# Diagnostic ($^{99}$Mo/$^{99m}$Tc) and Therapeutic ($^{67}$Cu) Radioisotopes Produced by Neutrons from C,Be(*d*,*n*)

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**Abstract**
New production routes to produce $^{99}$Mo and $^{67}$Cu by the $^{100}$Mo(*n*,2*n*)$^{99}$Mo and the $^{68}$Zn(*n*,*n'p*+*d*)$^{67}$Cu reactions using accelerator neutrons are discussed. A thermoschromatographic system was developed to separate high quality $^{99m}$Tc from $^{99}$Mo of low specific activity with high efficiency. The pharmaceutical quality of $^{99m}$Tc pertechnetate solution obtained from $^{99}$Mo met the United States Pharmacopeia requirements. The calculated $^{99}$Mo yield from a 100 – 150 g $^{100}MoO_3$ sample indicates that about 50% of the demand for $^{99}$Mo in Japan can be met with a single accelerator capable of 40 MeV, 2 mA deuteron beams for an irradiation time of 24 h. The radionuclide purity of $^{67}$Cu is quite high. The measured biodistribution of $^{67}CuCl_2$ in colorectal tumor-bearing mice showed a high uptake of $^{67}$Cu in the tumor, which suggests that $^{67}CuCl_2$ can be a potential radionuclide agent for cancer radiotherapy.

**Keywords**
medical radioisotope, accelerator neutrons, neutron induced reaction, PET, SPECT, immunotherapy

## 1 Introduction

More than 80% of all diagnostic procedures in the world are carried out every year using $^{99m}$Tc ($T_{1/2}$ = 6 h) separated from $^{99}$Mo ($T_{1/2}$ = 66 h). Currently, most $^{99}$Mo is produced by the fission reaction of enriched $^{235}$U in about nine research reactors around the world [1]. However, an unscheduled shutdown of some of the reactors in 2008–2009 caused a shortage of $^{99}$Mo worldwide. The shortage of $^{99}$Mo due to the incident has triggered widespread discussions on the medium- and long-term supplies of $^{99}$Mo. In fact, a variety of alternative methods to produce $^{99}$Mo and/or $^{99m}$Tc in reactors and accelerators have been proposed [2]. Nagai and Hatsukawa proposed a new route of producing $^{99}$Mo via the $^{100}$Mo(*n*,2*n*)$^{99}$Mo (hereafter, (*n*,2*n*)$^{99}$Mo) reaction using accelerator neutrons produced by the C(*d*,*n*) reaction using deuteron beams [3]. The neutron source for (for example) 40 MeV deuterons provides a continuous spectrum from thermal energy to about 40 MeV with a most probable energy of 14 MeV and a peak at forward angles with respect to the deuteron beam direction [4].

Noninvasive radionuclide therapy is playing an important role in the treatment of various cancers. Among various radionuclides useful for diagnostic imaging and in targeted radionuclide therapy (hereafter, theragnostic radionuclide), Cu radionuclides are known to have unique potentials [5,6]. $^{64}$Cu ($T_{1/2}$ = 13 h) is used for PET imaging and $^{67}$Cu ($T_{1/2}$ = 62 h) is considered to be a promising theragnostic radionuclide [3]. $^{67}$Cu emits the 91, 93 and 185 keV $\gamma$-rays suitable for SPECT imaging, and $\beta$-rays with a mean energy of 0.141 MeV to kill targeted cancer cells. Owing to the low availability of $^{67}$Cu, however, there have been few medical studies with the use of $^{67}$Cu. Currently, the $^{68}$Zn(*p*,2*p*)$^{67}$Cu reaction is used to produce $^{67}$Cu, but the production of $^{67}$Cu is about 3.7 GBq per month worldwide [7], which might be too low for the study of medical applications. A new route

was proposed by Kin et al. to produce a significant amount of $^{67}$Cu by the $^{68}$Zn($n$,$n'p$+$d$)$^{67}$Cu reaction by using accelerator neutrons mentioned above [8].

