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Receptor-targeted technetium-^{99m}Tc radiopharmaceuticals: increasing access to molecular imaging in healthcare

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The γ -emitting radionuclide, technetium-^{99m}Tc, is widely accessible from ^{99m}Tc generators, and is routinely incorporated into diagnostic imaging radiopharmaceuticals that measure perfusion or anatomical process in disease. There is potential to expand the use of ^{99m}Tc to molecular radiopharmaceuticals, and leverage well-established and existing nuclear medicine infrastructure and resources (including nuclear reactor and ^{99m}Tc generator supply chains, radiopharmacies, γ -scintigraphy and SPECT cameras, and trained nuclear medicine staff) to increase patient access to the benefits of receptor-targeted molecular imaging, particularly in oncology. To achieve this, suitable chemistry is required to develop new ^{99m}Tc-labelled radiopharmaceuticals that incorporate ^{99m}Tc into biomolecules. This review describes how existing ^{99m}Tc chemistry has recently been applied to such innovations: chelator and ligand motifs (including mercapto-peptide, amine oxine, phosphine, isonitriles) that are already used for kit-based synthesis of ^{99m}Tc perfusion agents have been derivatised with biomolecular pharmacophores for receptor-targeted molecular imaging. Recent clinical trials have established an evidence basis illustrating the utility of these new receptor-targeted ^{99m}Tc radiopharmaceuticals. This work also describes the potential for an economical companion "theranostic" approach with the β^- -emitter, rhenium-188 (¹⁸⁸Re), which can also be produced using generator technology. Initial preclinical and clinical studies have demonstrated that chemically analogous ^{99m}Tc and ¹⁸⁸Re radiotracers show highly similar biodistribution patterns.

KEYWORDS

generator, molecular imaging, peptide, radiopharmaceuticals, receptor, rhenium-188, SPECT, technetium-^{99m}Tc

Introduction

The advent of molecular radiopharmaceuticals (Sullivan et al., 2024) has been transformative in treatment for neuroendocrine cancer (Strosberg et al., 2017) and metastatic castration-resistant prostate cancer (Sartor et al., 2021). These radiopharmaceuticals (or tracers) consist of a radionuclide appended to a pharmacophore or biomolecule that targets receptors over-expressed on the surface of cancer cells. There are many metallic radionuclides that have utility for molecular diagnostic

imaging or systemic radiotherapy. These radioactive metal centres are attached to biomolecules via chelators (Jackson et al., 2020).

In a “theranostic” approach with pairs of “look and treat” radiopharmaceuticals a radioactive imaging tracer first provides a whole body diagnostic imaging scan of receptor expression in a patient (Langbein et al., 2019; Weber et al., 2023; Bodei et al., 2022). If the scan shows that the patient’s disease is positive for the target receptor, a second radiotherapeutic tracer can be administered to the patient. For both the imaging and therapeutic tracers, the same pharmacophore is employed to enable delivery of the radioactive cargo to diseased tissue (Sullivan et al., 2024; Strosberg et al., 2017).

In neuroendocrine cancer, the somatostatin 2 receptor (SSTR2) is targeted by ^{68}Ga -DOTA-octreotate (Figure 1), (DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) for diagnostic PET (Positron Emission Tomography) imaging, and ^{177}Lu -DOTA-octreotate for delivery of a cytotoxic dose of β^- -irradiation for systemic radiotherapy (Strosberg et al., 2017). In the past - and indeed still in centres where PET imaging is unavailable - ^{111}In -DTPA-octreotide (DTPA, diethylenetriaminepentaacetic acid) has been used to diagnose SSTR2-positive neuroendocrine cancers using γ -scintigraphy or SPECT (Single Photon Emission Computed Tomography) imaging (Shi et al., 1998).

In prostate cancer, the prostate specific membrane antigen (PSMA) is targeted most typically with a urea-containing dipeptide, appended to a PET isotope (^{68}Ga , or ^{18}F) or a radiotherapeutic isotope. The most common pairing is ^{68}Ga -PSMA-11”, using a derivative of the HBED (*bis*(2-hydroxybenzyl) ethylenediaminediacetic acid) chelator, for diagnostic PET imaging, alongside companion ^{177}Lu -PSMA-617”, using the DOTA chelator, for systemic radiotherapy (Figure 1) (Sartor et al., 2021).

There are a range of new therapeutic radionuclides that are being investigated for the utility of their β^- , α and Auger electron particle emissions in cancer treatment. This is likely to have further impact in oncology treatment, and pharmaceutical investment in receptor-targeted cancer theranostics is in the multibillion dollar range (Sullivan et al., 2024). The availability of companion diagnostic agents will be critical to the clinical success of these future radiotherapy treatments. Currently, receptor-targeted PET agents are the state-of-the-art in molecular imaging, however, there are limitations here:

- There are shortfalls in availability of ^{68}Ga , as a result of demand for ^{68}Ga outstripping supply (Kumar, 2020).
- Whilst the development of ^{18}F -labelled radiotracers for imaging PSMA in prostate cancer can potentially mitigate ^{68}Ga -HBED-PSMA supplies, this is subject to existing limitations of PET/CT. First, many healthcare settings do not have access to PET/CT scanners (Sh and into, 2017; Verduzco-Aguirre et al., 2019; Al-Ibraheem et al., 2025). Second, ^{18}F , which is produced in cyclotrons, has a half-life of 109 min, and so ^{18}F PET radiopharmaceuticals are prepared onsite at hospitals or at centralised distribution facilities. Current radiosyntheses require multistep reactions and procedures, prolonged reaction times at high temperatures, and purification to remove unreacted radionuclide and other components. This necessitates costly equipment and highly trained staff. This can lead to shortages in radiopharmaceutical supply, disruption to patient treatment and geographical

disparities in availability. In many lower to middle income countries, the costs, infrastructure and resources associated with ^{18}F and PET/CT are barriers to implementation (Al-Ibraheem et al., 2025).

