Compelling Case for Fostering Titanium-45 for Positron Emission Tomography Tracer Applications

Abstract
The growth of diagnostic nuclear medicine is substantially based on the development, availability, and regular clinical use of cyclotron-based positron emission tomography (PET) tracers. Apart from $^{18}$F (110 min) products, the radiometal $^{68}$Ga isotope (68 min) has found an increasingly wide clinical acceptance. There is hence much merit in identifying and fostering other radiometal positron emitters, of preferably longer half-life. Titanium-45 (3.08 h) fits the bill well in this context, as it is easy to produce using natural scandium metal target and Ep of 13–14 MeV for Sc(p, n) Ti reaction. This Commentary cites a compelling case to foster the development of Ti products for PET imaging.

Keywords: Gallium-68, medical cyclotron, mononuclidic target, positron emission tomography tracer; scandium target, Titanium-45

Introduction
The increasing importance and growth of diagnostic nuclear medicine (NM) are substantially attributable to the development, availability, and regular clinical use of cyclotron-based tracers with positron emission tomography (PET)/computed tomography, going well beyond $^{18}$F (110 min) products (fluorodeoxyglucose [FDG] and others). There are over 1200 cyclotrons in countries across the world, most of them being of the compact type called medical cyclotron (MC). The natural complement to organic PET tracers (of $^{11}$C, $^{18}$F) available from these MC is the radiometal-chelate-binder conjugate; in this context, the radiometal $^{68}$Ga isotope (68 min, 89% positron emission, $\beta^-$ end-point energy 1.92 MeV) has found renaissance and clinical acceptance.

Gallium-68
The generator-based availability of $^{68}$Ga, which is surely an advantage, has however led to a monopoly hold by $^{68}$Ge-$^{68}$Ga vendors, including through their influence on the limited number of $^{68}$Ge (271 days) producers. Naturally, this has led to researchers exploring alternate options for $^{68}$Ga, given the growing number of MC available around the world. A consequential success recently reported is in terms of the daily production and supply of $^{68}$Ga produced by Sc(p, n) Ti reaction in curie (GBq) level, as well as the scope to use both solid and liquid (enriched) targets of $^{68}$Zn. This is an important milestone in NM and was specifically highlighted in the International Atomic Energy Agency (IAEA) event “International Symposium on Trends in Radiopharmaceuticals (ISTR-2019)” by many groups. For example, up to 140 GBq of $^{68}$Ga was produced following 90-min irradiation of pressed powder target of $^{68}$Zn. The overall recovery yield of $^{68}$GaCl$_3$ was 89% with $\pm 5$ GBq/µmol at the end of bombardment. A group from Portugal reported a liquid target system for $^{68}$Ga production and is in daily use for curie-level production and supply.

Titanium-45
In view of the above fruitful development, a natural poser can be: Is there an alternate, or supplement, to the direct production of the PET tracer $^{68}$Ga in MC? Based on the literature available and certain recent publications and presentations, it is envisaged that the positron emitter $^{45}$Ti can eminently meet such a need. $^{45}$Ti has a half-life of 3.08 h, 85% decay by positron emission (rest 15% by electron capture), and a $\beta^-$ end-point energy of 1.04 MeV. More importantly, the target required

Address for correspondence:
Dr. Natesan Ramamoorthy, 141 KBL Enclave, Vijayanagara, 4th Stage, 2nd Phase, Mysore - 570 032, Karnataka, India.
E-mail: nramasta@gmail.com

Received: 23-03-2020
Revised: 25-03-2020
Accepted: 28-03-2020
Published: 01-07-2020

How to cite this article: Ramamoorthy N. Compelling case for fostering Titanium-45 for positron emission tomography tracer applications. Indian J Nucl Med 2020;35:200-2.
for its production is natural scandum, a mononuclidic element ($^{45}$Sc). The reported cross-section for the $^{45}$Sc (p, n) $^{44}$Ti reaction is in the range of 200–400 mb depending on incident energy, $E_p$ 12–14 MeV. At the University of Alabama, Birmingham, USA, 18 MeV MC was used with an energy degradation Al foil; typical yield reported (1): $^{45}$Sc(p, n) $^{44}$Ti, $E_p$ 13–14 MeV, 0.5 h, 10 μA, 63 mCi (2.35 GBq). Irradiation for an hour with 50 μA current will result in 23.5 GBq production of $^{45}$Ti, a substantial quantity for regular use. The existing distribution schemes worked out for $^{18}$F products: $^{18}$F-FDG, in particular, will be adoptable for the supply of $^{45}$Ti, for both intra-city and inter-city supplies.