We report the experimental procedure and the results for producing $^{99}$Mo/$^{99m}$Tc and $^{67}$Cu by using accelerator neurons from the Be,C($d$,$n$) reaction with a deuteron energy of 40 and 50 MeV.

## 2. Production of $^{99}$Mo/$^{99m}$Tc

### 2.1 $^{99}$Mo production by $^{100}$Mo(n,2n)$^{99}$Mo

We found that accelerator neutrons have a great potential to produce a large quantity of high-quality $^{99}$Mo with a minimum level of radioactive wastes without $^{235}$U. The characteristic points of the $^{99}$Mo production methods are as follow. The evaluated cross section of the ($n$,2$n$)$^{99}$Mo reaction in the neutron energy ($E_n$) range between 10 and 20 MeV is quite large, about 1.5 barn [9]. On the other hand, the cross sections of the ($n$,$\alpha$), ($n$,$n'p$), and ($n$,$p$) reactions on $^{100}$Mo, which can produce impurity radionuclides other than $^{99}$Mo, are less than a few mb at $E_n$ ~ 14 MeV. A large amount of $^{100}$Mo sample (> 100 g) can be used. In addition, intense neutrons with the energy of 11 – 18 MeV, necessary to produce $^{99}$Mo with good specific-activity, are available as discussed later.

### 2.2 $^{99}$Mo yield

The cross section of the ($n$,2$n$)$^{99}$Mo reaction has not yet been measured using accelerator neutrons from the C($d$,$n$) reaction at the deuteron energy of 40 MeV ($E_d$ = 40 MeV). Note that the neutron energy and angular distributions at $E_d$ = 40 MeV have been measured by two groups; the latest result of the neutron flux is approximately a factor of two larger than that of older one [4]. The cross section of the ($n$,2$n$)$^{99}$Mo reaction was measured at 8.5 ≤ $E_n$ ≤ 20.5 MeV [10]. Note that the neutrons have a continuous energy spectrum from the thermal energy to about 40 MeV. An accurate measurement of the $^{99}$Mo yield for a large mass $MoO_3$ sample of approximately 100 g is necessary to solve the discrepancy of the neutron flux between existing data including the evaluated cross section of the ($n$,2$n$)$^{99}$Mo reaction. The measurement would also provide information in considering the economic sustainability of the proposed production method by the ($n$,2$n$)$^{99}$Mo reaction.

We used four pellet $^{nat}MoO_3$ samples having each mass of about 26 g mass. Schematic of the experimental setup is shown in Fig. 1.

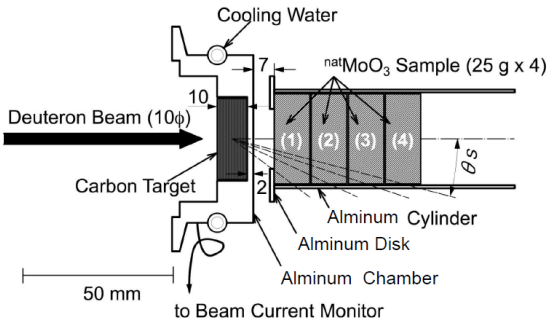


**Fig. 1.** Schematic of the experimental setup at the $^{nat}MoO_3$ sample position [12].

Here, $\theta_s$ indicates an opening angle between the lines connecting the outer edge of the sample to the geometric centers of the sample. This arrangement of the samples was aimed at being a rigorous test of the measurement of the energy and angular distributions of the accelerator neutrons including the

evaluated cross section. The measurement was performed by using accelerator neutrons provided by the C(*d*,*n*) reaction of 40 MeV deuterons at the Takasaki Ion Accelerators for Advanced Radiation Application of the National Institutes (TIARA) for Quantum and Radiological Science and Technology, and at Cyclotron and Radioisotope Center, Tohoku University [11,12].

