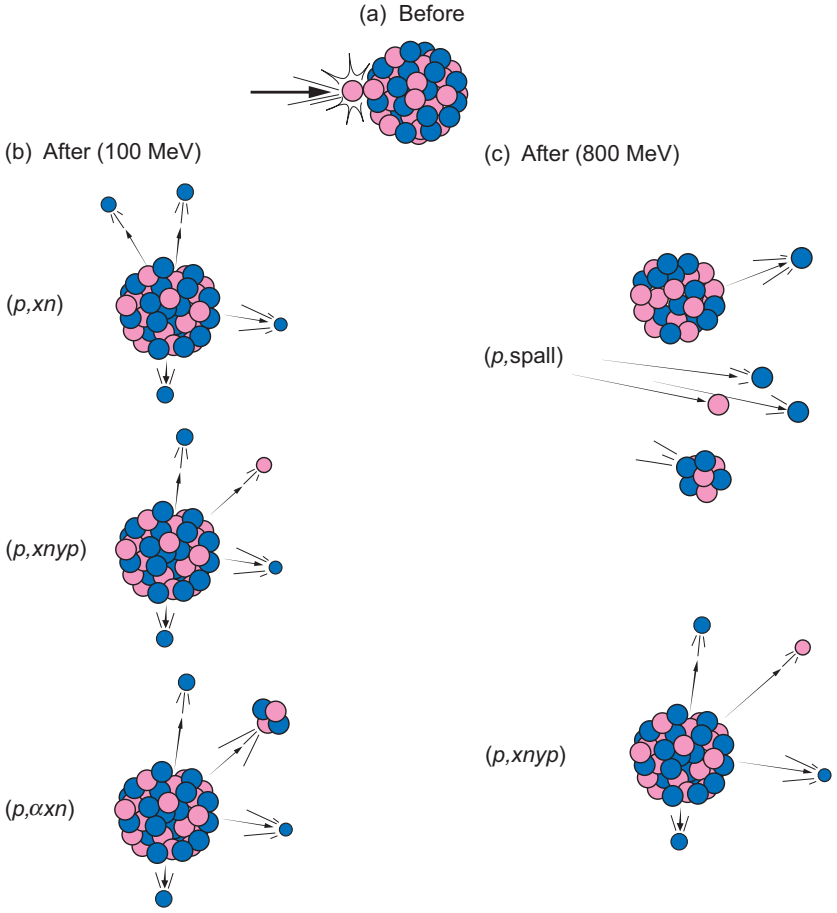


Figure 2. Proton-Induced Nuclear Reactions at 800 and 100 MeV
(a) At 800 MeV, protons induce spallation reactions that break apart the nucleus into chunks or cause large numbers of neutrons and smaller numbers of protons to evaporate from the nucleus. (b) At energies of up to 100 MeV, protons cause the release of one or several neutrons and sometimes the release of a proton or an alpha particle, in addition to neutrons.