It is required to ensure that the right energy of incident protons is used so as to avoid (p, 2n) reaction on $^{45}$Sc, which will result in the production of traces of long-lived $^{44}$Ti (60 years). Further, the envisaged short duration of MC irradiation of $^{45}$Sc target, namely, about an hour or two, will also help minimize the formation of traces of long-lived $^{44}$Ti. Thus, naturally, $^{45}$Ti production deserves much attention by every MC facility, including in India, which has already a suitable solid target station (e.g., SGPGIMS, Lucknow; INMAS, Delhi; and Cyclone-30 of VECC-BRIT, Kolkata), or where it may be possible to install one. It is necessary to also encourage the direct production of $^{68}$Ga from enriched $^{68}$Zn target, despite the logistics challenges due to its 68-min half-life. Wherever $^{45}$Ti can be used in the place of $^{68}$Ga, it should be encouraged, as it will reduce the requirement of $^{68}$Ga to that extent.

Demands on MC industry will accordingly change with the requirement of solid target stations to be an essential part of new MC establishments, in order to make the production of many radioisotope (RI) (e.g., $^{64}$Cu, $^{68}$Ga, and $^{89}$Zr) of emerging importance, including $^{45}$Ti. MC of $E_p >13$ MeV energy (variable, preferably) would be in demand, for adopting the required reaction options for more RI production, i.e., MC of 10–11 MeV is no more likely to be attractive. The simplicity of compact, fixed-energy proton accelerator – cyclotron – has to make way for needs-based alterations/additions, to avail of the required incident energy of projectiles on the target(s) for medical RI production.

$^{45}$Ti radiopharmaceuticals

There has been interest in $^{45}$Ti product reported even in 2005,[4] The chemistry of gallium and titanium is not identical; also, titanium is more prone to hydrolysis in certain conditions. Although this may be held against $^{45}$Ti, especially for the theranostic approach, where the pair of $^{68}$Ga and $^{17}$Lu has got so well established, radiopharmacists and allied scientists have adequate expertise and scope to develop suitable new products of $^{45}$Ti for potential clinical use. The recent review by Costa et al. is deemed an important literature in this context.[3] One can cite first the high interest and clinical importance in PET tracer-based high-resolution imaging of infection and of myocardial perfusion (MPI), the latter aided further by the superior quantification advantage of PET technique. Development of PET products for such use will be a much welcome addition, for example, one can explore $^{45}$Ti- ubiquicidine (UBI) fragment for infection imaging (akin $^{68}$Ga-UBI and $^{99m}$Tc-UBI). Many ligands (e.g., acetylaceone, nioxime) studied or used with $^{99m}$Tc could be similarly potential candidates for developing $^{45}$Ti-based MPI agents (e.g., $\text{[Ti} (L)_2 \text{]}^{3-}$ type). The early launch of one or more such product will give a big thrust to PET-based nuclear cardiology.

This is not to say that $^{45}$Ti cannot be used for peptide-like binder-based radiopharmaceutical for targeted tumor imaging. Both known chelators and novel ones are possible for using with $^{45}$Ti and conjugation to a specific binder moiety, for example, peptide, antibody, and enzyme inhibitor to target tumors and other lesions, which present the corresponding binding site, for example, receptor and antigen, overexpressed on the tumors. Deferoxime is currently the chelator being used with another longer lived PET tracer $^{89}$Zr (3.27 days, 22.3% positron emission; also producible from natural target $^{89}$Y),[1,3] and it can be a good starting point for $^{45}$Ti too (due to the similarity of M (IV) chemistry).

Concluding remarks (Please see footnote)

This brief note (Commentary) is aimed at triggering multipronged R&D efforts by willing researchers and their institutions, including through harnessing synergies and collaborations, to strive to pragmatically expand the inventory of easy-to-access $^{45}$Ti-based PET radiopharmaceuticals of clinical utility. The IAEA has been requested to consider supporting such measures, for example, through a Coordinated Research Project (CRP).[3] These will help to effectively supplement and complement the growing use of $^{68}$Ga-based PET tracers, apart from signaling the end of vulnerability to the undesirable monopoly effect of some vendors!

Footnote text

For performing exploratory studies on titanium-based products for potential medical use, one can use as a starting point, the long-lived $^{45}$Ti (60 d) producible by (p,2n) reaction on $^{45}$Sc target in a suitable cyclotron on a campaign mode, and/or use the very short-lived $^{17}$Ti (5.76 min; not carrier-free) producible repeatedly in fairly good quantity using a suitable neutron source, including a reactor, where available/accessible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.
References
1. Book of Abstracts of the IAEA Int. Symposium on Radiopharmaceuticals (ISTR). Vienna: IAEA; 2019. Available from: https://www.iaea.org/sites/default/files/19/10/cn-276-programme-and-abstracts.pdf. [Last accessed on 2020 Mar 23].
2. Proceedings of the IAEA Int. Symposium on Radiopharmaceuticals (ISTR) 2019. Vienna: IAEA; 2020.
3. Costa P, Metello LF, Alves F, Naia MD. Cyclotron Production of Unconventional Radionuclides for PET Imaging: the Example of Titanium-45 and Its Applications, Instruments 2018;2:8-17.
4. Vävere AL, Laforest R, Welch MJ. Production, processing and small animal PET imaging of titanium-45. Nucl Med Biol 2005;32:117-22.