Rhenium-188 Radiochemistry: Challenges and Prospects

Philip J. Blower*

King's College London, Division of Imaging Sciences and Biomedical Engineering, St Thomas' Hospital, London SE1 7EH, UK

Abstract: After a lull in development of new chemistry for rhenium-188 and technetium-99m since 2000, there has been new investment in production facilities for Mo-99/Tc-99m coupled with increasing interest in rhenium-188 radionuclide therapy, particularly in developing countries. Much of the chemistry developed in the 1990s is not readily amenable to supporting modern radiopharmaceutical development, which places increased emphasis on molecular targeted radiopharmaceuticals. Consequently there is a need for new radiolabelling chemistry to incorporate these radionuclides into biomolecules using simple, kit-based methodology. This review provides an update on progress towards simple rhenium-188 labelling methods since 2000.

Keywords: Rhenium-188, Technetium-99m, Bioconjugates, Kit, Radionuclide therapy.

INTRODUCTION

The rhenium-188 generator is an attractive source of a therapeutic radionuclide, for a variety of reasons, in certain settings and applications. It can provide daily availability, by a simple elution process entirely analogous to the elution of a technetium-99m generator. The capital cost (*i.e.* purchase of a generator) may be high but in a setting where many patients can be treated, it can be very economical compared to commercially available batch-produced therapeutic radionuclides such as lutetium-177. It is, in principle at least, versatile and can be incorporated into a range of types of vehicle suitable for molecular targeting. Its β-energy is high E_{max} 2.21 MeV, comparable to that of phosphorus-32 and yttrium-90), delivering a high radiation dose, and the half-life of 17 hours is compatible with the pharmacokinetics of many small molecules and antibody fragments. Its low abundance gamma emissions (155 KeV, 15%) allow gamma camera imaging. These properties are less favourable in some circumstances; for example, the high energy β-emission is not likely to be effective in eradicating smaller tumours and micrometastases, and the 17 hour half-life is too short to be fully compatible with the pharmacokinetics of whole IgG antibodies whose blood half-life is typically several days. Nevertheless, the favourable logistics and economics associated with generator-based availability make it very attractive, particularly in locations where these features are particularly important, such as economically less developed countries.

The development of the chemistry of ^{188}Re radiopharmacueticals has to an extent shadowed that of ^{99m}Tc, with which its coordination chemistry is highly analogous by virtue of its periodic position [1]. The analogy includes the chemical basis of the generator – both rely on β-decay of MO_4^{2-} (M = ^{99}Mo or ^{188}W) to give MO_4^- (M = ^{99m}Tc or ^{188}Re), which is more readily eluted from the alumina solid phase by saline. The development of the chemistry of ^{99m}Tc radiopharmacueticals since the 1960s, following the advent of the ^{99}Mo/^{99m}Tc generator and the gamma camera, can be traced in three phases.

The first phase comprises radiopharmaceuticals coming into routine use in the 1970s, such as the complexes of dimercaptosuccinic acid (DMSA), bisphosphonates (*e.g.* methylene diphosphonate, MDP), diethylenetriamine pentaacetic acid (DTPA) and glucoheptonate. The development of these was based on almost no knowledge of the basic coordination chemistry of technetium, and in most cases the molecular structures and oxidation states of the technetium in these radiopharmaceuticals remain unknown even today. Indeed, they are likely to be complex mixtures of structures. This early phase was characterised by very little understanding of either technetium chemistry or the mechanisms by which the specific targeting of the tracers occurred *in vivo.* Hence their nuclear medicine utility is best described as "functional imaging."

In the second phase emerging in the 1980s, new ^{99m}Tc radiopharmaceuticals with well-defined structure appeared, building on new basic research in technetium chemistry by pioneers such as Davison and Deutsch. This research led to identification of the more stable "technetium core" complex types in which ligand

*Address correspondence to this author at the King's College London, Division of Imaging Sciences and Biomedical Engineering, St Thomas' Hospital, London SE1 7EH, UK; Tel: +44(0)2071889513;
Fax: +44(0)2071883056; E-mail: Philip.Blower@kcl.ac.uk