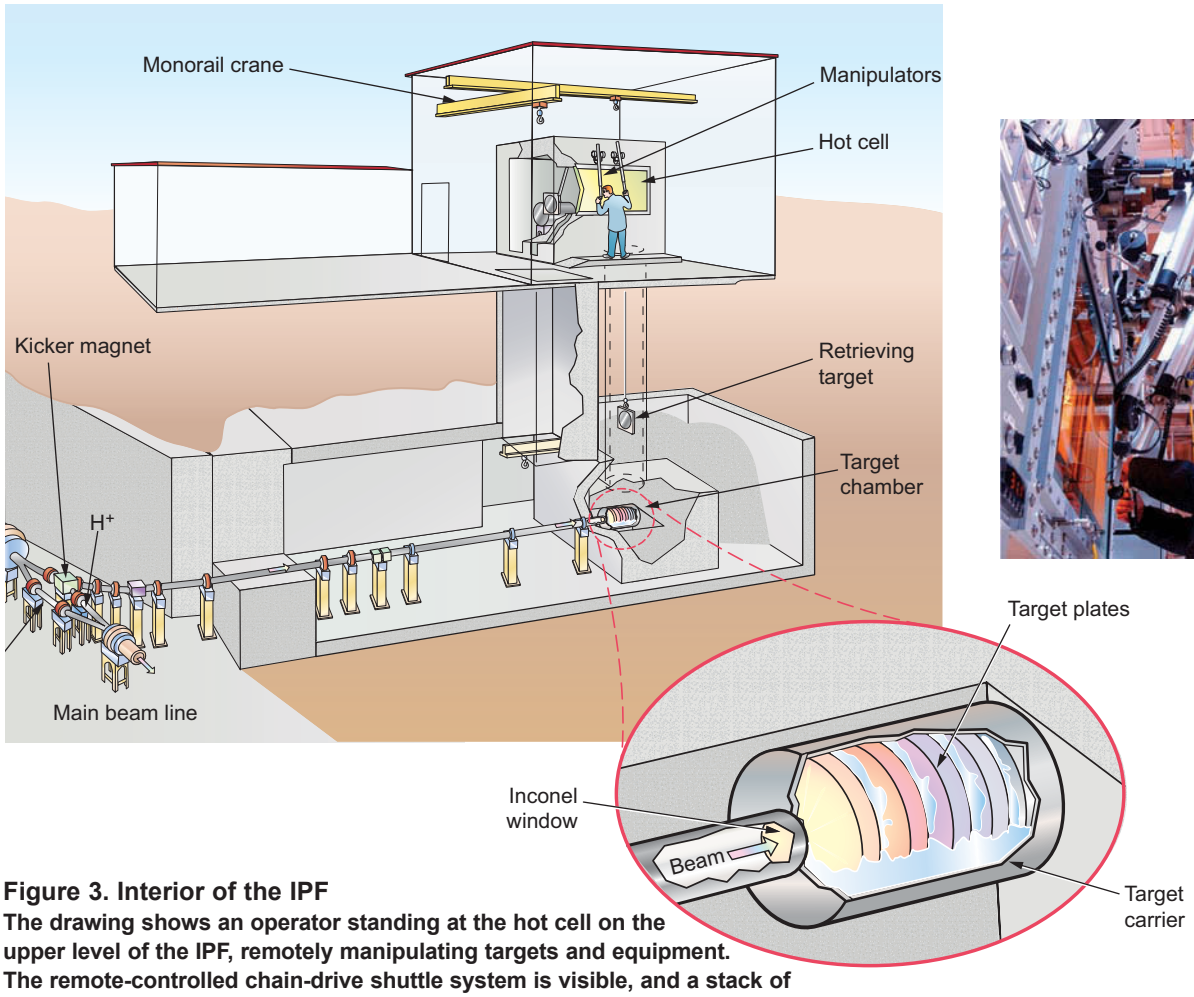


Figure 3. Interior of the IPF
The drawing shows an operator standing at the hot cell on the upper level of the IPF, remotely manipulating targets and equipment. The remote-controlled chain-drive shuttle system is visible, and a stack of targets is in the cave on the lower level, being irradiated with protons. The blowup shows the proton beam entering the target chamber through an inconel window and cooling water flowing through the spaces between the stacked targets. The photo shows a technician remotely manipulating targets in the hot cell.

ventative maintenance and of repair in radiation fields was considered extensively. Although radioisotope production is an inherently dangerous activity, radiation shielding, remote-handling equipment, a closed-loop target-cooling system, and other design features make the facility operationally safe and compliant with all environmental rules and regulations. Moreover, contingency plans ensure that, if anything were to go wrong, safety would not be compromised. For example, multiple safety systems are in place to shut off the proton beam if any facility or irradiation parameters vary from expected values. If an upset condition is detected, the beam is shut off instantaneously.

Because the proton beam line passes 40 feet underground, the IPF was built on two levels (see Figure 3). Belowground is a thick cave of concrete and lead shielding that houses the targets during irradiation by energetic protons and shields the surroundings from harmful radiation; aboveground is a "hot cell" (an enclosure with windows that shields the upper surroundings from radiation) for the remote handling of both the radioactive targets and the equipment that supports the operation of the beam line. A remote-controlled chain-drive shuttle system connecting the hot cell and the cave is used to lower targets into the cave for irradiation and raise them back up to the hot cell, where they are put into heavily shielded containers for transport to the Chemistry Division facilities.

