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New Accelerator Produced Radiopharmaceuticals*

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A search for radionuclides with optimum physical and chemical properties for the development of new radiopharmaceuticals has resulted in a revived interest in accelerators due to their versatility in introducing a wide variety of materials. During the next few years the multi-purpose, high-current linear accelerator (Linac) which can generate greater than 50-MeV particles can be expected to have a significant impact on radionuclides and radiopharmaceuticals available to nuclear medicine. Such machines have the capability of producing simultaneously and thus economically a wide variety of radionuclides in relatively large quantities. The first facility to explore the radionuclide production potential of such an accelerator is the Brookhaven Linac Isotope Producer (BLIP) which started operation early in 1973[1].

The BLIP serves as a beam stop and utilizes the excess beam capacity of a new Linac that injects protons into the Alternating Gradient Synchrotron, a 33-GeV machine used in high-energy physics research at Brookhaven National Laboratory. The Linac was designed to generate up to ten pulses of 200-MeV protons per second providing a time-averaged beam current of

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approximately 180 microamperes available for radioisotope technology development as well as other research and development activities. The optimal proton energy, relatively high beam current, and the normal 24 hours per day operation of the machine offer the potential for preparation of large quantities of certain difficult-to-produce radionuclides important to nuclear medicine.

Figure 1 is a drawing of the BLIP tank with the beam entering an irradiation chamber located at the bottom under 32 feet of water. The water serves as a flexible, transparent shield against high-energy neutrons that are produced by proton interactions with target materials. The target handling guide tubes and individual target cooling systems are illustrated schematically. Up to 10 target assemblies may be irradiated simultaneously and introduced or removed from the proton beam independently. As the protons traverse an array of targets they are degraded in energy. The specific position of any target in an array is determined by the nuclear reaction involved and the optimum proton energy required for the maximum yield and purity. Following irradiation targets are transferred through guide tubes to the top of the tank and into lead shielded caves where they are placed in casks for transport to target processing facilities.

A number of potentially important radionuclides are under development and can be expected to result in many new radiopharmaceuticals. Technology development is currently underway on iodine-123, iron-52, xenon-127, thallium-201, ruthenium-97, and others. Table 1 lists pertinent information regarding method of production, rate of production, expected yields,

and potential applications for radionuclides presently being evaluated as BLIP products. Experimental production of iodine-123 and iron-52 has been carried out at the multi-millicurie level and the yields and purity have been in relatively close agreement with predicted values. Preparations are underway for the experimental production of small quantities of xenon-127. The production of larger quantities of all three isotopes should begin in the near future. The roles that these radionuclides can play in improved diagnostic procedures and reduced radiation dose to the patient are well known and will not be covered in this report.

Thallium-201 appears to have considerable potential as a tracer for coronary artery disease, a major cause of death and disability in the world today. Non-invasive, accurate methods of assessing myocardial damage are required to determine the extent of damage and to properly evaluate efficacy of treatment as well as to select patients for operative procedures. All of the radionuclides that have been evaluated or that are used for myocardial studies, including the potassium and cesium isotopes, suffer from inadequate physical properties or from general availability at a reasonable cost. Preliminary studies by Harper, et al. in Chicago[2] and work at Brookhaven[3] indicate that thallium, a physiological analog of potassium, has excellent potential for this application. Table 1 indicates that satisfactory quantities of thallium-201 can be produced with the linear accelerator. Although the photon yield for thallium-201, as indicated in the Table, is quite low the energies, 135 and 167 keV, are excellent. When the collimator plus detection efficiency are taken into

account the net counts are equal to or greater than other radionuclides. Also, the radiation dose is low due to the absence of beta radiation. The 73-hour half-life gives a good shelf-life and makes thallium-201 available for emergency procedures.

Animal studies indicate that the myocardial uptake for thallium is about equal to that for potassium while the blood clearance falls between potassium and rubidium and is considerably faster than for cesium. Excellent scintigraphs of a goat's heart have been produced with thallium-201 using the gamma camera and a technetium collimator.

