26. Production and Utilization of Radioisotopes

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Abstract: A plan of developing radioisotopes with a high power proton accelcrator of the Neutron Science Project is presented. The status of production and utilization of radioisotopes in Japan is briefly discussed. The radioisotopes to be produced for biomedical use are discussed together with the facility for production of those radioisotopes and for research with the products.

Introduction

The artificially-produced radioisotopes are indispensable for modern medicine, industry and science. In Japan, a variety of radioisotopes are produced by JAERI using nuclear reactors and by companies using low to medium energy cyclotrons. In addition, a lot of long-lived radioisotopes are imported from abroad. However, some short-lived important or potentially useful radioisotopes are not available because of limitations of the neutron fluxes and the charged-particle energies. Therefore, we are proposing the construction of a facility to produce a substantial portion of these radioisotopes, in particular those to be used in medicine and life science, using high energy protons in the Neutron Science Project.

Production and utilization of radioisotopes in Japan

As an industrialized country, Japan has advanced its use of radioisotopes together with the research and development of the production and utilization of radioisotopes. The status is briefly described here with an emphasis on JAERI's contribution.

The number of hospitals and medical laboratories using radioisotopes is steadily increasing in Japan. According to the recent statistics,[1] there exist 1266 nuclear medicine facilities in which *in vivo* and/or *in vitro* diagnosis or some therapy is performed. For nuclear medicine, these facilities must be equipped with expensive instruments: for diagnosis 800 gamma-cameras, 1100 systems of single photon emission computed tomography, 20 compact cyclotrons and 23 systems of positron emission computed tomography have been installed; and for therapy 193 remote after loading systems (RALS) and 12 gamma-knives.[2]

The total amount of radioactivity needed in Japan is also increasing, but the demand to individual

isotopes is changing with the development of nuclear medicine and nuclear technology. Major radioisotopes used *in vivo* in 1996 are listed in Table 1 together with their half-life, production reaction and total radioactivity consumed. One can notice that the $^{99}Mo/^{99m}Tc$ generator and the ^{99m}Tc solution constitute a substantial part of the total radioactivity. This is because ^{99m}Tc, which has ideal nuclear characteristics for imaging in diagnosis, can be obtained as a carrier-free product and a variety of ^{99m}Tc-labeled radiopharmaceuticals for different diseases have been found. The amounts of the reactor-produced (n, γ) products ^{51}Cr and ^{59}Fe, which are not carrier-free, are decreasing, while those of the cyclotron-produced isotopes ^{201}Tl, ^{123}I, ^{67}Ga, $^{81}Rb/^{81m}Kr$, ^{111}In, which are obtainable as a carrier-free product, are greatly increasing. It should be pointed out that, as a development of nuclear medicine, the element thallium, which is toxic in its macro amount, can be used as an analog to potassium. For the production of the radioisotopes listed in Table 1, the (n,f) products are imported from abroad. The cyclotron-produced isotopes, which are rather short-lived, are produced domestically on a commercial basis with small and medium-size cyclotrons by two private companies.

Table 1 Radioisotopes used in Japan in 1996 *in vivo*

Isotope	Half-life	Production reaction	Radioactivity used/GBq
$^{99}Mo/^{99m}Tc$*	66 h/6.0 h	$^{235}U(n,f)$	181,521
^{99m}Tc	6.0 h	$^{235}U(n,f)$	216,171
^{133}Xe	5.3 d	$^{235}U(n,f)$	16,160
^{131}I	8.0 d	$^{235}U(n,f)$	5,344
^{51}Cr	28 d	$^{50}Cr(n,\gamma)$	12
^{59}Fe	45 d	$^{58}Fe(n,\gamma)$	2
^{201}Tl	3.0 d	$^{203}Tl(p,3n)^{201}Pb(\beta^+)$	27,582
^{123}I	13 h	$^{124}Xe(p,x)^{123}Xe(\beta^+)$	22,096
^{67}Ga	3.3 h	$^{68}Zn(p,2n)$	18,407
$^{81}Rb/^{81m}Kr$*	4.6 h/13 s	$^{82}Kr(p,2n)$	968
^{111}In	2.8 d	$^{112}Cd(p,2n)$	250

*Generator

Using research reactors, JAERI has supplied radioisotopes used *in vivo*, such as ^{24}Na, ^{42}K, ^{51}Cr, ^{64}Cu, ^{198}Au and so on, although the amount of these radioisotopes is not large in the entire Japanese market. However, JAERI has recently withdrawn from the routine production of 18 radioisotopes to go into being more research-oriented. In collaboration with universities and other organizations, several radioisotopes such as ^{89}Sr, ^{186}Re and ^{188}Re are under development, which are expected to be used in cancer therapy. For example, production methods of ^{186}Re and ^{188}Re, and their labeled compounds, including monoclonal antibodies, have been studied together with their behavior in an animal model.[3)]