Target Configuration for Maximized Production. The target configuration was designed to maximize production of the desired isotopes. It consists of three disc-shaped targets, each 2 inches in diameter. They are stacked in a carrier. Spacers separate individual targets by 5 millimeters (Figure 4). Stacking allows us to vary the energies of the protons impinging on each target from 10 to 90 MeV. The target carrier fits into a

Figure 4. Target Stack and Carrier
Disc-shaped targets of varying thicknesses and compositions are placed in the carrier (shown here without its upper part). The protons travel from left to right through the target stack and lose energy as they undergo Coulomb scattering in the target materials. Protons strike the first (leftmost), second, and third targets in the stack with nominal energies of approximately 90, 65, and 40 MeV, respectively.

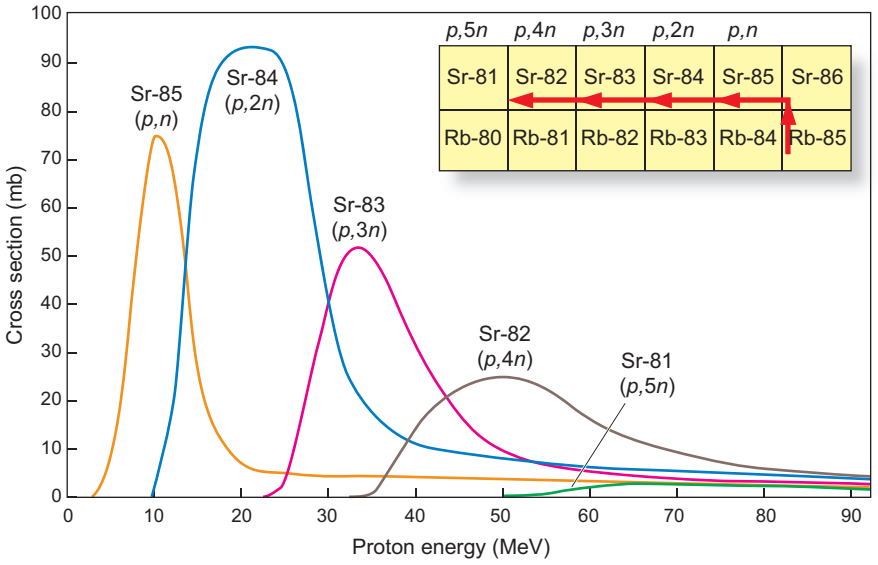


Figure 5. Nuclear Cross Sections for Protons on Rubidium-85
Strontium-82 is made by bombarding with protons the stable isotope rubidium-85. The cross section as a function of energy has a peak at about 50 MeV, and so the rubidium target is placed in the middle of the target stack for maximum production of strontium-82.

target chamber, making a water seal along the chamber walls so that, when the carrier is lowered into the water-cooling loop inside the cave, the full cooling-water stream flows upward along the faces of each target (Figure 3 inset).

During irradiation, 100-MeV protons enter the target chamber through an inconel window and follow successively through the first cooling channel, the first target, the second cooling channel, the second target, the third cooling channel, the third target, and finally, the fourth cooling channel. Target thicknesses are chosen to ensure that protons lose about 20 MeV through Coulomb scattering as they pass through each target. Target positions within the stack are chosen to maximize the rate at which the desired isotope will be produced. For example, when a rubidium-85 target (typically in the form of a chloride) is used to make strontium-82 (the relevant nuclear reaction is p + Rb-85 → Sr-82 + 4n), it is placed in the middle of the stack because the cross section for that production reaction is greatest for incident protons with energies between 45 and 65 MeV. Figure 5 shows the energy-dependent cross sections for protons incident on rubidium-85 nuclei. Isotope production rates for each target are predicted from Monte Carlo and other calculations and depend on the position in the stack, the reaction cross section, and the target thickness. Irradiation times are determined by those production rate calculations and the amount of material that must be produced to satisfy customer requirements for the isotope.