E-ISSN: 2408-9788/17

design was well-matched to the coordination preferences of the metal in its different oxidation states. These include the Tc(V)oxo ($[TcO]^{3+}$) and Tc(V)nitride ($[TcN]^{2+}$) cores with their characteristic tetragonal pyramidal geometry, the Tc(V) dioxo core ($[TcO_2]^{+}$), well defined Tc(III) complexes, and the Tc(I) cores based on π-accepting ligands (isonitrile and carbonyl). In this phase, molecular structure was well-defined (for example, ^{99m}Tc-HMPAO, ^{99m}Tc-MAG3, pentavalent ^{99m}Tc-DMSA, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin and ^{99m}Tc-NOET are all based on stable cores and are well-characterised structurally). *In vivo* mechanisms, however, remained obscure until later when, for example, mitochondrial uptake of the lipophilic cations ^{99m}Tc-sestamibi [2] and ^{99m}Tc-tetrofosmin was identified and evidence of pentavalent ^{99m}Tc-DMSA entering cells via specific phosphate transporters [3] emerged.

The third phase, emerging in the 1990s, coincided with the transition of nuclear medicine into the age of "molecular imaging" in which specific molecular pathways and receptors began to be targeted with specifically designed radiopharmaceuticals, often based on bioconjugates, in order to answer specific biomedical questions. Up the present time, this third phase is incompletely developed. Methods for conjugating ^{99m}Tc to biomolecules using various bifunctional chelators (HYNIC, MAG3 and other sulfur-nitrogen combination chelators that bind the $[TcO]^{3+}$ core effectively) and direct labelling approaches (binding of $[^{99m}Tc(CO)_3]^{+}$ to histidine tags and binding of reduced ^{99m}Tc to cysteine thiolate groups generated by reduction of antibody disulfide bonds) have been developed and available since the 1990s, but they have made little clinical impact. This may be in part because, unlike the phase 1 and 2 ^{99m}Tc radiopharmaceuticals, which were amenable to one-step kit formulation and reconstitution, none of the phase 3 labelling methods are technically easy and efficient to perform. In addition, it may be in part because the period since 1990 has coincided with the expansion of clinical PET, with research and development funds both in industry and academia being redirected towards molecular imaging with positron emitters.

The historical development of ^{99m}Tc tracers has provided the template for development of ^{188}Re radiopharmaceuticals too, albeit with a much lower degree of academic and commercial effort by comparison with ^{99m}Tc. The ^{188}Re-bisphosphonate complexes, of unknown and heterogeneous structure, were the first to emerge in clinical application (palliative treatment of painful bone metastases in prostate cancer). The first structurally well-characterised example was the pentavalent ^{188}Re-DMSA complex, with potential application in radionuclide therapy of medullary thyroid carcinoma and bone metastases in prostate cancer, which also emerged in the 1990s, [4-7] along with use of the ^{188}Re-MAG3 complex as a soluble β-emitting agent to fill balloons in coronary angioplasty (aiming to prevent restenosis) to guarantee rapid renal excretion in the event of balloon rupture [8]. Use of sulfur-nitrogen based bifunctional chelators such as MAG3, initially developed for ^{99m}Tc, were used to link the $[^{188}ReO]^{3+}$ core to peptides and proteins and incorporate ^{188}Re into particulates and emulsions for radioembolisation therapy. Direct labelling of proteins with histidine-tags using $[^{188}Re(CO)_3]^{+}$, and antibodies by reduction of disulfide bonds, followed the corresponding ^{99m}Tc developments. However, as has been the case with ^{99m}Tc, most of these agents and methods were established in the 1990s and although clinical applications have begun to take hold (all of which are based on "phase 1" and "phase 2" chemistry described above, as illustrated in other contributions to this issue), little new ^{188}Re chemistry development has occurred since that time. This unfortunate trend is reflected in the chart shown in Figure **1**, which shows that publications describing new ^{188}Re chemistry and clinical research have plummeted since their peak in 2000.