There is an alternative to complex radiopharmaceutical production: *one-step, rapid, kit-based radiosyntheses of radiopharmaceuticals, which decrease the need for infrastructure, personnel and expense*. This approach is already applied with “traditional” technetium-99m ($^{99\text{m}}\text{Tc}$). $^{99\text{m}}\text{Tc}$ emits γ -photons ($t_{1/2} = 6$ h; 90% γ , 140 keV) and is widely used in γ -scintigraphy and SPECT imaging radiopharmaceuticals for perfusion/function imaging. $^{99\text{m}}\text{Tc}$ is universally available from $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generators, with well-established supply chains from nuclear reactors, and $^{99\text{m}}\text{Tc}$ radiopharmaceuticals are routinely prepared by technicians in radiopharmacies, using aqueous $^{99\text{m}}\text{Tc}$, commercial “kits” (containing reagents and chelator) and a syringe. The chelators rapidly bind $^{99\text{m}}\text{Tc}$, enabling simple radiosyntheses (Jackson et al., 2020; Rivas et al., 2021).

Due to all these existing resources, $^{99\text{m}}\text{Tc}$ imaging is significantly more accessible than PET imaging. For example, it is estimated that $^{99\text{m}}\text{Tc}$ is used in over 30 million scans worldwide per year. In the UK, there are 252 National Health Service (NHS) nuclear medicine departments (as of 2021), which routinely undertake $^{99\text{m}}\text{Tc}$ imaging procedures. From 2013 to 2023 within NHS England, there were 4,263,180 γ -scintigraphy and SPECT scans undertaken, and 1,621,835 PET/CT scans (NHS England, 2023).

The development of molecular $^{99\text{m}}\text{Tc}$ radiopharmaceuticals would leverage existing healthcare and infrastructure resources, enabling increased population-wide access to receptor-targeted molecular imaging. These resources include SPECT and γ -scintigraphy cameras, which are more prevalent than PET/CT cameras (Weber et al., 2023; Bodei et al., 2022; Shi et al., 1998). Essential resources, including trained staff, radiopharmacies and nuclear medicine infrastructure, already exist.

The β^- -emitting radioisotope, ^{188}Re , is also available from a benchtop $^{188}\text{W}/^{188}\text{Re}$ generator, and the β^- decay properties ($t_{1/2} = 17$ h; 100% β^- , $E_{\text{max}} = 2.12$ MeV; 15% γ , 155 keV) of ^{188}Re are suitable for systemic radiotherapy (Lepareur et al., 2019). Furthermore, systemic radiotherapeutics are potentially economically viable and accessibly in Lower and Middle Income Countries (LMICs), where there are significant barriers to accessing radiopharmaceuticals (Shinto, 2017; Bernal et al., 2008). Recognising the potential of ^{188}Re as an affordable basis for systemic radiotherapies, in the early part of this century, the International Atomic Energy Agency (IAEA) sponsored multinational clinical trials of ^{188}Re -labelled Lipiodol for treatment of inoperable liver cancer in LMICs (including India, Mongolia, Philippines, Thailand and Vietnam). ^{188}Re -labelled Lipiodol proved effective and inexpensive (Bernal et al., 2008; Bernal et al., 2007). ^{188}Re -labelled bisphosphonates have also been extremely beneficial in palliative treatment of bone metastases in LMICs (Shinto et al., 2018). $^{188}\text{W}/^{188}\text{Re}$ generators currently supply ^{188}Re for “Rhenium-SCT” brachytherapy (Baxi et al., 2024) for highly prevalent basal and squamous cell carcinomas, the most common skin cancers. “Rhenium-SCT” has been recently approved in Europe, South Africa and Australia.