Closed-Loop Cooling System. During the irradiation process, heat is generated at an enormous rate. At a maximum proton beam current of 250 microamperes, the energy loss of 20 MeV per proton translates into energy being dissipated into heat at

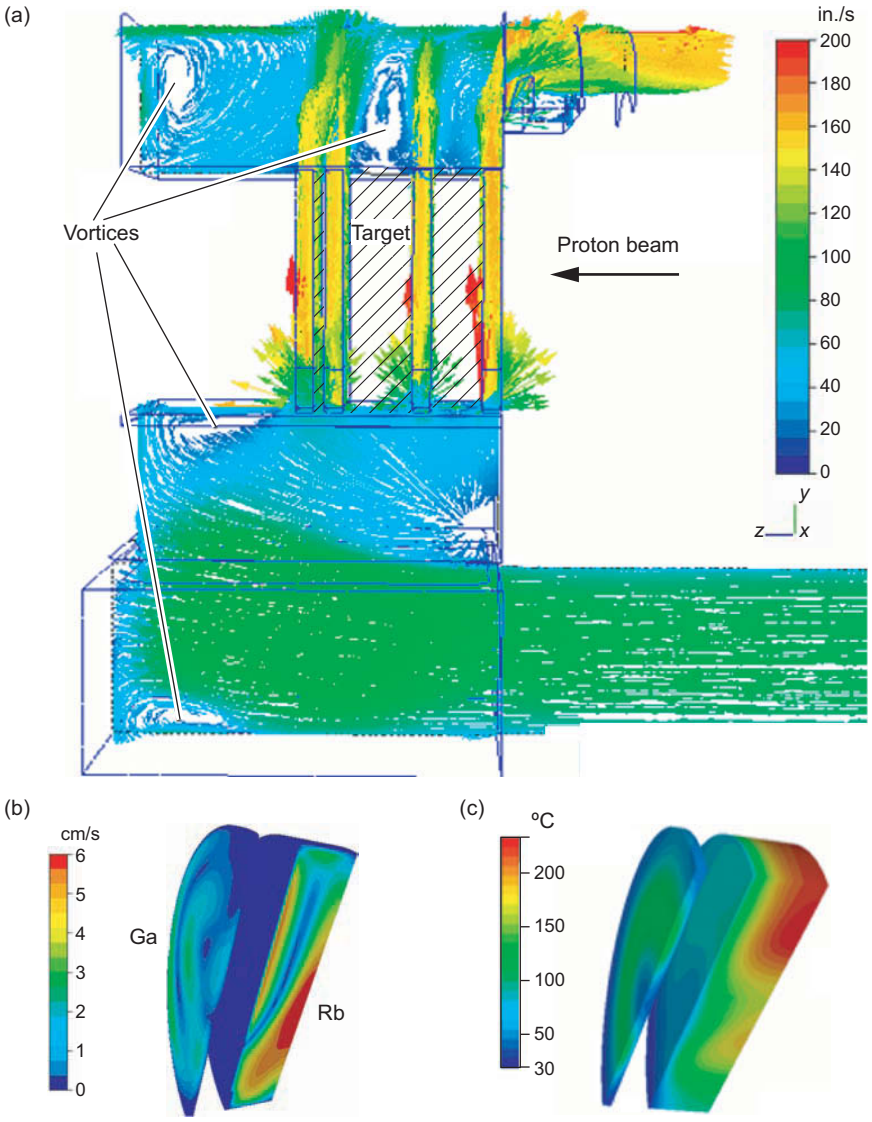


Figure 6. Modeling and Thermal Analysis of the Target-Cooling System
This figure shows calculated results for (a) the temperature of the cooling water as it flows past the targets in a closed-loop configuration, (b) the velocity distributions on the faces of the targets, and (c) the temperature distributions on the faces of the gallium and rubidium targets. Similar analyses are performed for each new set of targets.