The measured yield of $^{99}$Mo at the end of irradiation (EOI) agrees well with the calculated one as given in Table 1. The calculated yield was obtained by using the latest data on the neutron flux and the neutron-nucleus reaction cross sections given in the fourth version of the Japanese Evaluated Nuclear Data Library (JENDL-4.0) [9].

| | | | | |
|---|---|---|---|---|
| $^{nat}MoO_3$ (g) | 25.869 | 25.868 | 25.483 | 25.220 |
| $^{99}Mo_{meas.}$($10^4$ Bq) | 3.9 ± 0.2 | 2.6 ± 0.1 | 1.7 ± 0.1 | 1.3 ± 0.1 |
| $^{99}Mo_{cal.}$($10^4$ Bq) | 3.6 ± 0.7 | 2.3 ± 0.4 | 1.5 ± 0.3 | 1.0 ± 0.2 |

**Table 1.** Measured $^{99}$Mo yield ($^{99}Mo_{meas.}$) at the EOI compared with the calculated yield ($^{99}Mo_{cal.}$) [12]

The agreement provides reliable evidence to determine the best conditions for obtaining the calculated maximum yield of $^{99}$Mo under a given condition such as a $^{100}MoO_3$ sample mass and the distance between the carbon target and the $^{100}MoO_3$ sample. In fact, using 40 MeV, 2 mA deuterons the calculated yields of $^{99}$Mo at the end of irradiation for an irradiation time of 24 h for the $^{100}MoO_3$ samples of 100 – 150 g mass would meet about 50% of the demand for $^{99}$Mo in Japan [11,12].

### 2.2 Separation of $^{99m}$Tc from the $^{99}$Mo of low-specific activity

There have been two key issues in obtaining high-quality $^{99m}$Tc for any alternative $^{99}$Mo production method other than the fission reaction of $^{235}$U. Firstly, the specific activity of alternative $^{99}$Mo is so low that one cannot use a conventional $^{99}$Mo/$^{99m}$Tc generator. The second key issue is that the pharmaceutical quality of $^{99m}$Tc pertechnetate ($^{99m}TcO_4^-$) solution obtained from ($n$,2$n$)$^{99}$Mo has yet to satisfy the United States Pharmacopeia (USP).

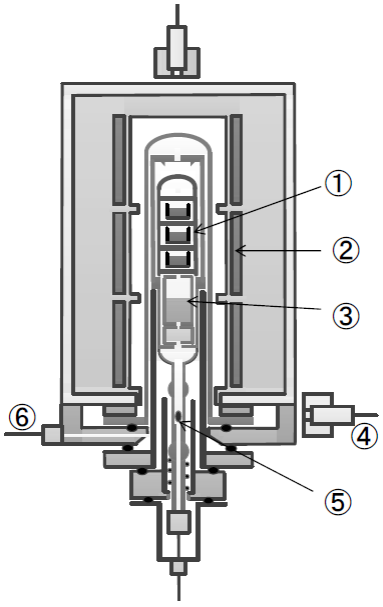


Fig. 2. Schematic of the experimental setup of the thermochromatographic separation. [13 ]

Among various methods to separate $^{99m}$Tc from the $^{99}$Mo of low-specific-activity, we employed the thermo-separation method in an electric furnace [13]. Note that the method could allow us to obtain $^{99m}$Tc with a high radioactive concentration, and to reuse an irradiated enriched $^{100}$Mo sample. Despite the progress so far made concerning the method, several problems to challenge remain: the separation efficiency of $^{99m}$Tc is low, diminishes markedly with repeated milking tests, and decreases with an increasing mass of $MoO_3$ loaded into a sublimation furnace at a time [14].