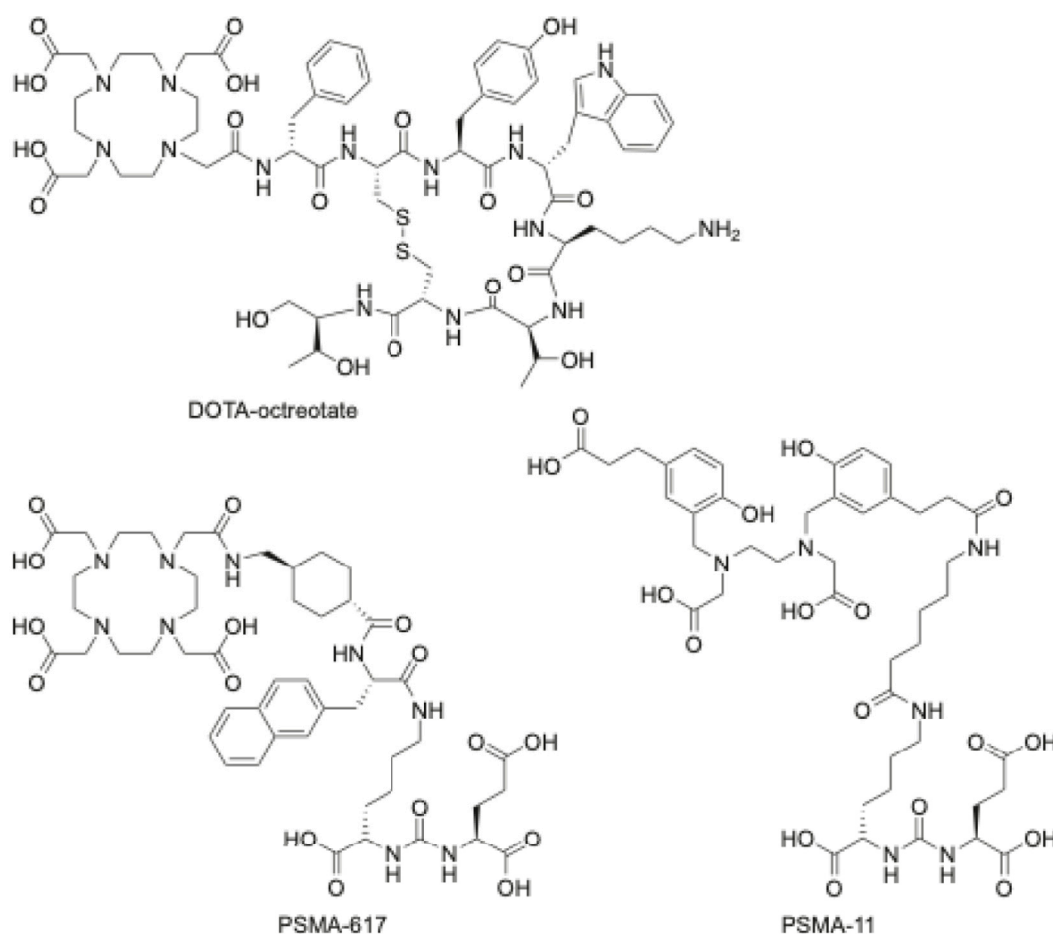


FIGURE 1

Structures of DOTA-octreotate (top), which is used to deliver $^{68}\text{Ga}^{3+}$ or $^{177}\text{Lu}^{3+}$ to SSTR2-expressing neuroendocrine tumours, and PSMA-617 and PSMA-11 (bottom), containing the DOTA and HBED chelators respectively. ^{177}Lu -PSMA-617 and ^{68}Ga -PSMA-11 are theranostic radiopharmaceuticals used for treatment of PSMA-expressing prostate cancer.

Tc and Re often form isostructural and isoelectronic complexes, leading to the possibility of pairs of complexes with near identical biodistributions, including accumulation patterns in diseased tissue, *in vivo*. Pairs of $^{99\text{m}}\text{Tc}$ and ^{188}Re radiopharmaceuticals are often considered “theranostic pairs”, with the $^{99\text{m}}\text{Tc}$ radiotracer providing a diagnostic image of disease, to stratify patients for systemic radiotherapy using an analogous ^{188}Re radiotracer (Blower et al., 2000; Bordoloi et al., 2015; Spyrou et al., 2021).