an average rate of 5 kilowatts per target. If it were not for the cooling system, which was designed to ensure that the targets withstand this maximum rate of heat generation, target and/or encapsulation materials would melt under bombardment and release radioactive material into the cooling system. As an additional precaution against radioactive contamination, the target-cooling water is circulated in a closed loop to prevent contact with other facility components and the external environment. The final target-cooling configuration is based on extensive modeling using computation fluid dynamics (CFD) and thermoanalysis. For example, calculations showed that sweeping the beam in a circular motion across the faces of the targets rather than keeping the beam stationary would lower the peak power density, and therefore the thermal effects, on the target by a factor of 2. Calculations also showed that maintaining cooling-water velocities through the channels at values ranging between 2 meters per second (m/s) and 4 m/s would prevent boiling, ensure even flow distribution across all four channels, and maintain adequate cooling of all target and beam window surfaces. Each new target material undergoes CFD modeling and thermoanalysis to determine the optimum combination of beam parameters and cooling-water parameters for material survivability. Figure 6 shows some results from the modeling efforts.

Efficient isotope production at the new IPF is only one step in a carefully orchestrated cycle that begins and ends at Los Alamos. This cycle is presented in the box "The Isotope Production Cycle" on the next page.

The Los Alamos Products

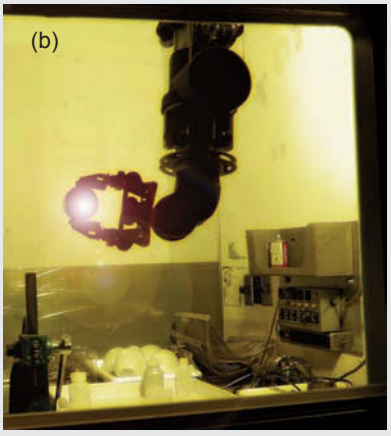
The Los Alamos Isotope Program fills an important niche in the worldwide market by producing isotopes that are either unavailable or not sufficiently available elsewhere. For example, Los Alamos and Brookhaven, two DOE laboratories, are the only domestic manufacturers of germanium-68, which, as mentioned above, is used as a radiation source to calibrate the detection sensitivity and other instrument parameters of PET scanners. Without germanium-68, the scanners would quickly lose their usefulness in clinical settings.

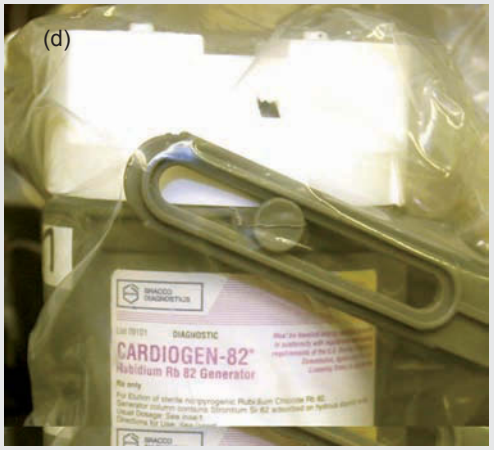
Los Alamos has also resumed its role as a major producer of strontium-82, the isotope that decays to the very short-lived radiotracer rubidium-82, used for diagnosis of heart disease. In fact, the IPF's first commercial product was 4.5 curies of strontium-

The Isotope Production Cycle

After the targets have been irradiated at the Isotope Production Facility (IPF), they are placed into heavily shielded containers. (a) The container pictured here was specially designed and built in the United Kingdom to ensure safe transport of radioactive materials. It weighs approximately 4 tons and is lifted onto a truck for transport of radioactive targets to the primary Hot Cell Facility at the Laboratory's main radiochemistry site.

Los Alamos workers observe strict safety procedures for placing the irradiated targets into the multipurpose "dispensary" cell, where all materials are received and from which all materials leave the radiochemistry site. This cell is connected to 12 processing cells, where the isotopes of interest are separated from the original target materials and byproducts. (b) Remote manipulation of an irradiated target inside a processing cell requires considerable skill, which is acquired during rigorous training over a period of two years. The separation processes follow standard chemical procedures, such as ion exchange, solvent extraction, electrochemistry, and distillation. (c) Inside this cell, strontium-82 is being chemically separated from other target materials.