Radiation sources for industrial and medical use have been routinely produced using the research reactors of JAERI and shipped as summarized in Table 2 for fiscal year 1996. Further, a new application of brachytherapy sources like ^{192}Ir-RALS sources to coronary restenosis is under development. This source should be smaller in size to be inserted into a blood vessel and stronger in radioactivity for a short-period irradiation. For the same purpose, a radioactive "stent," which is used

Table 2 Radiation sources produced by JAERI in FY1996

	Isotope	Radioactivity/ GBq	Number of pieces
Industrial use	^{60}Co	131	280
	^{192}Ir	1,292,100	2,100
	^{169}Yb	1,359	10
Medical use	^{192}Ir		
	Hairpin etc.	760	4796
	RALS	20,820	60
	^{198}Au	4,026	3,367
	^{153}Gd	15	5

in angioplasty, is also developed by ion-implanting ^{133}Xe into a stent. Because a stent is implanted into a blood vessel and β -rays are available for irradiation, the radioactivity of a stent need not be so strong as 1 MBq.

For accelerator-produced radioisotopes, JAERI produced earlier ^{237}Pu[4] and ^{95m}Tc[5], which were needed as a tracer in environmental science, using proton and deuteron beams from the tandem accelerator at Tokai. Production of other various radioisotopes became possible when an AVF cyclotron with K=110 was constructed at Takasaki together with a radioisotope production facility, including a hot laboratory. So far, production methods of the neutron-rich isotopes ^{186}Re [6], ^{183}Ta [7] and ^{42}Ar [8] have been developed with proton and α beams. In particular the production method of ^{186}Re with a cyclotron was proposed for the first time. In addition, labeled compounds of the positron emitters ^{11}C, ^{13}N, ^{18}F and ^{48}V are produced for plant physiology,[9] and studies with a positron-emitting tracer two-dimensional imaging system have started.[10]

Although the development of radioisotopes and related techniques has been carried out, radioisotope-production resources in Japan are not enough in comparison with those in the North America and Europe. In particular, high-flux reactors and high-power high-energy proton accelerators are not available.

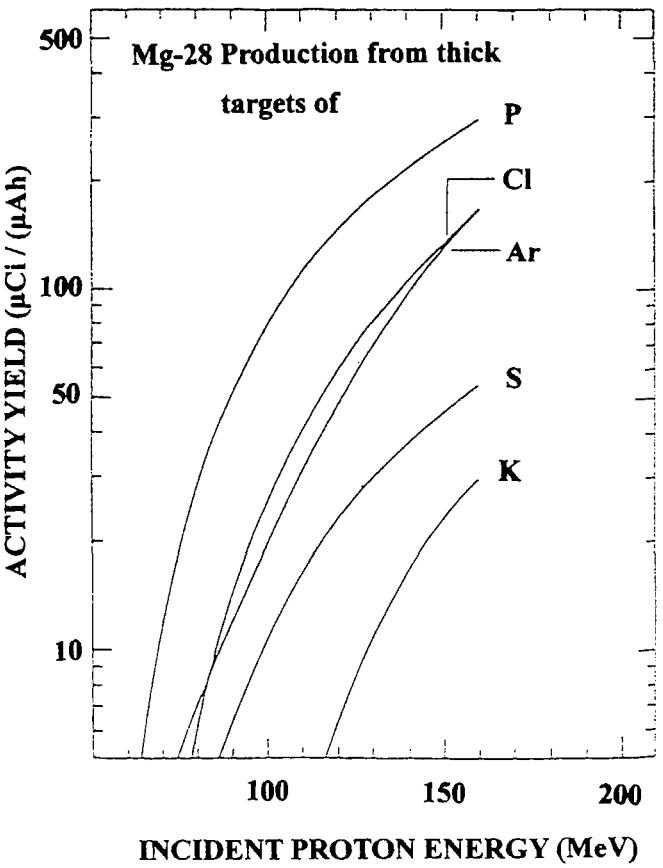

Fig. 1 Yields of thick target for the production of ^{28}Mg

Radioisotopes to be produced with a high-power high-energy proton accelerator

The high-energy high-power proton accelerator will enable us to produce radioisotopes needed to further medicine and life science. They include useful or potentially useful radioisotopes that are not available or difficult to produce at present in Japan. Typical ones are as follows:

