THE PRODUCTION OF SPALLATION RADIONUCLIDES FOR MEDICAL APPLICATIONS AT BLIP*

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Summary

The Brookhaven LINAC Isotope Producer (BLIP) is the first facility to demonstrate the capability of a large linear accelerator for efficient and economical production of difficult-to-make, medically useful radionuclides. It utilizes the excess beam capacity of a LINAC that injects 200-MeV protons into the 33-GeV Alternating Gradient Synchrotron. The LINAC provides an integrated beam current of 60 μA for radionuclide production, operating 24 hours per day, 7 days per week. The 200-MeV proton energy is very suitable for isotope production since the spallation process provides a route to copious quantities of radionuclides unavailable at lower energy accelerators, or reactors. Further, the energy is high enough to allow simultaneous irradiation of multiple targets leading to reduced cost per nuclide. Careful choice of target position in the array makes it possible to select the proper proton energy range to maximize the yield of a particular nuclide from a given target and minimize the amounts of undesirable by-products. The proton beam enters the BLIP irradiation chamber under 32 feet of water which serves as a transparent shield for gamma rays and the high-energy neutrons produced by spallation interactions. Guide tubes are used for introducing independent target assemblies into the proton beam, enabling both very short irradiations and very long ones. The targets are individually water cooled by means of a flexible stainless steel water hose that travels with the assembly. The basic target types are encapsulated salt pellets, gases, and metallic foils. The medically important isotopes ^{123}I, ^{81m}Kr, ^{52}Fe, and ^{127}Xe are routinely produced. These and other potentially important radionuclides can result in improved diagnostic and therapeutic procedures in nuclear medicine with reduced patient dose, and lead to a better understanding of physiological processes in health and disease.

Introduction

The potential of large linear accelerators to be prolific producers of radionuclides by spallation reactions has begun to be exploited. There are many advantages of the spallation process for isotope production compared to thermal neutron capture, the fission process, or low energy particle reactions. Isotope production by (n,γ) reactions is limited by the availability of suitable stable isotopes with reasonable capture cross sections and it does not yield products of very high specific activity. Fission can provide high specific activity but is limited to neutron rich products between atomic mass 69 and 167. Spallation can produce almost any nuclide with mass number lower than that of the target, but neutron deficient radionuclides predominate. The high energy of the bombarding protons thus gives access to some desirable nuclides far removed from the stability line that are not easily reached by low energy particles. Also by virtue of the high energies involved the beam can penetrate and produce reactions in thick target stacks up to 10's of grams per cm^2. The large numbers of target atoms involved usually compensates for reaction cross sections lower than those often associated with low energy interactions. The simultaneous irradiation of multiple targets with the beam actually stopping in the last target makes use of all available protons and helps reduce the cost per nuclide. The ability to choose the target position in the array allows some control of the proton energy incident on each target. This makes it possible to optimize desired reaction probabilities and minimize the amounts of unwanted by-products. The 200 MeV proton energy available at BLIP is fortunately very appropriate for radionuclide production because at higher energies various problems become more severe. Using appreciably higher bombarding energies requires impractically thick targets to stop the entire beam. In addition, beam attenuation, beam spreading and energy straggle can increase objectionably at higher energies with very thick targets. As energies rise there is a considerable increase in production of high energy neutrons which can greatly complicate the shielding problems. These neutrons also produce unwanted secondary nuclear reactions in the targets. Finally, as the bombarding energy goes up, the spallation yield vs product mass curve flattens out, leading to relatively more contaminating by-products.

The main disadvantages of spallation for large-scale radionuclide production relate to the massive targets used and the limited specificity of high energy interactions. Most irradiated targets require elemental separation with wet chemistry techniques. Large, unwieldy solution volumes are sometimes encountered and must be handled with remote apparatus. This can be a difficult and time consuming endeavor. Much effort and ingenuity is required in developing remote separation methods.

The BLIP Facility

The LINAC typically generates 60 mA pulses, 220 μs in duration, five times per second. The AGS acceleration and external beam extraction cycle only require LINAC injection approximately once every 3 seconds. The excess LINAC pulses are available for radionuclide preparation and provide a time-averaged beam current of 60 μA, operating parasitically 24 hours per day, 7 days per week. Protons from the end of the LINAC are deflected into the BLIP beam line by a pulsed bending magnet. Figure 1 depicts the BLIP beam line and irradiation stations located in the bottom of an 8-ft diameter, 34-ft deep water tank. The water serves as an inexpensive, transparent shield for gamma rays and high energy neutrons produced in the targets. Beam intensity is measured by a current transformer in the LINAC. The beam position and spot size are monitored by a multi-wire proportional chamber placed in the beam line just upstream of the irradiation chamber. The initial spot size is kept fairly large, about 3 cm in diameter, in order to spread out the heat deposition in the targets.