Since 2000, repeated world-wide shortages of ^{99}Mo, and hence ^{99m}Tc, due to planned and unplanned down-time of the major nuclear reactors supplying the nuclear medicine community, have created crises in the field. At the same time, β-emitting radionuclides such as yttrium-90 and lutetium-177, which have been developed into clinical application without need for development of new chelate chemistry, have become prominent and drawn attention away from ^{188}Re, leading to a reduction in availability of ^{188}Re generators. The nuclear medicine community has had to consider hard decisions regarding the future of ^{99m}Tc availability and gamma camera imaging, in the face of growing availability of PET with the potential to replace long-established gamma camera imaging procedures (such as bone scanning with ^{99m}Tc-bisphosphonate complexes) with PET imaging (such as bone scanning with $[^{18}F]$fluoride). Far from signalling the demise of gamma camera imaging and ^{99m}Tc radiopharmaceuticals, we have seen as a result major investment in new reactors, and development of new accelerator-based routes to production of ^{99}Mo and ^{99m}Tc. These developments give credence to the notion and

technetium radiopharmaceuticals are here to stay, for the foreseeable future. Alongside the recent growth in adoption of ^{188}Re radionuclide therapies in some countries, [9, 10] ^{188}Re generator availability is improving again and the scene is set for a resurgence of development of both ^{99m}Tc and ^{188}Re chemistry development, reversing the recent trend (see Figure **1**) that has seen the collapse of basic research on the chemistry of these radionuclides since 2000.

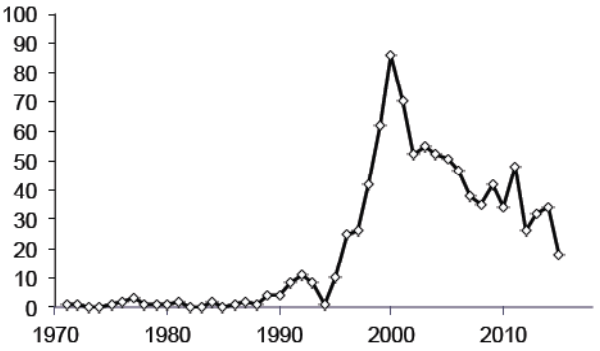

Figure 1: Total publications on rhenium-188 by year (data from Web of Knowledge, ©2017 Thomson Reuters).

The most comprehensive review of ^{188}Re radiopharmaceutical chemistry dates back to 1999 [11] and the reader is referred to that review for a summary of the state-of-the-art pre-2000, as well as to reviews published within the last decade covering bifunctional chelator and bioconjugation development for labelling peptides and proteins with both ^{99m}Tc and ^{188}Re [12-14]. The purpose of this article is to provide a brief update of developments since that time, identifying limitations of well-established coordination chemistry, with a focus on novel and well-characterised chemistry that has potential for application in the modern age of molecular imaging, rather than clinical applications of older, less well-characterised ^{188}Re agents, particulate and non-molecular materials (such as nanoparticles, liposomes, emulsions, stents and patches) and antibodies labelled using older methods.

DISCUSSION

Rhenium (V) Complexes

The Re(V) mono-oxo-core $[ReO]^{3+}$ has been evaluated as a means of direct attachment to amino acid side chains of antibodies and peptides containing cysteine-thiol groups, often generated by reduction of disulfide bonds. This has become a mainstay of labelling whole antibodies after reduction of inter-chain disulfide bonds, offering versatile applicability and moderate stability of the labelled protein [11]. However, in the context of smaller proteins and antibodies where the structural impact of labelling is greater, use of native amino acid backbone and side chain donor groups (amide and thiolate) to bind the $[ReO]^{3+}$ core (and its Tc analogue) directly has been problematic; either they are poorly characterised [15] or studies using mass spectrometry and molecular modelling have shown that it leads to heterogeneous mixtures of multiple isomers and monomeric and dimeric structures [16-19]. This direct labelling approach is therefore not recommended as a strategy for peptide labelling.