^{28}Mg: Magnesium is biologically essential. Studies with a magnesium radioisotope are

expected in medicine and life science. One difficulty is the lack of a readily available and suitable radioisotope of magnesium. The only one with a half-life long enough for practical use is ^{28}Mg with a half-life of 21 h. Magnesium-28 is also used as the ^{28}Mg→ ^{28}Al generator.[11] However, the yield of ^{28}Mg in proton- and α-induced reactions with a small or medium-size cyclotron does not reach an amount enough for biomedical experiments. As shown in Fig. 1, several targets bombarded by protons in energies higher than 100 MeV are expected to yield a substantial amount of ^{28}Mg [12].

^{52}Fe: Iron is also an important metallic element in plants and the human body. As seen from Table 1, ^{59}Fe, decaying by β-ray emission with a half-life of 45 d, has been used in diagnosis, while its high energy γ-rays are not adequate for imaging. Iron-52 is a useful radioisotope for medical research because of its short half-life of 8.2 h, its positron emission and its soft γ-ray of 165 keV. This nuclide can be produced in proton-, ^{3}He- and α-induced reactions; in order to obtain a relatively high yield, ^{55}Mn(p,4n)^{52}Fe with a proton beam of 70 MeV and Ni(p,spallation) ^{52}Fe with that of 200 MeV or higher are proposed [13]. For the routine production of ^{52}Fe, the latter seems preferable because a high-purity nickel target is readily available.

^{67}Cu: In cancer therapy, development of radioisotopes for radioimmunotherapy by labeling a monoclonal antibody is highly expected. Copper-67 is considered a good candidate as an agent for radioimmunotherapy, because this nuclide possessing a half-life of 62 h decays by β^- emission with a maximum energy of 577 keV; its half-life is comparable to the uptake and residence time of antibodies for tumors and its β^- energies are considered to be appropriate to give a therapeutic dose to only targeted tumors. This nuclide can be produced in the ^{67}Zn(n,p)^{67}Cu reaction with a high-flux reactor and in the ^{68}Zn(p,2p)^{67}Cu reaction with a high-energy proton beam of 200 MeV [14].

The production of this nuclide, however, is rather difficult, because the thermal cross section of the ^{116}Sn(n, γ)^{117m}Sn is known to be as low as 0.006 b. Rather than this reaction, the ^{117}Sn(n,n' γ)^{117m}Sn reaction with fast neutrons is used for production of a therapeutic dose at an order of 500 MBq with a specific activity of *ca.* 200 MBq/mg, because its effective cross section of natural tin for fission neutrons is 0.2 b [16]. However, these conditions require the use of a high (fast-neutron) flux reactor with ϕ_f=3x10^{14} cm^{-2} s^{-1}, even if a ^{117}Sn-enriched to 100% target is bombarded. Instead of a high flux reactor, a high-power high-energy proton accelerator may be used, although the chemical process will be complicated for separation of tin from a target such as antimony.

Other isotopes to be produced with a high energy proton accelerator are summarized by Srivastava[17] based on the experience with the LAMPF[18] at Los Alamos National Laboratory and the BLIP[19] at Brookhaven National Laboratory.

Facility for production of radioisotopes

In planning the facility, the proton energy is our primary concern for determining the specifications of the accelerator. This matter is discussed here with a concept on the facility.

As mentioned above, we want to produce radioisotopes to be used as an agent in therapy or as a