Typically, after initial separation, the chemical solutions containing the desired isotope are further purified in the radiochemistry and analytical laboratories surrounding the Hot Cell Facility. The isotopes are then put in special packages certified for shipment of radioactive material and taken by regular carriers (for example, Federal Express) to their destination. After the radioactive products have outlived their useful life, they are returned to Los Alamos for disposal or recycling. (d) This photo shows a CardioGen-82® generator of the rubidium-82 tracer used in PET scans of the heart. It was returned to the Laboratory after clinical use, and the strontium-82 remaining may be used in the next generator.

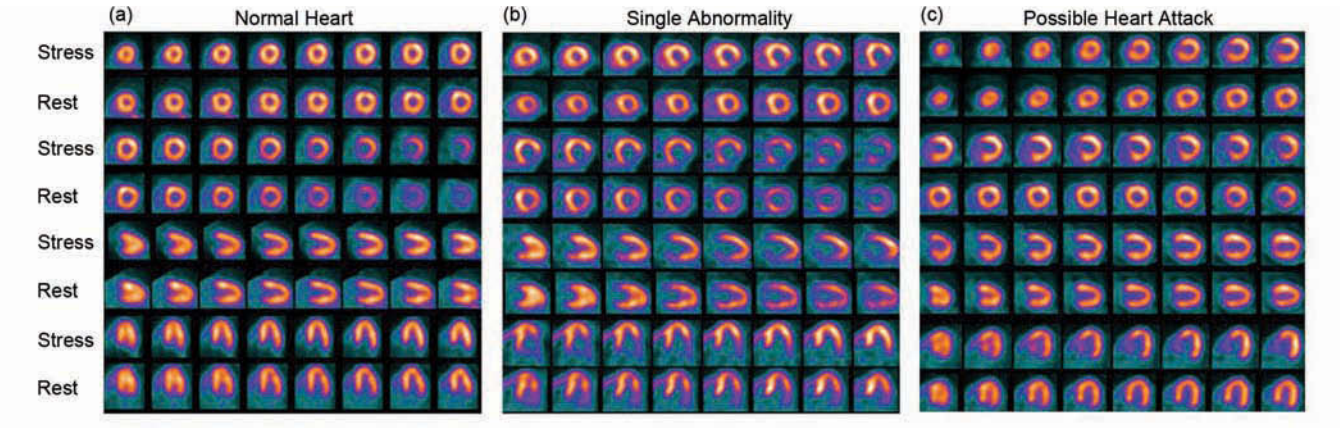


Figure 7. PET Scans of the Heart
These PET scan images of blood flow through the heart show a normal (a), slightly abnormal (b), and severely abnormal (c) heart. The results in (c) indicate the possibility of a heart attack.

82, manufactured at the IPF from a rubidium chloride target. On April 11, 2005, this radioisotope was sent to General Electric Healthcare in South Plainfield, New Jersey, where it was manufactured into approximately 40 biomedical generators, distributed under the trademark CardioGen-82®. Those generators produced enough rubidium-82 for 6000 PET scans of blood flow through the heart.

The generator is basically an ion exchange column on which strontium-82 is immobilized. Strontium-82 (with a half-life of 25.4 days) decays continuously to the daughter rubidium-82 (with a half-life of 75 seconds). Right before a PET scan, the proper amount of rubidium-82 is eluted by pumping a specified quantity of saline solution through the generator: Some of the sodium ions in solution exchange places with rubidium-82 ions on the column. The resulting solution containing the rubidium-82 is injected into a patient's bloodstream.

Rubidium, whose chemistry is similar to that of potassium, is preferentially taken up by the heart. As it travels through the bloodstream and the heart, the rubidium-82 ions decay to the stable isotope krypton-82 as they emit a positron. Each positron annihilates with an electron, producing two gamma rays that go off in opposite directions. By detecting the gamma rays, the PET scanner can reconstruct where the positron originated, and by recording many such decays, the scanner produces a three-dimensional image of the flow of blood in the heart. This procedure is done fast because, within a few minutes, 99.9 percent of the rubidium injected into the bloodstream has decayed to krypton, which is eliminated as a gas through breathing. Because of the very short half-life of rubidium-82, not only does most of it decay within a few minutes, but so many ions are decaying within a short time that this radiotracer produces a strong signal while it passes through the heart and can easily be detected by PET scanners. (Refer to the box below for the reactions involved from the production of strontium-82 to the recording of the PET scan.)