Other potential applications for thallium-201 include renal studies, because of its localization in the kidney medulla, and possible tumor localization, particularly in melanoma. It should also be noted that lead-203, another radionuclide with possible medical applications, is produced simultaneously with the thallium-201 and can be recovered as a byproduct of the thallium production.

Ruthenium-97 is another radionuclide with a great potential for an important role in nuclear medicine applications. It decays by electron capture with a 2.9-day half-life and emits 215-keV photons in 91% abundance. Both the half-life and gamma-ray energy are excellent for many applications. The chemical properties of ruthenium offer a potential for manipulation and thus the preparation of many labeled compounds, complexes and colloids. Ruthenium can exist in eight valence states; in the lower states ruthenium behaves similar to iron, while in the higher states it acts like platinum. Preliminary studies carried on at Brookhaven indicate

the possibility of ruthenium-labeled colloids for use in lymphangiography as well as a label for proteins and other complexes. It is also evident from the Table that relatively large amounts of the radionuclide could be made available with the BLIP facility.

References

1. P. Richards, E. Lebowitz, and L. G. Stang. The Brookhaven Linac Isotope Producer (BLIP). BNL 17740. Presented at the IAEA Symposium on New Developments in Radiopharmaceuticals and Labelled Compounds, Copenhagen, Denmark, March 26-30, 1973.

2. M. Kawana, H. Kuzek, J. Porter, K. Lathrop, D. Charleston, and P. V. Harper. Use of ^{199}Tl as a potassium analog in scanning. J. Nucl. Med. 11, 333 (1970).

3. E. Lebowitz, M. W. Greene, P. Bradley-Moore, H. Atkins, A. Ansari, P. Richards and E. Belgrave. BNL 18094. Presented at the 20th Annual Meeting of the Society of Nuclear Medicine, Miami Beach, Florida, June 12-15, 1973.