Guide tubes are used for placing independent target assemblies into the proton beam. The stainless steel target assemblies are individually cooled by means of a flexible metallic water hose that travels with the assembly. Continuous stainless steel cables attached to the target assemblies are used to drive them in and out of the irradiation chamber through the guide tubes. Figure 2 is a schematic diagram of the BLIP with the beam entering the irradiation chamber at the bottom of the tank. It shows a typical guide tube, hose reel and the target cooling water circulating system. Cooling water (distilled) enters each target assembly through the attached hose, flows across the target faces and discharges into the guide tube. This water travels to the top, allowing time for decay of short-lived radioactivities, combines with water from the other guide tubes, and collects in a surge tank. The water is then pumped through a filter, heat exchanger, and back through the hoses to the targets.

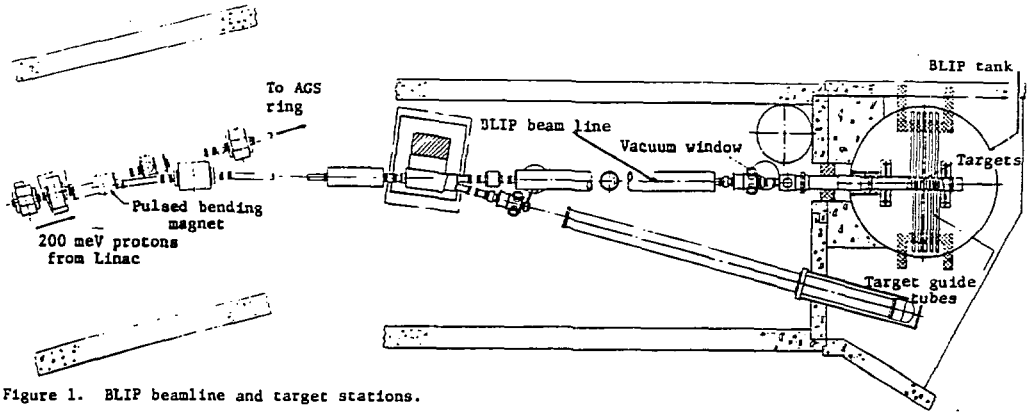

Figure 1. BLIP beamline and target stations.

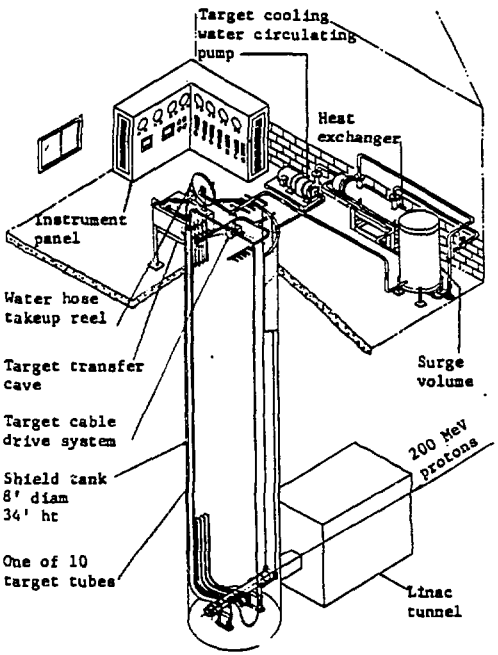

Figure 2. Schematic of BLIP facility.

This water is not mixed with the shield tank water to avoid contaminating it. The irradiation chamber is filled with a helium pressure sufficient to support the column of water in the guide tubes and keep the chamber free of water. Automatic equipment monitors sensors for radiation levels, helium pressure, water pressure, temperature, and flow rate. This equipment has both regulation and alarm capabilities to allow unattended operation except during insertion and removal of targets. Safety interlocks automatically divert the LINAC beam from BLIP if a malfunction is detected. This also reduces the number of staff necessary for continuous operation.

Figure 3 shows a typical encapsulated salt target in a mock (lucite) target holder assembly. Each such assembly can contain up to 5 targets, depending on the type and thickness. A cross section of the irradiation chamber, the water connection, guide tube and the cable return tube can also be seen.