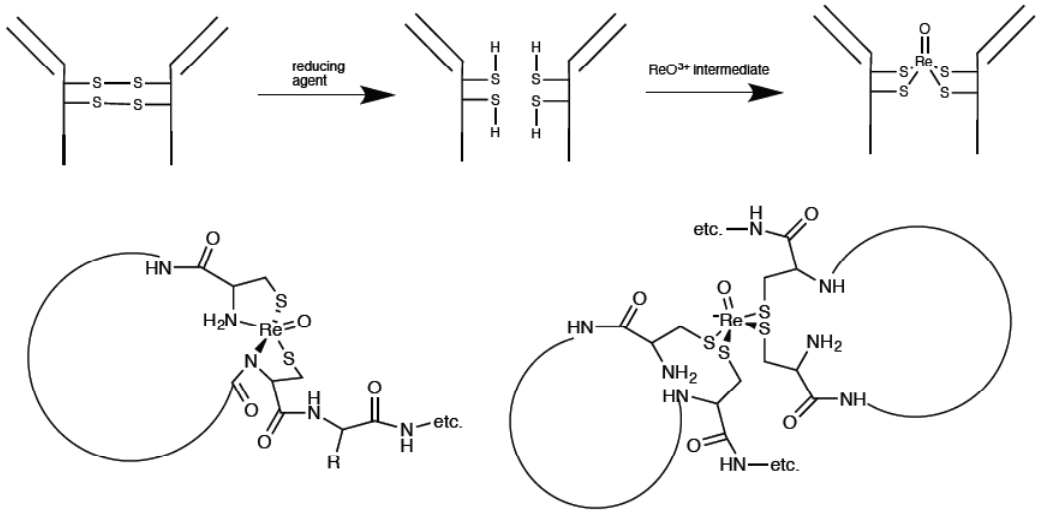

Figure 2: Direct labelling with $[^{188}ReO]^{3+}$ via protein/peptide cysteine residues. Top: schematic showing whole IgG antibody labeling via reduction of interchain disulfide bonds followed by reaction with a pre-prepared $[^{188}ReO]^{3+}$ complex (*e.g.* with tartrate, citrate, bisphosphonate etc., ref. 11); bottom: possible structural motifs, identified by mass spectrometry, formed by reaction of $[ReO]^{3+}$ precursor with a reduced cyclic peptide (salmon calcitonin, ref. 16).

Bifunctional chelators designed to accommodate the structural preferences of the $[ReO]^{3+}$ offer a more reliable strategy. Use and further design [20] of tetradentate ligands containing a combination of amino/amido and thiolate donors [21] such as MAG3 [22] (Figure **3a**) and cysteine-containing amino acid sequences [23, 24] (Figure **2**), developed in the 1990s, [11] have remained popular for attachment to lipids [25, 26] and peptides, [22, 27-32] or simple complexes designed for rapid renal excretion in the context of radionuclide therapy during balloon angioplasty, [33, 34] has continued.

Following the identification of the structure of the pentavalent technetium *meso*-dimercaptosuccinic acid complex $[^{99m}TcO(DMSA)_2]^-$, [35, 36] the ^{186}Re and ^{188}Re analogues were synthesised and shown to have identical structure and isomerism [6, 7] (Figure **3b**) and biodistribution (targeting medullary thyroid carcinoma and bone metastases in prostate, lung and breast cancer) [4, 5]. The simple synthesis of the ^{188}Re complexes and wide interest in these applications led to development of kit-based labelling, [37, 38] and preclinical evaluation in normal mice [39, 40] and in other tumours (*e.g*. cervical carcinoma models [41]). Further study showed that the individual isomers showed no significant differences in biodistribution, and underwent interconversion, in rats [42] and (in the case of $[^{99m}TcO(DMSA)_2]^-$) in humans [43]. The analogous complexes of the racemic DMSA ligand (Figure **3c**) were evaluated [44] in PC-12 tumours in nude mice and showed higher tumour uptake than the *meso*-