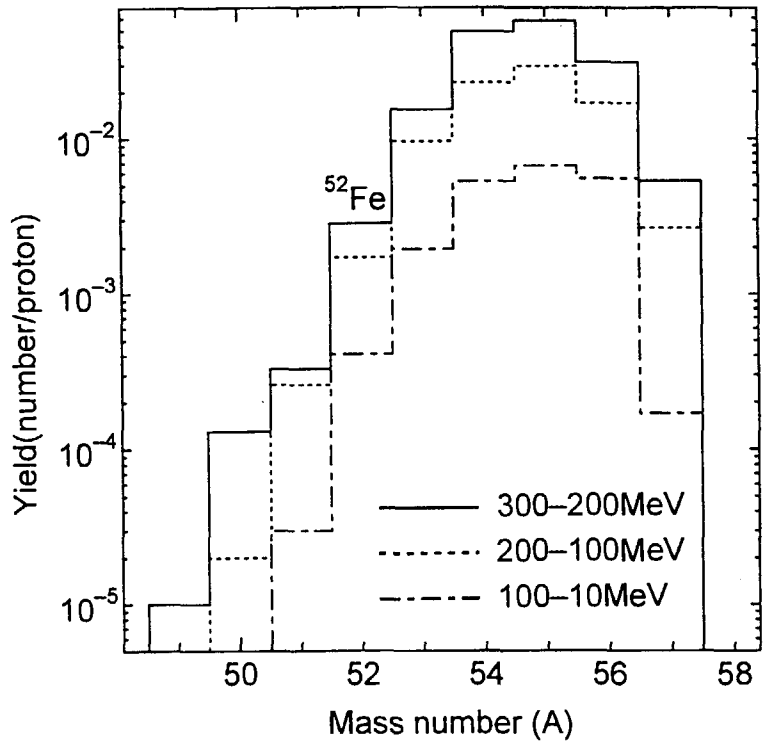

Fig. 2 Yields of Fe (Z=26) isotopes in the bombardment of ^{58}Ni, given by the NMTC/QMD code

tracer in biomedical science. To see the energy dependence of the yield, we have calculated the differential yield up to 300 MeV for the production of ^{28}Mg, ^{52}Fe, ^{82}Sr, ^{117}Sn (not ^{117m}Sn) and ^{203}Pb in the bombardment of ^{32}S, ^{58}Ni, ^{82}Rb, ^{121}Sb and ^{209}Bi targets, respectively. This calculation was done using the NMTC/JAERI code and the NMTC/QMD code.[20] Both the codes include nucleon evaporation and fission of excited fragments produced in the initial direct interaction and intranuclear cascade.

The results indicated that the NMTC/QMD code predicts the production of a broader range of isotopes than the NMTC/JAERI code. This difference is critical for the production of ^{28}Mg and ^{52}Fe, which are very far from the stability line. For ^{28}Mg, experimental yields are reported, as shown in Fig. 1. For ^{52}Fe, experimental yields are also reported for proton energies up to 200 MeV. Although both the experimental data are given for a target with natural

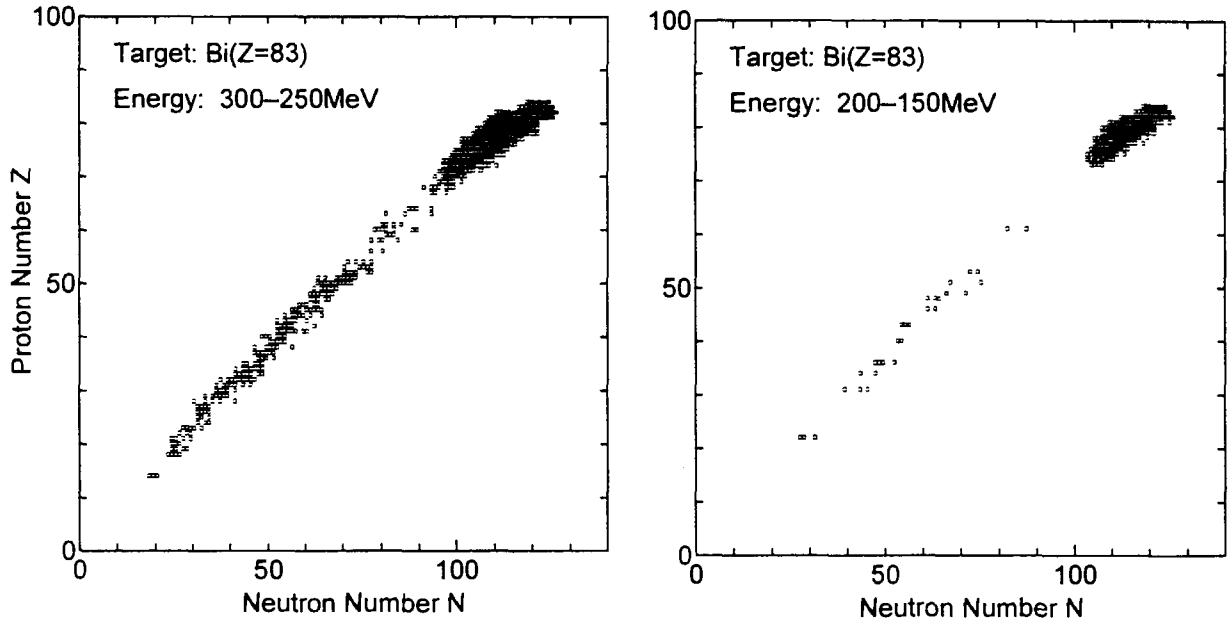

Fig. 3 Nuclides produced in the bombardment of a ^{209}Bi targets with protons during energy loss of 300-250 MeV and 200-150 MeV