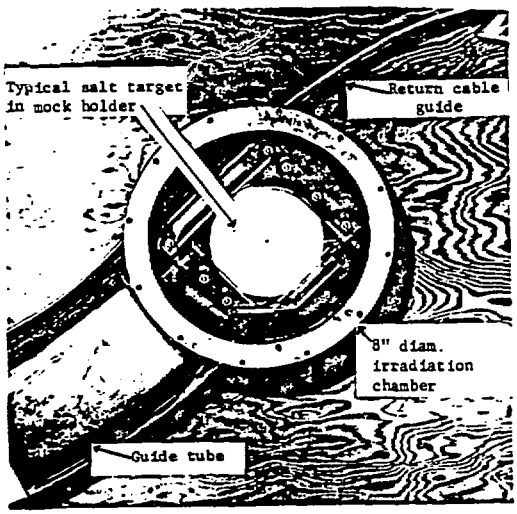

Figure 3. Mock-up of target in position in irradiation chamber.

Following irradiation, the target holder is pulled by its cable into a shielded cave at the top of the guide tubes. Here targets are removed from the holder, placed in a heavily shielded transfer cask, and transported to the remote handling facility for processing.

Radionuclide Program

The BLIP serves as a radionuclide source for on-site research programs as well as for a number of outside collaborative efforts. In addition, as a service to the nuclear medicine community, the facility distributes at cost several troublesome radionuclides. Table 1 lists those that are presently supplied routinely, along with some associated production parameters. The basic target types used are metallic foils, gases and encapsulated salt pellets.

Table 1. Routinely Distributed Radionuclides

Isotope	$t_{\frac{1}{2}}$	Target	Nuclear reaction	Proton energy (MeV)	EOB yield (μCi/μAh)
^{52}Fe	8.3h	Ni	Ni(p,spall)	200	36
		Mn	$^{55}Mn(p,4n)$	70	90
^{68}Ge	288d	Ga	Ga(p,xn)	55	9
^{81m}Kr	13.3s	Kr	$^{84}Kr(p,4n)^{81}Rb\rightarrow$	70	330
^{109}Cd	453d	In	$^{115}In(2p,5n)$	200	25
^{123}I	13.0h	NaI	$^{127}I(p,5n)^{123}Xe\rightarrow$	70	3700*
^{127}Xe	36.4d	CsCl	$^{133}Cs(p,2p5n)$	175-80	110

*Yield at time of separation

The simplest target to make, irradiate and process is a metallic foil. Thin foils (.001"-.020") are simply clipped to stainless steel support plates and can be inserted in any water passage in a target holder. A nickel foil of this type is used to prepare ^{52}Fe, an 8.3h positron emitter of medical interest for studying the distribution of hemopoietic marrow and diseases of the blood forming organs. It is also the parent of ^{52m}Mn, a 21 min positron emitter with potential for evaluating blood flow in heart muscle (myocardial perfusion) and for monitoring the effects of intervention on this pertusion. Utilization of ^{52}Fe has been limited because of the difficulty in preparing sufficient quantities on the available cyclotrons. The total radioactivity routinely produced at BLIP in a 16 hr irradiation is 35 mCi with a 0.20" nickel foil target and 60 mCi with a manganese target. An increase in nickel thickness (or a second target) proportionately increases the yield. The ^{52}Fe from a manganese target is purer than from nickel (~0.3% ^{55}Fe, versus ~1.0% ^{55}Fe, 0.17% ^{59}Fe). However, the nickel target is simpler to use and when the ^{52}Fe is used in a generator these iron impurities present no problem to the radionuclidic purity of ^{52m}Mn since they are retained on the generator column.

The $^{81}Rb/^{81m}Kr$ generator system makes the use of this very short-lived nuclide practical for lung ventilation imaging. A generator that delivers 18 mCi is produced weekly for on-site pulmonary research. This is considerably hotter than generators normally available. The target is 13 atmospheres of natural krypton gas contained in a stainless steel capsule 0.75 in. thick with 0.063" windows. After irradiation the krypton gas is vented through a gas fitting on the target and ^{81}Rb is rinsed off the interior walls of the capsule.

However, most of our targets are encapsulated solids. A most important example of this type is involved in the production of ^{123}I. This isotope has very desirable imaging, dosimetry and chemical properties allowing the development of superior radiopharmaceuticals for thyroid, brain, heart, and kidney studies. However, problems in production, radiopurity and availability have limited its widespread application. The BLIP now regularly achieves approximately 375 mCi (at time of xenon-iodine separation) of high purity ^{123}I (0.2% ^{125}I, no ^{124}I). The process involves bombarding sodium iodide targets with 70 MeV protons for 2 hr to produce ^{123}Xe. The target, a pie-shaped wedge 0.83 cm thick, is made by pressing NaI powder at 70 tons per square inch. The wedge is sealed in an electron beam welded cylindrical inconel capsule containing a gas fitting for connection to the processing equipment.