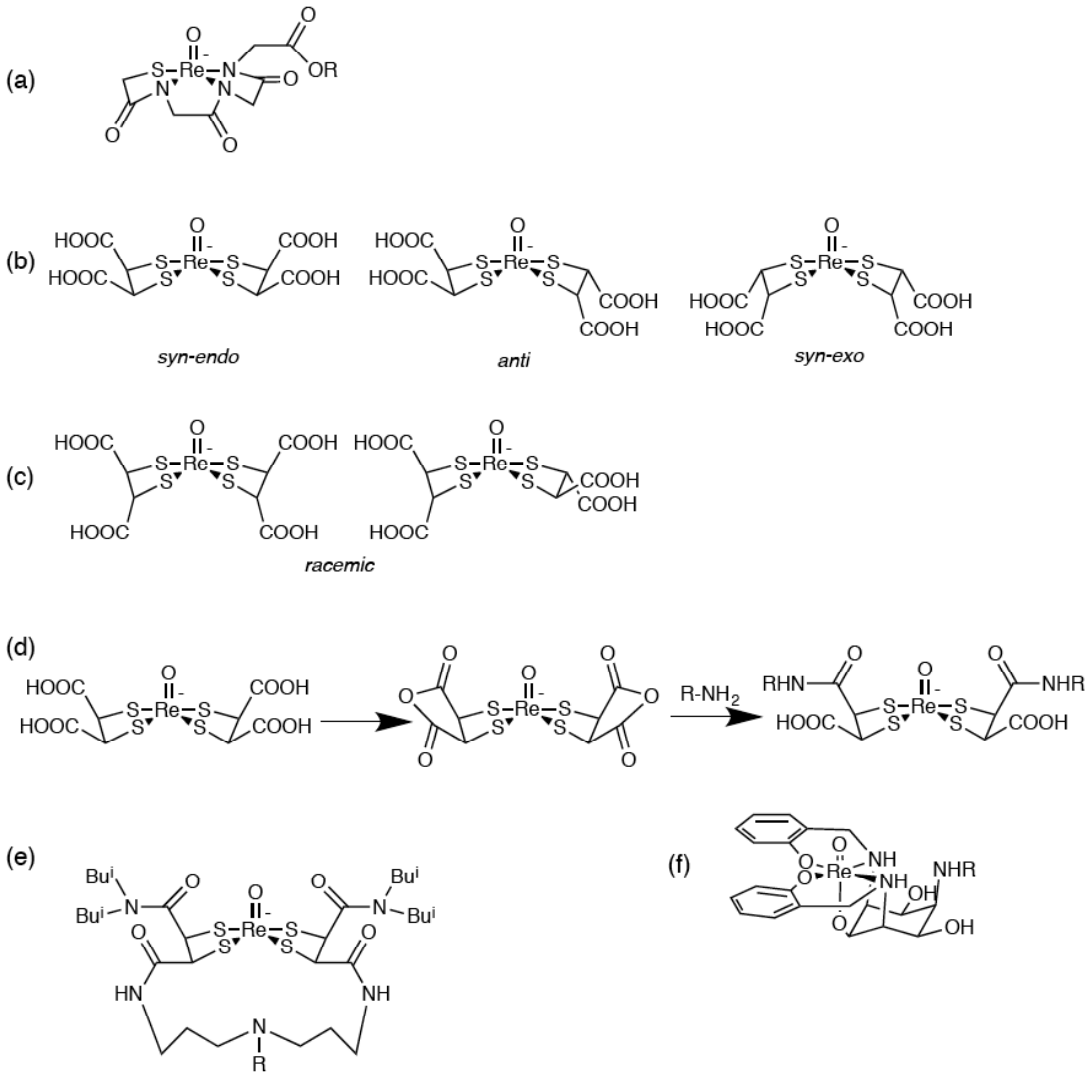

Figure 3: $[ReO]^{3+}$ complexes with synthetic ligands. (**a**) MAG3 complex (R = H) and its esters (R = alkyl or peptide) (ref. 22); (**b**) isomers of the pentavalent *meso*-DMSA complex (ref. 7); (**c**) isomers of the racemic DMSA complex (ref. 44); (**d**) formation and use of the anhydride of the pentavalent *meso*-DMSA complex to label bioconjugates (R = peptide, antibody etc.; ref. 46); (**e**) tetradentate derivative of *meso*-DMSA (ref. 47); (**f**) pentadentate bhci ligand (ref. 49).

complexes. A range of ester derivatives of the complexes showed promising tumour uptake and reduced bone uptake in animal models [45].

The high stability *in vivo* in humans, [5] combined with the relatively simple synthesis, prompted evaluation of the DMSA ligand as a bifunctional chelator, by converting the $[^{188}ReO(DMSA)_2]^-$ core to its dianhydride (Figure **3d**) to enable coupling to antibodies and peptides [46]. A limiting factor in this strategy is the potential for bridging to form "divalent" structures and mixed isomers, but the labelled conjugates thus prepared were well-characterised and very stable. The authors also reported promising use of acetyl hydrazine as an alternative to stannous chloride for reduction of perrhenate. Oxalate ions, alongside stannous ions, have also found a role in reduction of perrhenate to Re(V) in the context of the DMSA complex; [38] whether the oxalate functions as a reducing agent, intermediate chelator or both remains an open question. The work with acetyl hydrazine also led to the first preferential synthesis of the single (*syn-endo*) isomer, offering a possible solution to the problem of isomerism [46]. To overcome the bridging problem, tetradentate derivatives constructed from two DMSA units linked by a linear triamine (Figure **3e**) were synthesised and shown to form ^{188}Re complexes readily (by direct reduction of perrhenate in the presence of the ligand). The complexes showed very high resistance to ligand exchange reactions in plasma, and can be linked to targeting molecules via the central amino group; however, the problem of multiple isomers persists [47, 48].