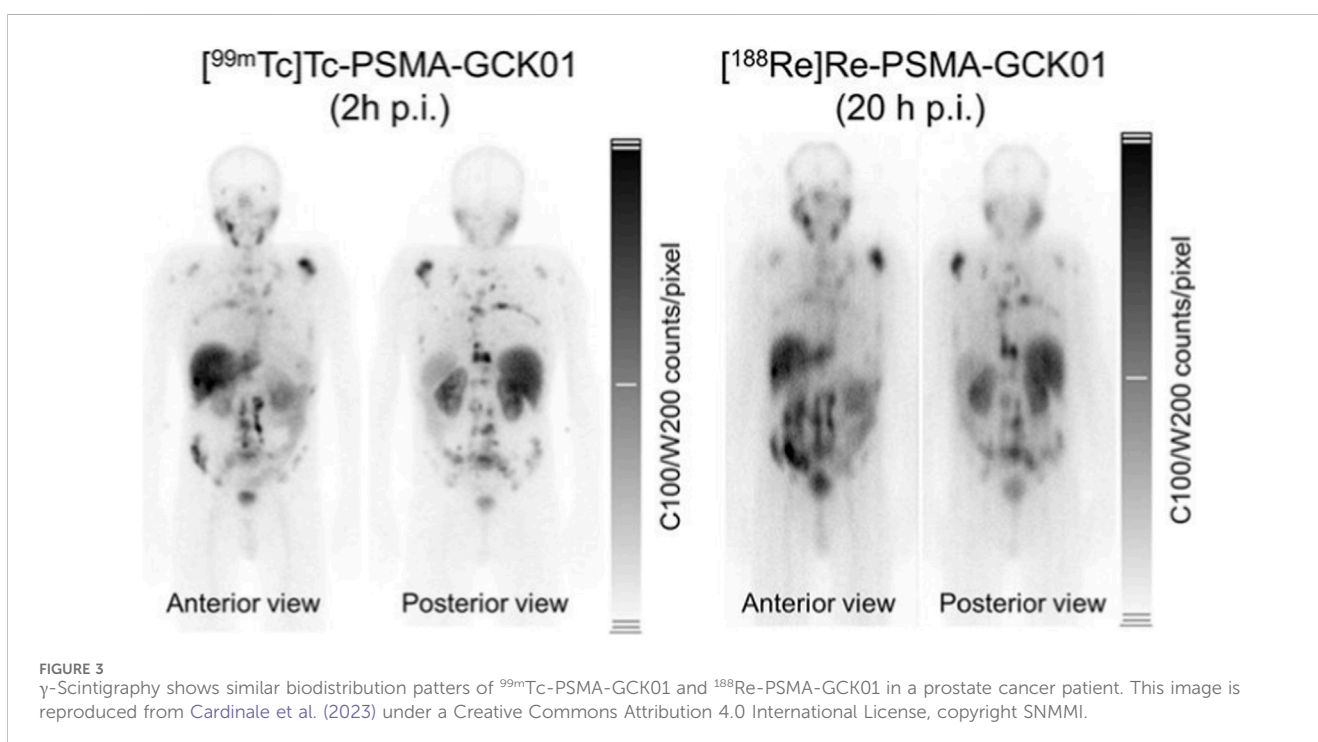
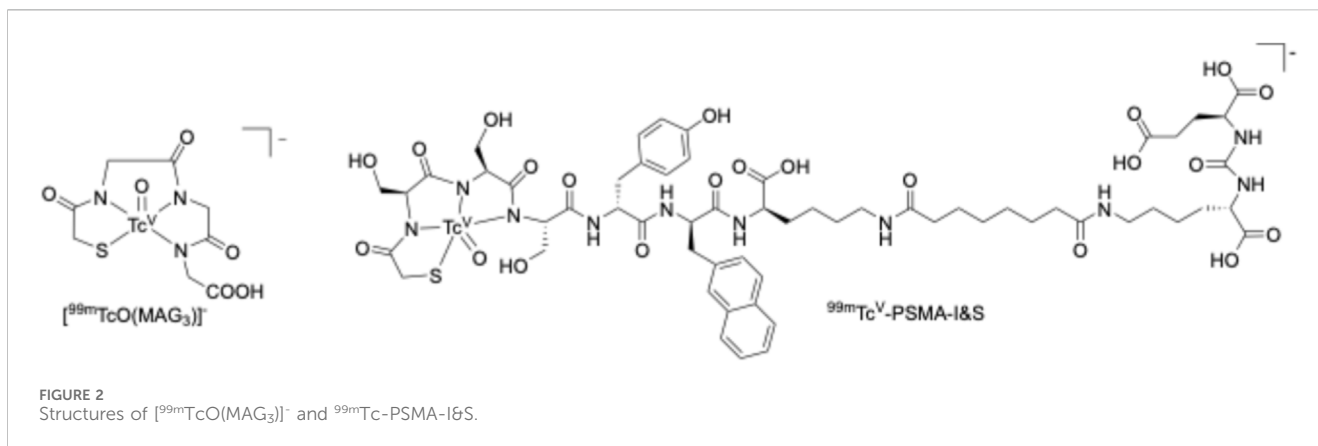
$^{99\text{m}}\text{Tc}$ chemistry and its application has been a dynamic and international field of research for the last 8 decades, and alongside the routine clinical use of $^{99\text{m}}\text{Tc}$ perfusion and anatomical radiopharmaceuticals, there are many elegant examples of $^{99\text{m}}\text{Tc}$ tracers that have entered first-in-human studies (Alberto, 2023a; Alberto, 2023b; Riondato et al., 2023; Duatti, 2021; Shi and Liu, 2024). This review will summarise how well-established $^{99\text{m}}\text{Tc}$ chelator and coordination chemistry, such as that used for $^{99\text{m}}\text{Tc}$ perfusion imaging agents, has been applied to develop the latest state-of-the-art radiopharmaceuticals that have recently entered clinical evaluation for receptor targeted imaging. It will also describe selected innovations in ligands designed specifically

for $^{99\text{m}}\text{Tc}$ that demonstrate the breadth and scope of Tc coordination chemistry.

MAG₃ and mas₃ radiotracers

The “MAG₃” (mercaptoacetyl-triglycine) chelator consists of a mercapto function attached to three glycine amino acids. The deprotonated amide groups in combination with the thiol donor group provide a N₃S tetradentate chelator that coordinates a [$^{99\text{m}}\text{Tc}^{\text{VO}}$]³⁺ motif, to furnish a five-coordinate, distorted square pyramidal complex, [$^{99\text{m}}\text{TcO}(\text{MAG}_3)$]⁻ (Grummon et al., 1995), used routinely for diagnostic renal imaging (Figure 2) (Marta et al., 2013).

The chemistry of [$^{99\text{m}}\text{TcO}(\text{MAG}_3)$]⁻ has been successfully adapted for molecular imaging. Early studies established that glycine residues can be substituted for other amino acids without ameliorating [$^{99\text{m}}\text{Tc}^{\text{VO}}$]³⁺ coordination (Cantorias et al., 2007; Cyr et al., 2007). NMR experiments have indicated that in this case, in which glycine is substituted for optically active amino acids, two distinct isomers are formed, as the amino acid sidechains can be



positioned either *syn* or *anti* relative to the Tc=O bond (Cantorias et al., 2007; Cyr et al., 2007).