Following bombardment the target capsule is transported to the remote processing facility and attached to a gas train (Fig. 4). The target seal is then ruptured with a hollow needle and the capsule is heated to 780°C to melt the sodium iodide. Xenon diffusing out of the molten salt is carried by a helium stream through a dry ice trap to remove condensables, over a metallic silver mesh heated to 400°C and a silver loaded silica gel trap to react any traces of iodine contamination. The xenon is then frozen on a stainless steel spiral at liquid nitrogen temperature. After collection this xenon is cryogenically transferred to special glass ampoules, allowed to decay into ^{123}I for 4 hr, and then pumped off. The details of the ^{123}I process and apparatus have been reported elsewhere.[1]

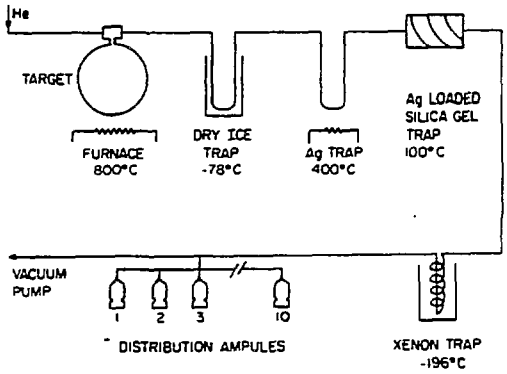

Figure 4. ^{123}I processing equipment.

Other radionuclides with potential applications in medicine that are now being investigated include ^{7}Be, ^{82}Sr, ^{97}Ru, ^{117m}Sn and ^{118}Te. The creation of ^{7}Be by spallation reactions on Li_2CO_3 is being studied for use as an excitation source of ^{7}Li by nuclear resonance absorption. This could lead to a non-invasive method to determine the brain lithium content in-vivo of individuals on lithium psychotherapy. Li_2CO_3 was chosen because it is soluble, high melting, inexpensive and its constituent elements all produce ^{7}Be without any other long-lived radionuclides. In a recent bombardment of this target 130 mCi of ^{7}Be was formed. Also, ^{7}Be activated carbon dust was produced for a study of the distribution of particulate material intratracheally introduced in rats. ^{82}Sr is of interest as the parent of ^{82}Rb, a short-lived (75s) positron emitter with potential for visualization of the myocardium. We have determined that BLIP can produce useful quantities of ^{82}Sr (2.2 mCi/hr) from a RbCl target with only 33% ^{85}Sr impurity.

Ruthenium-97 has many potential applications as a label for versatile new radiopharmaceuticals because of its excellent physical properties (a high abundance, essentially monoenergetic gamma ray of 216 keV and a half-life of 2.9 days) and the high chemical reactivity of the element ruthenium. In-vivo experiments in mice, rats, and dogs demonstrated considerable promise for clinical utility of several ^{97}Ru-labeled preparations: transferrin (tumor and abscess localization); iminodiacetate derivatives (hepatobiliary function imaging); dimercaptosuccinic acid (kidney studies); DTPA (cisternography); and oxine and acetylacetone derivatives (cell labeling); etc.[2] In small animal tests, ruthenium-labeled transferrin has shown tumor localizing properties superior to the currently used agent. Carrier-free ^{97}Ru is produced at BLIP from proton spallation of high-purity (99.9%) rhodium foil by the $^{103}Rh(p,2p5n)^{97}Ru$ reaction. With a 0.010" thick foil, bombarded at 200 MeV, yields of 33 μCi/μAh have been

achieved. Recent excitation function data we have obtained at the Indiana University Cyclotron Facility suggests that the ^{97}Ru yield substantially increases at 80 MeV.

Tin-117m has attractive radionuclidic properties (159 keV γ, 86%, 14 d half-life) and is being investigated for the development of diagnostic and possibly therapeutic agents. Preliminary studies have demonstrated that several ^{117m}Sn labeled compounds localize almost exclusively in bone and thus show promise for bone radiotherapy and for the diagnosis of metabolic bone disease. The specific activity of reactor produced ^{117m}Sn is not high enough for clinical studies. The preparation at BLIP of carrier-free ^{117m}Sn from an antimony target is under development. Adequate amounts have been produced but the required chemical separation is difficult. It is still being investigated. Finally, ^{118}Te is a bonus in that it is produced simultaneously with ^{117m}Sn from antimony. It is the parent of ^{118}Sb, a short-lived positron emitter with potential for single-pass coronary angiography.

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References

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