The separation of $^{99m}$Tc from the irradiated $^{100}MoO_3$ sample was carried out using a three-zone electric furnace which contained a quartz tube, three platinum boats to hold irradiated $MoO_3$ samples, and crumpled gold wire to trap vaporized $^{99m}$Tc oxide as shown in Fig. 2 [13]. The maximum temperature of the furnace zone was set at around 830°C to melt the irradiated $MoO_3$ samples. The high separation efficiency of 95% was achieved for the 20.3 g molten $MoO_3$ sample [13]. It should be added that a 99% recovery of an enriched $^{100}MoO_3$ sample of over 100 g mass was achieved by using the thermochromatography apparatus [15]. Note that an enriched $^{100}MoO_3$ sample is very expensive, so recycling of the sample by recovering it with high efficiency is crucial for the economical production of $(n,2n)^{99}$Mo.

The results of the quality assessments of the $(n,2n)^{99m}TcO_4^-$ saline solution and several $^{99m}$Tc-radiopharmaceuticals commonly used for the imaging of brain perfusion ($^{99m}$Tc-ECD), myocardial perfusion ($^{99m}$Tc-MIBI), and kidney ($^{99m}$Tc-MAG3), to ensure the safe clinical use of $(n,2n)^{99m}$Tc are summarized in Table I [16]. The quality of $^{99m}TcO_4^-$ should be noted to satisfy the United States Pharmacopeia (USP), which stipulates regulatory requirements on the radionuclide purity of $^{99m}$Tc, radiochemical purity of $^{99m}TcO_4^-$, radiochemical yields of $^{99m}$Tc radiopharmaceuticals, and the concentration of aluminium (Al) in the $^{99m}$Tc product.

| Parameter | USP | Exp. 1 | Exp. 2 | Exp. 3 | Exp. 4 |
|---|---|---|---|---|---|
| pH | 4.5 to 7.5 | 7.23 | 7.16 | 6.66 | 6.58 |
| Endotoxins | <175 EU/V | <0.03 EU/mL | >0.03 EU/mL | <0.03 EU/mL | <0.03 EU/mL |
| Radionuclidic purity<br>- non fission | $^{99}$Mo/$^{99m}$Tc<0.015%<br>Other $\gamma$s/$^{99m}$Tc<0.05% | <0.015%<br><0.05% | <0.015%<br><0.05% | <0.015%<br><0.05% | <0.015%<br><0.05% |
| Aluminum | <10 ppm | <10 ppm | <10 ppm | <10 ppm | <10 ppm |
| Molybdenum | Not specified | - | 0.138 ppm | 0.020 ppm | 0.034 ppm |
| Radiochemical purity | >95% $^{99m}TcO_4^-$ | >99% | >99% | >99% | >99% |

| | | | | | |
|---|---|---|---|---|---|
| Radiochemical yield | >90% | $^{99m}$Tc-MIBI >95% | $^{99m}$Tc-ECD >95% | $^{99m}$Tc-MAG3 >95% | $^{99m}$Tc-MDP >95% |

**Table 2**. Results of the quality control tests of the $^{99m}TcO_4^-$ saline solution and $^{99m}$Tc-radiopharmaceuticals and USP specifications. [16]

## 3. Production of $^{67}$Cu

### 3.1 Radionuclide purity of $^{67}$Cu produced by the $^{68}$Zn($n$,$n'p$+$d$)$^{67}$Cu reaction

So far, many studies were performed to produce as much $^{67}$Cu as possible by using reactors via the $^{67}$Zn($n$,$p$)$^{67}$Cu reaction and accelerators via the $^{68}$Zn($p$,2$p$)$^{67}$Cu, $^{68}$Zn($\gamma$,$p$)$^{67}$Cu, $^{67}$Zn($n$,$p$)$^{67}$Cu, $^{70}$Zn($p$,$\alpha$)$^{67}$Cu, and $^{70}$Zn($d$,$\alpha n$)$^{67}$Cu reactions [17].