The most significant application of this chemistry to ^{99m}Tc molecular imaging involves replacement of the three glycine amino acids for serine amino acids, and concomitant functionalisation with PSMA-targeted peptide sequences (Figure 2) (Robu et al., 2017). It is notable that incorporation of “unnatural” D-serine in place of biogenic L-serine results in increased metabolic stability of the ^{99m}Tc radiotracer.³³ ^{99m}Tc -PSMA-I&S is the most clinically studied of these mac_3 -derived PSMA-targeted tracers to date. ^{99m}Tc -PSMA-I&S has demonstrated utility in detecting tumour lesions at various stages of prostate cancer, including primary and advanced disease, and in biochemically recurrent prostate cancer (Werner et al., 2020). However, when lesions are small or the biochemical markers of recurrence are low, ^{99m}Tc -PSMA-I&S imaging detects fewer lesions

than PSMA PET imaging (Albaloooshi et al., 2020). ^{99m}Tc -PSMA-I&S has also been clinically assessed for detection of prostate cancer metastases using a hand-held γ -detector, during surgery. The aim of this endeavour is to improve surgical resection of prostate cancer tissue (Maurer et al., 2019).

More recently, a new PSMA-targeted mac_3 -peptide derivative, PSMA-GCK01,³⁷ has been developed for coordination of both the $[^{99m}\text{TcO}]^{3+}$ and $[^{188}\text{ReO}]^{3+}$ motifs. In a first in human study, both tracers showed equivalent biodistributions in a prostate cancer patient, as evidenced by γ -scintigraphy (Figure 3). Such innovation shows the feasibility and possibility of chemically analogous $^{99m}\text{Tc}/^{188}\text{Re}$ dual molecular imaging/systemic radiotherapy tracers.

New directions, including application of mercapto-peptide chelating derivatives to alternative pharmacophores and their receptor targets – for example, small molecules that target cancer-associated fibroblasts of aggressive, hard-to-treat

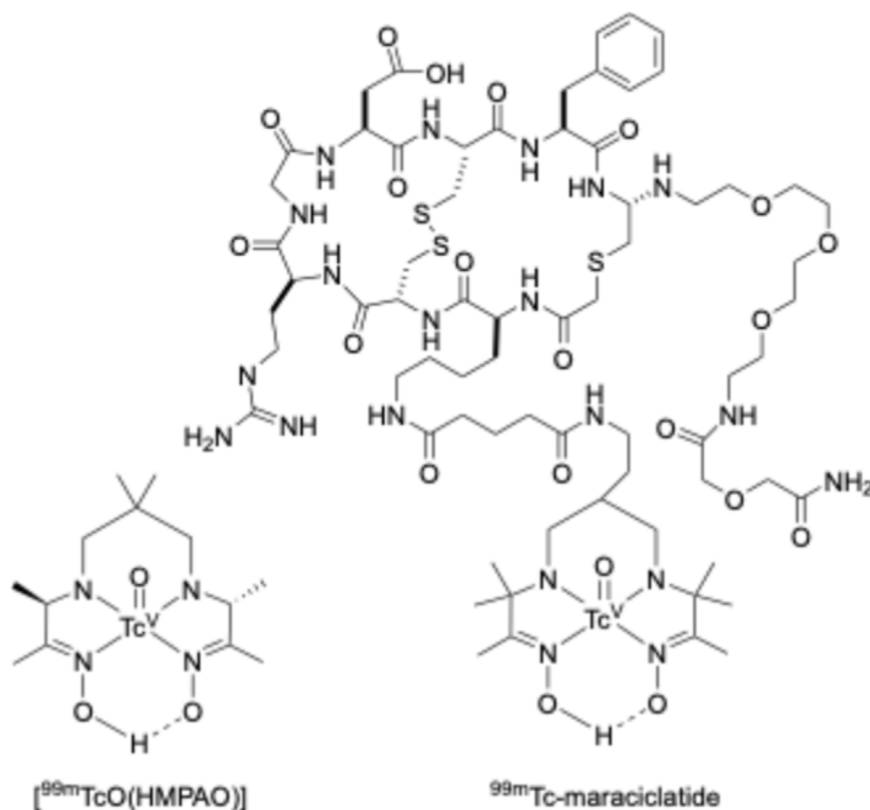


FIGURE 4
Structures of $[^{99m}\text{TcO}(\text{MAG}_3)]^-$ and ^{99m}Tc -PSMA-I&S.

cancers — will further expand the clinical utility of this chelator chemistry (Xu et al., 2025).

HMPAO and maraciclalide

Like MAG3, HMPAO (hexamethylpropylene amine oxine) coordinates a $[^{99m}\text{Tc}^{\text{V}}\text{O}]^{3+}$ core (Figure 4). The resulting neutral, lipophilic complex can pass the blood-brain barrier, and $[^{99m}\text{TcO}(\text{HMPAO})]$ is routinely used to detect changes in cerebral perfusion in stroke patients (Neirinckx et al., 1987).