PET studies of myocardial perfusion, or blood flow through the heart, lead to reliable diagnosis of heart function and coronary artery disease (see Figure 7). The PET cardiac procedure distinguishes patients needing further costly intervention from those who do not need such intervention. Translated into economic benefits, the clinical use of the CardioGen-82®/PET procedure leads to more than $10 million in health care economic benefits and untold savings per month through improved cardiac health care. The generator system must be replaced each month because, after one half-life of the strontium-82

Reactions from Isotope Production to Scanning Process

Nuclear reaction produces strontium-82:

$$p + {}^{85}\mathrm{Rb}_{37} \rightarrow {}^{82}\mathrm{Sr}_{38} + 4n \quad (1)$$

Beta decay from strontium-82 produces rubidium-82 in CardioGen-82®:

$${}^{82}\mathrm{Sr}_{38} \rightarrow {}^{82}\mathrm{Rb}_{37} + e^{+} + \nu \quad (2)$$

Beta decay reaction during PET Scan releases innocuous krypton gas:

$${}^{82}\mathrm{Rb}_{37} \rightarrow {}^{82}\mathrm{Kr}_{36} + e^{+} + \nu \quad (3)$$

Positron annihilation produces detectable gamma rays.

$$e^{+} + e^{-} \rightarrow 2\gamma \quad (4)$$

Radioisotopes Produced at Los Alamos and Their Applications

Medicine

Isotope	Half-Life	Application
Strontium-82, parent of rubidium-82	25.5 days	Used in cardiac perfusion studies with PET
Germanium-68, positron emitter	270 days	Used in calibration sources for all PET scanners in clinical use
Copper-67, research isotope	2.6 days	Shows promise in cancer detection and treatment
Rhenium-186, research isotope	3.2 days	In high specific activity, potentially strong cancer-cell killer
Arsenic-72, research isotope	26 hours	Used in PET diagnosis and cancer treatment
Arsenic-76, research isotope	26.4 hours	Used in PET diagnosis and cancer treatment
Bromine-77, one of the halogen isotopes	57 hours	Used as versatile tracer label
Lanthanide isotopes, research isotopes		Great potential in medical and biomedical applications

Weapons Applications

Isotope	Half-Life	Isotope	Half-Life	Isotope	Half-Life
Arsenic-73	80.3 days	Europium-149	1 day to 1 year	Tantalum-179	1.8 years
Rubidium-83	86.2 days	Europium-150	36.9 years	Tungsten-181	130 days
Yttrium-88	106.6 days	Terbium-157	>1 year	Gold-195	186 days
Zirconium-88	83.4 days	Terbium-158	>1 year	Bismuth-207	32.2 years
Rhodium-101	5.27 years	Lutetium-173	1.4 years		
Silver-105	1 day to 1 year	Lutetium-174	165 days		

Homeland Security

Isotope	Half-Life	Isotope	Half-Life
Beryllium-7	53.28 days	Strontium-85	64.8 days
Cobalt-56	77.1 days	Cesium-135	2.3 million years
Cobalt-58	70.9 days	Plutonium-237	45.6 days

(that is, approximately 25 days), the generator is considered expired by guidelines from the Food and Drug Administration.

Los Alamos also produces small quantities of radioisotopes whose possible medical applications are in the earliest stages of exploration, and it supports these efforts by charging the user community only a small fraction of the full production costs. In addition, the Laboratory produces isotopes for research in nuclear physics, biology, nuclear weapons studies, and homeland security. The box above lists a few of the isotopes produced at Los Alamos.

New Tracers, Isotope Availability, and the Future

As the field of nuclear medicine expands and more radioisotopes tailored to solve specific problems are sought, the Los Alamos Isotope Program is in a good position to increase its contribution to both the production of new radioisotopes and the development of new chelating agents that can bind those isotopes and serve as the delivery system to target organs or target molecules.