In this study the radionuclide purity of $^{67}$Cu produced by the $^{68}$Zn($n$,$n'p$+$d$)$^{67}$Cu reaction was investigated using an enriched $^{68}$ZnO sample and neutrons from the C($d$,$n$) reaction of 40 MeV deuterons [18]. The purity at EOI was shown to be high, thus solving the impurity problems of $^{64}$Cu and $^{65}$Zn which were coproduced together with $^{67}$Cu by the $^{68}$Zn($p$,2$p$)$^{67}$Cu reaction [18].

| | Beam energy (MeV) | Ratio to $^{67}$Cu | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $^{64}$Cu | $^{66}$Ga | $^{67}$Ga | $^{69m}$Zn | $^{65}$Zn | $^{65}$Ni | $^{66}$Ni |
| $^{68}$Zn($p$,2$p$)$^{67}$Cu | 100 → 20 | 10 | ~12 | ~2.5 | | ~0.1 | | |
| $^{70}$Zn($d$,$\alpha n$)$^{67}$Cu | 19.5 → 18.4 | 0.1 | 0.03 | 0.07 | 2.3 | | | |
| Present Exp. $^{68}$Zn($n$,$x$) | | <0.016 | ~0 | ~0 | 0.14 | $6.7\times10^{-4}$ | 2.6 | $(2.4–5.0)\times10^{-3}$ |

Table I. Activity ratios of impurity radionuclides to $^{67}$Cu produced by $^{68}$Zn($p$,2$p$)$^{67}$Cu, $^{70}$Zn($d$, $\alpha n$)$^{67}$Cu, and $^{68}$Zn($n$,$n'p$+$d$)$^{67}$Cu reactions at EOI. [18]

### 3.2 Chemical separation of $^{67}$Cu from Zn

Stable copper isotopes in the $^{68}$ZnO samples were removed by chelating ion-exchange column chromatography to obtain high specific activity of $^{67}$Cu. The chemical separation of $^{67}$Cu from the neutron-irradiated $^{68}$ZnO sample was performed to obtain highly purified $^{67}$Cu to form $^{67}$CuCl$_2$ ($^{64}$CuCl$_2$) by using a cation-exchange column, a chelating ion-exchange column, and an anion-exchange column [19]. The separation yield of $^{67}$Cu was 91%.

The specific activity of $^{67}$Cu was determined to be 4.5 MBq/(μg Cu) at EOI. This value is much smaller than the typical specific activity of $^{64}$Cu produced by the $^{64}$Ni($p$,$n$)$^{64}$Cu reaction in the range of 2.4 – 11 GBq/(μg Cu) quoted from the recent study on the biodistribution of $^{64}$CuCl$_2$ in rats [20]. In low-specific-activity radiopharmaceuticals, stable isotopes such as $^{63}$Cu and $^{65}$Cu compete with radioactive isotopes, which results in poor radiolabeling and low uptake of the tracer in tissues. Hence, it is very interesting to study the role of $^{67}$CuCl$_2$ with low specific activity in the biodistribution of $^{67}$Cu ions in colorectal tumor-bearing mice.

### 3.3 Biodistribution of $^{67}$CuCl$_2$ in mice

Cu-based radiopharmaceuticals that can accumulate in cancer cells have been developed and widely used. Recently, $^{64}$CuCl$_2$ has been identified as a potential agent for PET imaging and radionuclide therapy. The results suggest that Cu metabolism is also important for many cancers, and prompted us to measure the biodistribution of $^{67}$CuCl$_2$ in colorectal tumor-bearing mice. The biodistribution of $^{67}$CuCl$_2$ in LS180 tumor-bearing mice was determined by using $^{67}$Cu of very low-specific-activity as shown in Fig. 3 [21]. It is very interesting that a high uptake of $^{67}$Cu in the tumor was found, which may indicate an important role of Cu metabolism in colorectal cancer. The accumulation of $^{67}$Cu in the

tumor was 7.0 ± 1.4 %ID/g at 48 h, comparable to that of $^{64}$Cu, ~5 %ID/g, in spite of the differences in the cancer cell lines and in the specific activities. $^{67}CuCl_2$ can be a potential radionuclide agent for cancer radiotherapy.