The radiopharmaceutical “ ^{99m}Tc -maraciclalide” is a derivative of HMPAO. In this ^{99m}Tc -labelled compound, the HMPAO chelator contains two additional methyl substituents, and is appended to a cyclic “RGD” peptide that targets the $\alpha\text{v}\beta 3$ integrin receptor (Figure 4), which is associated with inflammation and neovasculature. ^{99m}Tc -maraciclalide has been assessed in multiple first-in-human studies, and has shown utility for clinical imaging in imaging rheumatoid arthritis (Attipoe et al., 2020), cancer imaging (Cook et al., 2018) and more recently, in endometriosis, for which it has recently received FDA fast track designation.

HYNIC

The HYNIC motif, 2-hydrizinicotinamide, was pioneered in the 1990s (Abrams et al., 1990), and acts as both the linker and a

chelator. The coordination environment of ^{99m}Tc complexes has not been elucidated despite HYNIC’s prevalent use. Scientific literature often depicts HYNIC coordinating to Tc^{V} in a monodentate fashion (Figure 5), with five co-ligands for stabilization — for example, ethylenediaminediacetic acid (EDDA) — although existing data suggests that it is more likely to interact with Tc as a bidentate chelator, via the terminal hydrazine and pyridine nitrogen atom, with the latter requiring fewer co-ligands to fill the Tc coordination sphere (King et al., 2007; Meszaros et al., 2010). Attempts to prepare Re analogues of Tc complexes have largely been unsuccessful. Despite this, the radiopharmaceutical ^{99m}Tc -EDDA/HYNIC-octreotide is in occasional use for receptor targeted imaging of the somatostatin receptor over-expressed in neuroendocrine cancers (Gabriel et al., 2003), and ^{99m}Tc -HYNIC derivatives targeting $\alpha\text{v}\beta 3$ integrin (Zhu et al., 2012) and PSMA (Lawal et al., 2017) have recently undergone clinical studies in cancer imaging.

Organometallic complexes of $^{99m}\text{Tc}^{\text{I}}$

Organometallic complexes of $^{99m}\text{Tc}^{\text{I}}$ have exhibited sufficient kinetic stability to enable application in radiopharmaceuticals, and indeed, are useful exemplars in demonstrating the application of organometallic chemistry to healthcare. The homoleptic ^{99m}Tc complex, ^{99m}Tc -sestamibi, consists of six isonitrile ligands coordinated to a Tc^{I} metal centre in an octahedral environment (Figure 6) (Kronauge and Mindiola, 2016). The resulting lipophilic

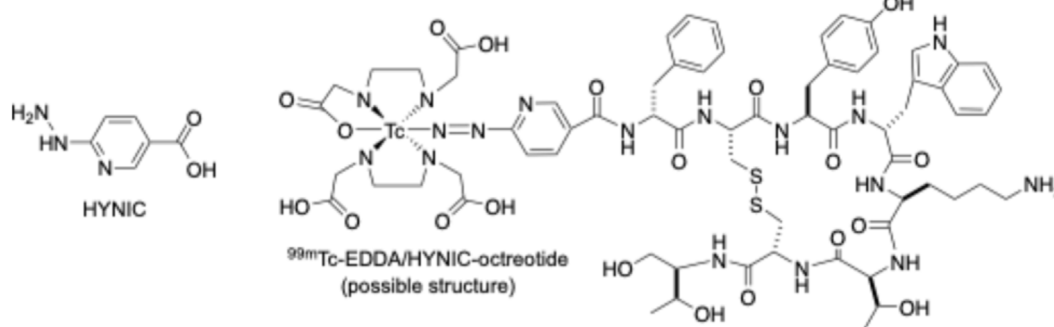


FIGURE 5
The structure of HYNIC, and a possible structure of ^{99m}Tc -EDDA/HYNIC-octreotide.

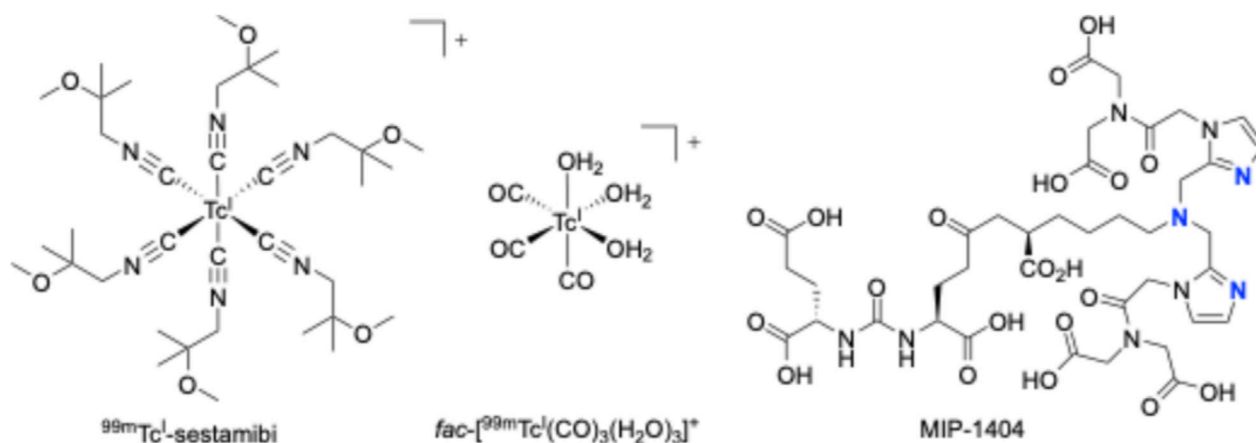


FIGURE 6
Structures of ^{99m}TcI -sestamibi, $\text{fac-}[^{99m}\text{TcI}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ and MIP-1404, which coordinates to $\text{fac-}[^{99m}\text{TcI}(\text{CO})_3]^+$ via three N donors (highlighted in blue).

