PASJ2017 TUP133

PHOTONUCLEAR PRODUCTION OF SELF-TARGETING MEDICAL RADIONUCLIDES USING AN X-BAND ELECTRON LINEAR ACCELERATOR: A FEASIBILITY STUDY

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Abstract

Motivated by the 2009–2010 global ⁹⁹Mo/^{99m}Tc supply disruptions, we recently designed an *X*-band electron linear accelerator intended for ⁹⁹Mo production. Further to this, we examined photonuclear production of radionuclides which can concentrate in body organs without biomolecules. Of particular interest are ⁵⁴Mn and ^{87m}Sr, which can be produced via ⁵⁵Mn(γ ,n)⁵⁴Mn and ⁸⁸Sr(γ ,n)^{87m}Sr, respectively. Here we present their radiopharmaceutical potentials, target designs, and expected yields.

INTRODUCTION

Technetium-99m (99m Tc), with which over 80% of all radiopharmaceutical scans are carried out [1], is generally obtained through the negatron (β^-) decay of molybdenum-99 (99 Mo). For decades, 99 Mo has been supplied as a fission product of 235 U [2]. Owing to aging of the involved reactors, however, this fission-based 99 Mo supply chain has become fragile, highlighting the need for an alternative 99 Mo production method. 99 Mo production via the 100 Mo photoneutron reaction is an example, for which we recently designed an *X*-band electron linear accelerator (linac) [3,4]. Thereafter, in an attempt to extend the range of available medical radionuclides, we studied electron-linac-based production of manganese-54 (54 Mn) and strontium-87*m* (87m Sr), which we deem potential imaging agents for the heart and bone, respectively.

SELF-TARGETING MEDICAL RADIONUCLIDES

A radiopharmaceutical is essentially a radiolabeled active ingredient (AI) designed to be concentrated in a specific body organ. For instance, when ^{99m}Tc-ECD is administered to a patient, the ECD is taken up by the brain [5], while the ^{99m}Tc provides their location information using its 140.5keV γ -rays. As such, it is mostly the AI that directs its radiopharmaceutical to the target organ, while the attached radionuclide is used merely for their detection.

Developing an AI requires, however, a substantial research budget and a long period of time. In order to circumvent this research barrier, and to make more radionuclides available for medicine and research, we investigated radionuclides which can concentrate in body organs without AIs and can be produced via photonuclear reactions. ⁵⁴Mn and ^{87m}Sr

Table 1: Decay Characteristics of	of ⁵⁴ Mn and	^{87m} Sr
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⁵⁴ Mn	^{87m} Sr
312.3 d	2.8 h
EC ^a γ 834.8 keV (99.9%)	IT ^b γ 388.5 keV (81.9%)
55 Mn(γ , n) 54 Mn	88 Sr(γ ,n) 87m Sr
⁵⁵ Mn: 100%	⁸⁸ Sr: 82.6%
Myocardium	Bone
	$\frac{54}{Mn}$ 312.3 d EC ^a γ 834.8 keV (99.9%) $^{55}Mn(\gamma,n)^{54}Mn$ $^{55}Mn: 100\%$ Myocardium

^a Electron capture.

^b Isomeric transition.

are such self-targeting medical radionuclides, of which the decay properties are given in Table 1 [6].

^{54}Mn

We are attempting to produce ⁵⁴Mn via the ⁵⁵Mn photoneutron reaction, or ⁵⁵Mn(γ ,n)⁵⁴Mn; the threshold energy is known to be 10.2 MeV [6].

Studies [7] have shown that the myocardial uptake of ⁵⁴Mn can be higher than that of ²⁰¹Tl, a popular heart imaging agent. This stems from the fact that mitochondria, in which manganese is localized, are abundant in the myocardium [7].

As ⁵⁴Mn exhibits a relatively long physical half-life T_{phy} , it is worth noting that the time during which a radionuclide stays in a body is not simply dictated by T_{phy} , but by the effective half-life T_{eff} :

$$T_{eff} = \frac{T_{phy}T_{bio}}{T_{phy} + T_{bio}}$$

where T_{bio} represents the biological half-life.

Moreover, reasonable production costs are expected from the isotopic abundance of the target material: 55 Mn accounts for 100% of naturally occurring manganese (nat Mn).

^{87m}Sr

^{87m}Sr can be produced via ⁸⁸Sr(γ ,n)^{87m}Sr, of which the threshold energy is approximately 11.1 MeV [6].

Belonging to the same group as calcium in the periodic table, strontium has a great affinity to bone matrix [8]. The skeletal system can therefore be visualized by 87m Sr.

Remarkable advantages of 87m Sr are its moderate T_{phy} and γ -ray energy, shown in Table 1. Affordable production costs are also expected, as the natural abundance of 88 Sr is as high as 82.6%.