isotopic abundance, the selected target nuclides are considered to contribute to the production of the nuclide of interest. Comparison between the experimental data and the calculated values indicates that the NMTC/QMD code gives a more reasonable result for the production of ^{28}Mg and ^{52}Fe. The yields of ^{52}Fe and other iron isotopes given by the NMTC/QMD code are shown in Fig.2 for energy loss of 300-200 MeV, 200-100 MeV and 100-10 MeV, respectively. The yield for ^{52}Fe during energy loss of 200-100 MeV is four times as large as that during energy loss of 100-10 MeV (Threshold is around 40 MeV). The yield during energy loss of 300-200 MeV is 1.7 times as large as that during energy loss of 200-100 MeV. One can say that the increase of the ^{52}Fe yield from energy loss of 200-100 MeV to energy loss of 300-200 MeV is not very large.

The production of fission products from the heavy target ^{209}Bi is not negligible. As shown in Fig.3, even the NMTC/JAERI code predicts that the target for energy loss of 300-250 MeV contains much more fission products than that for energy loss of 200-100 MeV. The fission products will make the radiochemical separations complicated.

From these yield calculations, the primary proton energy of 200 MeV is considered to be a good option. In addition, the advantage of this energy is that the beam will be stopped in a target with a reasonable thickness ranging between 25 and 40 g/cm^2, as discussed by Mausener *et al.*[19] In order that all available protons can be used for production of different radioisotopes that are produced in different proton energies, the target beam stop should be composed of multiple targets.

A schematic drawing of the beam lines for radioisotope production is shown in Fig. 4. The pulsed proton beam taken at a relatively-low energy stage of the accelerator bombards targets located at five target stations in a time-sharing mode. This makes possible simultaneous irradiation of different targets during different periods of time. Tentatively, the total averaged beam current is taken at 500 μ A. The irradiated targets would be transferred to shielded cells for chemical processing to separate radioisotopes of interest from the target. Designing of the facility, including target stations, a target transport system and a hot laboratory, is in progress.

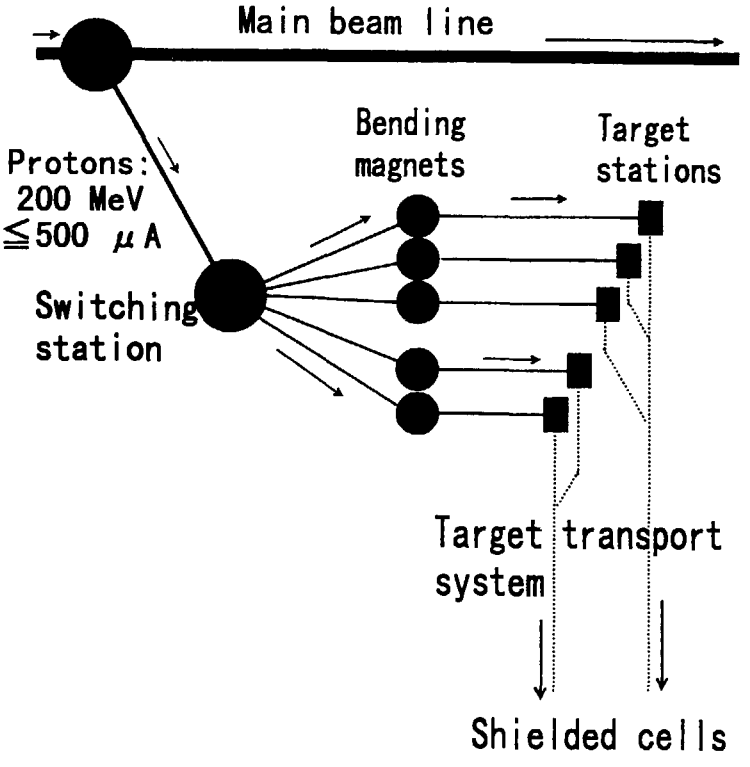

Fig. 4 Schematic of the proposed facility for radioisotope production

Products will be shipped to the users. It is also planned for biologists and other scientists to do experiments with short-lived radioisotopes within this facility.

Conclusions

Although Japan has a long history in use of radioisotopes, new radioisotopes to be produced with a high-power proton accelerator can promote research in medicine and life science. In particular, development of therapeutic agents is expected from the viewpoint of quality of life. The 200 MeV primary proton beam energy is considered to be a good option between production capability and convenience. Additionally, the Spallation Radioisotope Beam Project also can contribute to the production of medically useful radioisotopes by ion-implantation of radioisotopes into a material such as stents.

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