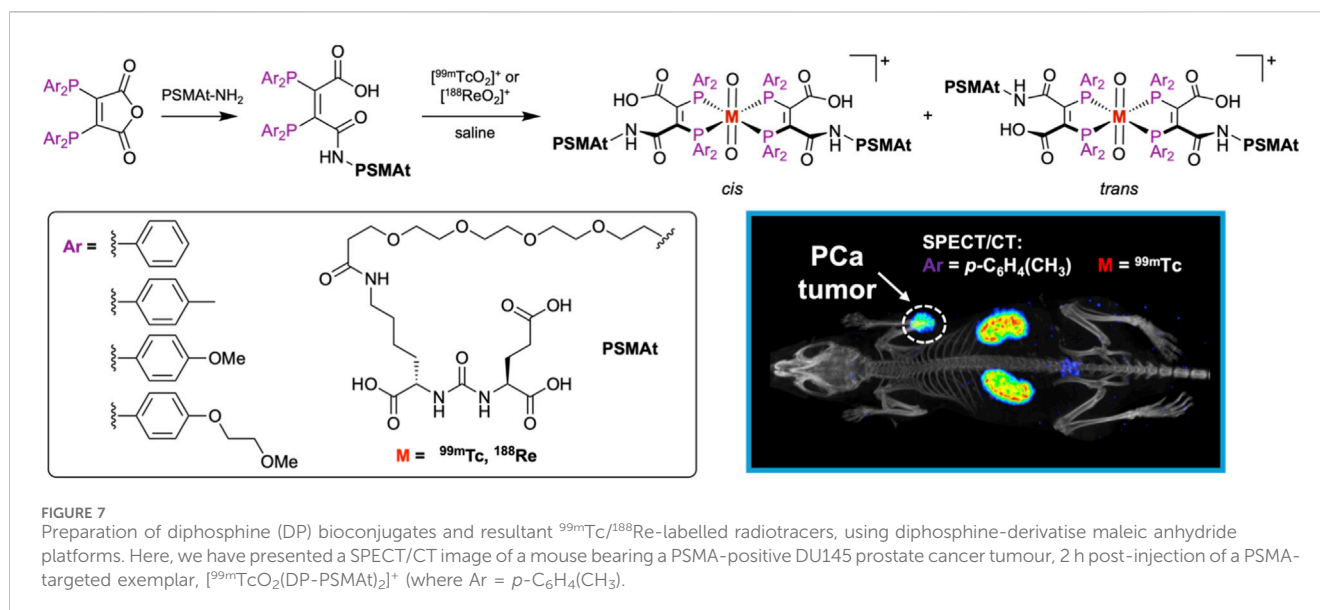
complex bearing a single positive charge, diffuses across the lipid bilayer of cell and then mitochondrial membranes, driven by membrane potentials. As ^{99m}Tc -sestamibi accumulates in tissue rich in mitochondria, such as the heart, ^{99m}Tc -sestamibi is routinely used for imaging cardiac perfusion.

Although they have not been assessed in the clinical, isonitrile ligands bearing receptor-targeted peptides have been developed for coordination to ^{99m}TcI (Mizuno et al., 2016). This approach, whereby multiple copies of a targeting motif are incorporated onto a single radioactive metal centre, is potentially advantageous in increasing the affinity of a molecular radiopharmaceutical for its cognate receptor.

At the turn of the century, the d^6 $\text{fac-}[^{99m}\text{TcI}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ complex was developed (Alberto et al., 2001; Alberto et al., 1998). The three water ligands undergo relatively rapid substitution, enabling coordination of chelator-pharmacophore bioconjugates. The $\text{fac-}[^{99m}\text{TcI}(\text{CO})_3]^+$ motif is used in the radiopharmaceutical ^{99m}Tc -MIP-1404 (also known as ^{99m}Tc -Trofolastat), in which the PSMA-targeted dipeptide is appended to a tridentate N_3 chelator consisting of a tertiary amine with two

pendant imidazole groups, which in turn is coordinated to the $\text{fac-}[^{99m}\text{TcI}(\text{CO})_3]^+$ motif, to form an octahedral complex (Figure 6) (Hillier et al., 2013). The radiosynthesis and purification of ^{99m}Tc -MIP-1404 is currently time-consuming compared to kit formulations of ^{99m}Tc perfusion radiopharmaceuticals: the former requires (i) formation of an intermediate $\text{fac-}[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ precursor prior to (ii) chelation with the tridentate MIP-1404 chelator-peptide, and finally (iii) purification and formulation before administration.