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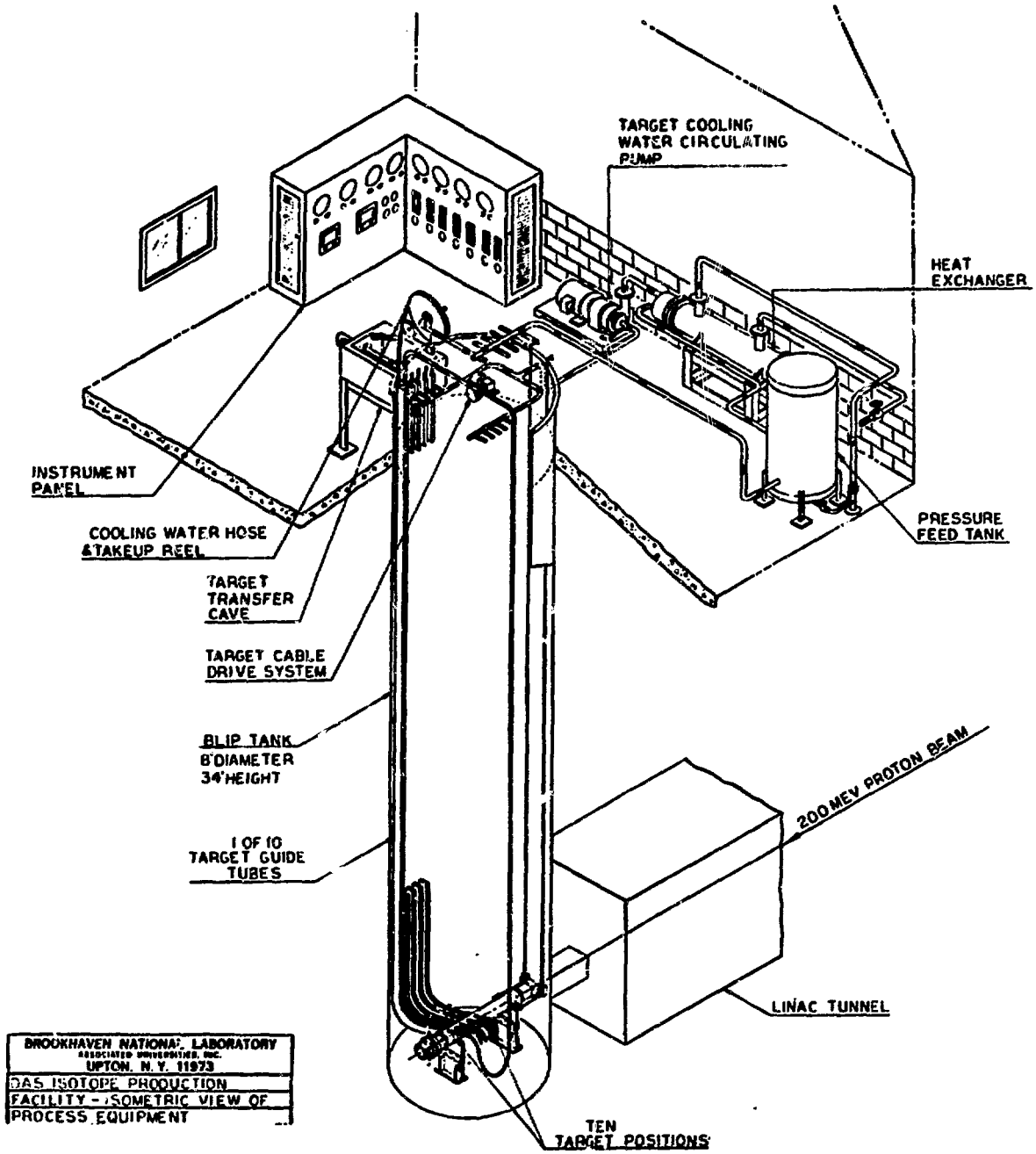

Figure 1

Neg. # 5-30-71

Table I

TYPICAL BLIP RADIONUCLIDES

Radio-nuclide	Half life	Major Photon Energies KeV	Target Material	Nuclear Reaction	Proton Energy MeV	Irrad. Time Hours	Yield* Curies	Remarks
^{123}I	13.1 h	159 (83%)	Potassium Iodide	$^{127}I(p,5n)^{123}Xe \xrightarrow{E.C.} {}^{123}I$	~65	2	5	≤0.1% ^{125}I contamination at EOB Thyroid function and imaging - Labeled molecules
^{127}Xe	36.4 d	172 (22%) 203 (65%) 375 (20%)	Cesium Chloride	$^{133}Cs(p,2p5n)^{127}Xe$	~100-200	720	15	Lung perfusion and ventilation - Blood flow measurements
^{52}Fe	8.5 h	165 (100%) 511 (112%)	Manganese	$^{55}Mn(p,4n)^{52}Fe$	~70	16	1	Bone marrow imaging - Labeled molecules
^{201}Tl	73 h	Hg X-rays 135 (2%) 167 (8%)	Thallium	$^{205}Tl(p,5n)^{201}Pb \xrightarrow{E.C.} {}^{201}Tl$	~50	9	2	Cardiac imaging - Kidney studies
^{97}Ru	2.9 d	215 (91%) 324 (8%)	Technetium-[illegible]	$^{[illegible]}Tc(p,3n)^{97}Ru$	~36	16	10	Excellent physical and chemical properties
^{82}Rb	75 s	511(192%) 777(9%)	Zirconium	$^{90}Zr(p,3p6n)^{82}Sr$ $^{82}Sr \xrightarrow[25\ d]{E.C.} {}^{82}Rb$	~100-200	600	12	Generator - Myocardial blood flow and function

*beam current ~180 μA; one target holder; at end of bombardment (EOB)