The Materials Test Station (MTS), which will be constructed at the end of the linear accelerator, offers several opportunities for Los Alamos to produce an expanded portfolio of isotopes. Targets could be placed in

the intense 800-MeV proton beam reaching the MTS, as well as in the very high flux of spallation fast and slow neutrons that will be generated at the MTS. Irradiation with 800-MeV protons would induce nuclear reactions of the type (*p,xnyp*) and produce neutron-rich isotopes, many of which cannot be produced in a reactor. Irradiation with neutrons at positions available at the MTS can be used to produce large amounts of isotopes, typically produced in reactors, that are not available commercially.

Another opportunity on the horizon is the production of multicurie amounts of high-specific-activity isotopes such as copper-67. Copper-67 (with a half-life of 2.6 days) is a promising medical isotope because it emits an energetic electron (0.6 MeV) that may be useful for cancer therapy, and it also emits a photon that has an energy of 184 kilo–electron volts and can be used to image tumors and assess therapeutic progress. During the 1990s, experiments and a brief human trial supported by the Los Alamos production of copper-67 at LANSCE tested the use of a monoclonal antibody labeled with copper-67 to treat non-Hodgkins lymphoma. The results suggested a high uptake ratio in the cancer tumors relative to the uptake ratio in other tissues. At the time, availability of copper-67 was too sporadic to support continued trials. The new IPF is very well configured to produce multicurie amounts of high-specific-activity copper-67 once isotopically enriched zinc targets are developed that are matched to the range of energies available in the stacked-target configuration of the IPF. In addition, new separation technology must be developed to recycle the enriched target materials, as well as to separate and purify the copper-67 from the target material and irradiation byproducts.

The American Cancer Society estimates that, by the end of 2005, there will have been 1.4 million new cancer cases and 570,000 deaths from cancer, or 1,500 deaths per day, in the United States. It is obvious that the need for improved methods of early detection and treatment of cancer is acute. Our goal is to combine the Los Alamos expertise in nuclear chemistry and radiochemistry and in the synthesis of molecular inorganic and organometallic complexes with the expertise of the University of California, the University of New Mexico (UNM), and the New Mexico State University in clinical trials and in vivo testing of the stability, biodistribution, and oncological effects of radiopharmaceuticals. The Center for Isotopes in Medicine and the Cancer Research and Treatment Center at UNM will be the focal points for this R&D directed at improved radiotherapy.

In order to develop more-effective therapy agents to target sites in a tumor mass or in cancer cells, we must first develop suitable delivery systems for the radioisotopes, providing the right combination of chemical and biological stability in an easy-to-make ligand. These new ligands would be designed to bind to specific molecular sites in biological systems expressed by tumors/cancer cell lines, thereby becoming potentially unique delivery systems with which to diagnose and treat disease. Designing ligands to bind to specific targets is at the core of how research in nuclear medicine science is being redefined as molecular science. Targets could be any biological molecule found in tissues, individual cells, or genetic material. Once radiolabeled ligands that bind to specific proteins are available, nuclear imaging could monitor specific gene expression (that is, the making of proteins specified by particular genes) and thereby provide greater understanding of developmental biology, cancer induction and pathogenesis, and ultimately, the clinical detection of inherited or acquired diseases. The capability to image the expression of any gene in any person would likely yield profound health benefits to society. Antisense radiopharmaceuticals (DNA-based targeting agents) analogous to existing chemotherapeutic drugs would be optimized for in vivo imaging by PET or single-photon-emission computed tomography (SPECT).

To date, PET imaging using molecules radiolabeled with fluorine-18 and iodine-124 have been quite promising. We expect that many high-specific-activity and high-purity radioisotope tracers will be available from the new IPF and will be key to advances in science and medicine. Compared with the old isotope station at Los Alamos, the new IPF has doubled its operating period every year with only minimal cost increase. In fact, the facility is designed to operate when the rest of LANSCE goes through maintenance outages. Above all, the efficiency, safety, and reliability of operations at the new IPF ensure domestic and international market demands for most isotopes for years to come. ■