^{99m}Tc -MIP-1404 has demonstrated clinical utility for detection of prostate cancer lesions in patients with intermediate and high grade prostate cancer before prostatectomy (Goffin et al., 2017), and in patients with biochemical recurrence of prostate cancer (after primary treatment with either prostatectomy or radiotherapy) (Schmidkonz et al., 2018). Recent clinical studies have confirmed its suitability as a companion diagnostic imaging agent to inform stratification of patients for systemic radiotherapy with ^{177}Lu -DOTA-PSMA (Derlin et al., 2025; Cook et al., 2023). As a result, ^{99m}Tc -MIP-1404 has recently been approved by the United Kingdom's MHRA for clinical use in imaging and detecting high risk prostate cancer,



biochemical recurrence of prostate cancer, and in assessing eligibility for ^{177}Lu -DOTA-PSMA systemic radiotherapy.

Other elegant organometallic ^{99m}Tc complexes have been developed, and although, like isonitrile-peptide derivatives for coordination of $^{99m}\text{Tc}^{\text{I}}$ (Mizuno et al., 2016), they have not yet been assessed in clinical studies, their ingenuity compels a mention. This includes piano-stool *fac*- $[\text{}^{99m}\text{Tc}^{\text{I}}(\text{CO})_3]^+$ complexes based on cyclopentadiene motifs bearing receptor-targeted peptides (Frei et al., 2019), dinuclear Tc complexes such as $[\text{}^{99m}\text{Tc}_2(\mu_2\text{-SR})_3(\text{CO})_6]^-$ ($\text{R} = \text{S}(\text{CH}_2)_2\text{N}(\text{Et})_2$), bridged by alkyl thiols (Bolliger et al., 2019), and $[\text{Tc}(\eta^6\text{-arene})_2]^+$ sandwich complexes (Nadeem et al., 2020), including those of functionalised arenes that have exhibited anti-tumour activity (Battistin et al., 2023).

Phosphine complexes

The $^{99m}\text{Tc}^{\text{V}}$ complex, ^{99m}Tc -tetrofosmin, consists of a $[\text{TcO}_2]^+$ motif coordinated to two bidentate diphosphine ligands, to furnish a lipophilic, singly charged cation, which, like ^{99m}Tc -sestamibi, is routinely used for imaging cardiac perfusion (Jones and Hendel, 1993). Like ^{99m}Tc -HMPAO, ^{99m}Tc -sestamibi and ^{99m}Tc -MAG3, ^{99m}Tc -tetrofosmin can be prepared using a single step kit, in which all the non-radioactive reagents are contained in a lyophilised, sterile vial, to which generator-produced $^{99m}\text{TcO}_4^-$ is added, to furnish ^{99m}Tc -tetrofosmin, typically in quantitative radiochemical yield.

Inspired by the efficiency of the kit-based radiosynthesis of ^{99m}Tc -tetrofosmin, we have recently developed diphosphine-derivatised maleic anhydride platforms to prepare bioconjugates of diphosphines with receptor-targeted molecules (targeting $\alpha\beta_3$ integrin (Hungnes et al., 2021), PSMA receptors (Hungnes et al., 2023; Pham et al., 2024; Nuttall et al., 2025)) and other receptors (Nuttall et al., 2025) (Figure 7). These diphosphine-based bioconjugates can be incorporated into a kit formulation (Hungnes et al., 2021; Hungnes et al., 2023; Pham et al., 2024; Nuttall et al., 2025; Nuttall et al., 2023). Addition of $^{99m}\text{TcO}_4^-$ in saline to a

lyophilised mixture of the diphosphine-peptide, reducing agent (stannous chloride), intermediate chelator (tartrate) and buffer (carbonate), yields the desired radiotracer, $[\text{}^{99m}\text{TcO}_2(\text{DP-peptide})_2]^+$ in high radiochemical yields.

By tuning phosphine ligand substituents of a diphosphine maleic anhydride derivative to increase electron donation of the phosphine ligands, we have shown that we can increase the radiochemical yield of the desired $[\text{}^{99m}\text{TcO}_2(\text{DP-peptide})_2]^+$ radiotracer (Hungnes et al., 2023; Nuttall et al., 2025). Furthermore, chemically analogous $[\text{}^{188}\text{ReO}_2(\text{DP-peptide})_2]^+$ compounds can also be accessed, using generator-produced ^{188}Re , and pairs of ^{99m}Tc and ^{188}Re radiotracers show near-equivalent biodistributions in mouse models of cancer (Pham et al., 2024). To date, the radiotracers we have prepared all show high tumour accumulation, fast clearance via a renal pathway and low off-target/healthy organ retention (Hungnes et al., 2021; Pham et al., 2024; Nuttall et al., 2025; Nuttall et al., 2023), suggesting that diphosphine platforms have utility for simple, kit-based preparation of ^{99m}Tc radiopharmaceuticals.

Concluding remarks

Chemical technology enabling development and clinical adoption of ^{99m}Tc receptor-targeted molecular imaging has demonstrated feasibility for clinical translation, and new, fit-for-purpose innovations in ^{99m}Tc and ^{188}Re chelator chemistry could enable the development of ^{99m}Tc and ^{188}Re receptor-targeted theranostic pairs. These advances match the availability of existing nuclear medicine infrastructure, including ^{99m}Tc generator supply chains, γ -scintigraphy and SPECT cameras, and radiopharmacies and nuclear medicine departments. The latter include staff skilled in formulation of kit-based ^{99m}Tc radiopharmaceuticals. Leveraging ^{99m}Tc chemistry alongside these resources and infrastructure could increase economical and accessible patient access to the benefits of molecular radiopharmaceuticals.

Author contributions

MTM: Writing – original draft, Writing – review and editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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