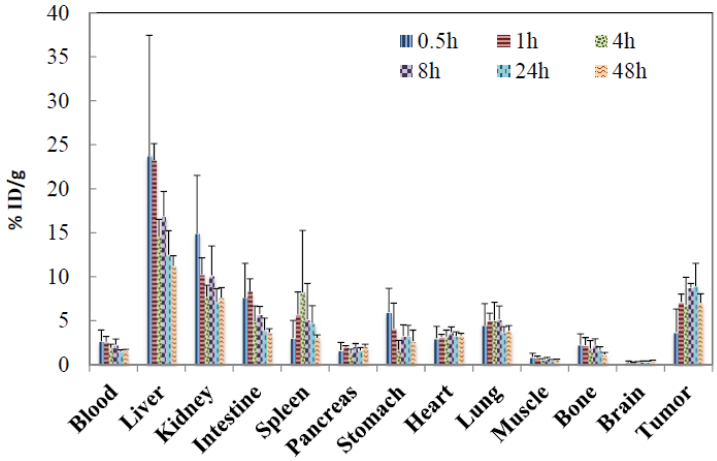


Fig. 2. Biodistribution of $^{67}CuCl_2$ in LS180 tumor-bearing mice with standard deviation. [21]

## 4. Production of accelerator neutrons

The intensity of neutrons having energies at $10 \leq E_n \leq 20$ MeV is the key issue for sufficiently producing $^{99}$Mo by the $(n,2n)^{99}$Mo reaction. Recently significant progress has been achieved in accelerator technology to obtain intense neutrons. In fact, at SPIRAL2 located at GANIL, neutrons with an intensity of $10^{15}$ n/s are expected to be produced by the C($d$,$n$) reaction using 40 MeV 5 mA deuterons [22]. A great advance has also been achieved with the development of a neutron converter, which can withstand the high power of the 40 MeV 5 mA deuteron beams [23]. On the basis of these developments, we propose to construct an AVF cyclotron with a deuteron beam intensity of 2 mA as a prototype facility, since a fixed radiofrequency cyclotron is robust in operation, compact in size, and relatively cheap compared to a linear accelerator.

## 5. Conclusions

A new method has been proposed for the generation of radioisotopes such as $^{99}$Mo and $^{67}$Cu with accelerator neutrons by deuterons (hereafter, GRAND). A prototype facility for the GRAND consists of a cyclotron to produce intense accelerator neutrons from the C($d$,$n$) reaction with 40MeV 2mA deuteron beams. The characteristic feature of the GRAND lies in its capability to produce a wide variety of high-quality, carrier-free radioisotopes with a minimum level of radioactive waste without using uranium. The separation of high quality $^{99m}$Tc from $^{99}$Mo of low specific activity, which was produced by the $^{100}$Mo($n$,2$n$)$^{99}$Mo reaction, was performed by developing a thermoschromatographic system. The pharmaceutical quality of $^{99m}$Tc pertechnetate solution obtained from $^{99}$Mo met the United States Pharmacopeia requirements. About 50% of the demand for $^{99}$Mo in Japan can be met with the prototype facility. The biodistribution of $^{67}CuCl_2$ in colorectal tumor-bearing mice was measured using $^{67}$Cu of high radionuclide purity that was produced by the $^{68}$Zn($n$,$n'p$+$d$)$^{67}$Cu reaction and a high uptake of $^{67}$Cu in the tumor was observed, which suggests that $^{67}CuCl_2$ can be a potential radionuclide agent for cancer radiotherapy. It should be mentioned that the potential of the GRAND for various medical radioisotopes coproduction provides an important indication of the economic sustainability,

demand risk mitigation and the ability to avoid creating other isotope shortage. The prototype system is compact in size, and easy to operate; therefore it could be used worldwide to produce radioisotopes for medical, research, and industrial applications.

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