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SIMULATION-BASED YIELD ESTIMATION

We performed Monte Carlo (MC) simulations using PHITS version 2.88 [9], for evaluating [4]

$$A_{i}(t_{\rm irr}) = \left[1 - e^{-\lambda_{i} t_{\rm irr}}\right] \mathcal{V}_{\rm tar} I_{b} \int_{E_{\gamma,\rm min}}^{E_{\gamma,\rm max}} \Phi_{\rm MC}(E_{\gamma}) \Sigma(E_{\gamma}) \, dE_{\gamma}$$
⁽¹⁾

where $A_i(t_{irr})$ is the activity of a radionuclide *i* during target irradiation time t_{irr} , λ_i is the decay constant of *i*, \mathcal{V}_{tar} is the target volume, I_b is the electron beam current, E_{γ} is the bremsstrahlung energy, $\Phi_{MC}(E_{\gamma})$ is the bremsstrahlung fluence obtained by an MC simulation program, and $\Sigma(E_{\gamma})$ is the macroscopic cross section for producing *i*.

The target configurations used in the simulation runs are summarized in Table 2, and illustrated graphically in Fig. 1. Besides, the beam energy and average current of the *X*-band electron linac we designed, found in Ref. [3], were 35 MeV and 260 μ A, respectively. Using these beam parameters, in addition to \mathcal{W}_{tar} of Table 2 and the photonuclear reaction cross sections contained in TENDL-2009 [10], we evaluated Eq. (1) for ⁵⁴Mn and ^{87m}Sr.

Table 2: Target Assembly Dimensions

Target	Shape	Parameter (cm)		Volume (cm ³)
nat 🗤	Dick	Radius	2.0	1.26
vv	DISK	Thickness	0.1	1.20
55Mm /	Turnerstad	Lower radius	0.5	
⁸⁸ Sr	cone	Upper radius	1.5	10.21
51		Height	3.0	



Figure 1: Bremsstrahlung tracks in the ^{nat}W-⁵⁵Mn target assembly simulated at electron beam energy $E_e = 35$ MeV.

As implied by the exponential term, however, the production rates of the two radionuclides differ to a great extent: the decay constant $\lambda = \frac{\ln 2}{T_{phy}}$ of 87m Sr is 0.248 h⁻¹, whereas that of 54 Mn is as low as 9.248 × 10⁻⁵ h⁻¹. Accordingly, rather than plotting their yields with respect to irradiation time, we coplot in Fig. 2 their microscopic cross sections with bremsstrahlung fluences averaged over the respective target volumes, and tabulate their activities in Table 3. Here t_{irr} for 88 Sr(γ ,n)^{87m}Sr was selected considering the time at which the 87m Sr activity converges to its maximal activity, which is approximately 7T_{phy}:

$$1 - e^{-\frac{\ln 2}{T_{\rm phy}} \left(7T_{\rm phy}\right)} \approx 0.992$$

On the other hand, because $7T_{phy}$ of ^{54}Mn is impractically long for target irradiation, t_{irr} for $^{55}Mn(\gamma,n)^{54}Mn$ was chosen taking into account the time during which the natural tungsten (^{nat}W) bremsstrahlung converter can withstand the thermal stress.



Figure 2: Microscopic cross sections contained in TENDL-2009 and volume-averaged bremsstrahlung fluences calculated at $E_e = 35$ MeV.

Table 3: Evaluation Results of Eq. (1)

Product	$t_{\rm irr}$ to saturation activity (~ 7T _{phy})	t _{irr}	$A_i(t_{irr})$
⁵⁴ Mn	2186.1 d	72 h	170.8 GBq
^{87m} Sr	19.6 h	18 h	14.5 TBq

Although the evaluated ⁵⁴Mn and ^{87m}Sr activities are the ones before chemical processing and delivery to end users, considering the activity loss factors of ⁹⁹Mo/^{99m}Tc supply chain and average dose of commercial radiopharmaceuticals, we find the resulting ⁵⁴Mn and ^{87m}Sr activities fairly high. Utilizing the compactness of the designed *X*-band electron linac, then, sufficient quantities of these self-targeting radionuclides can be supplied with satisfactory accessibility.

PASJ2017 TUP133

POST-IRRADIATION CHEMICAL PROCESSING

Following its production, a medical radionuclide should be chemically processed to meet pharmacopeial standards. Examples include pH adjustment and additive addition, and chemical separation if the radionuclide in question is obtained through its parent. Furthermore, as mentioned earlier, almost all medical radionuclides are compounded with organic molecules to form radiopharmaceuticals. In contrast, as ⁵⁴Mn and ^{87m}Sr are designed to be self-targeting, and can be produced directly from photonuclear reactions, simpler chemical processing is expected.

SUMMARY

Conventional radiopharmaceuticals are a mixture of biomolecules and radionuclides, the former of which make radiopharmaceutical development demanding. In a bid to bypass this involvement of biomolecules or AIs, and to extend the range of electron-linac-producible medical radionuclides, we examined the radiopharmaceutical potentials, photonuclear production methods, and yields of ⁵⁴Mn and ^{87m}Sr. We expect that using the *X*-band electron linac we recently designed can enable producing these self-targeting medical radionuclides in close proximity to radiopharmacies or laboratories.

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