A ligand system specifically designed to accommodate the $[ReO]^{3+}$ core, offering high symmetry, is the bhci system (Figure **3f**) which is pentadentate, differing from most other ligand sets in filling the position *trans* to the oxo-ligand and thus removing an associative pathway for ligand substitution and oxidation to perrhenate. It was conjugated to an antibody via the non-coordinated amino group using an N-hydroxysuccinimide active ester, but despite the excellent thermodynamics and kinetics of its $[ReO]^{3+}$ coordination capacity, it still had to pre-labelled with ^{188}Re before conjugation to the antibody [49].

The Re(V) dioxo core $[ReO_2]^+$ has also been suggested as the basis of bioconjugates; carbene complexes of the dioxo core proved insufficiently stable for radiopharmaceutical use, [50] but placing this core within a tetraamine ligand set, provided by two ethylene diamine ligands or one linear or cyclic tetramine (Figure **4a**), has been shown to provide excellent stability against ligand exchange and oxidation in serum, with moderately convenient aqueous synthesis (entailing reduction with stannous chloride in the presence of the ligand), except in the case of cyclic ligands such as cyclam where kinetic barriers to complexation were high [51]. Electrochemical studies showed that although the ethylene diamine complex is vulnerable to reduction when protonated, the 1,4,7,10-tetrazaundecane complex is not [52]. Neither optimisation to make radiolabelling more efficient and convenient, nor incorporation into bioconjugates, has been attempted, however. This approach was subsequently adopted for ^{99m}Tc and shown to be highly promising for labelling of bioconjugates using the 1,4,7,10-tetrazaundecane rhenium dioxo-complex (Figure **4b**), offering both mild and simple aqueous radiolabelling, high symmetry and excellent stability under biological conditions [53]. If satisfactory

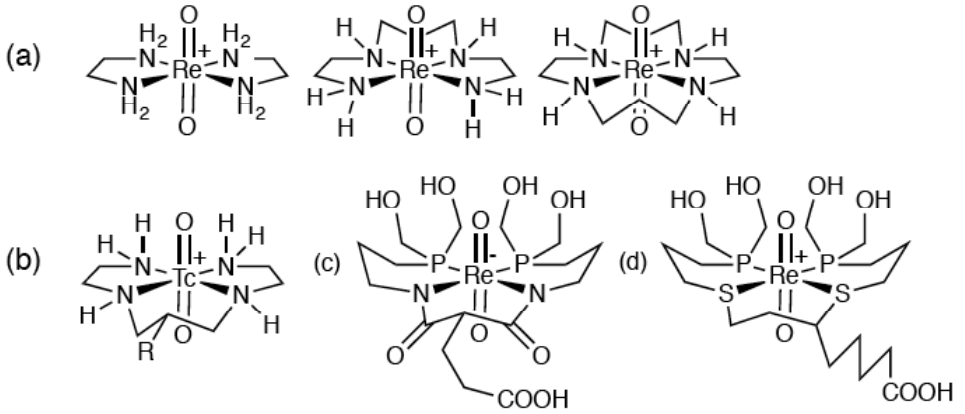

Figure 4: Complexes of the $[ReO_2]^+$ core. (**a**) left to right: ethylene diamine; 1,4,8,11-tetraazaundecane; and cyclam complexes (ref. 51); (**b**) $[TcO_2]^+$ core linked to peptide R via the 1,4,8,11-tetraazaundecane ligand (ref. 53); (**c**) $[ReO_2]^+$ diamido diphosphine complex (ref. 54); (**d**) $[ReO_2]^+$ dithioether diphosphine complex (ref. 55).

optimisation of the ^{188}Re-labelling procedure can be achieved, including perhaps selection of a more suitable reducing agent than stannous chloride, this potentially offers a simple solution to the problem of forming a stable bioconjugates without problems of isomerism and multi-step synthesis, and could lead to a "matched pair" theranostic combination of analogous ^{99m}Tc and ^{188}Re radiopharmaceuticals.

The $[ReO_2]^+$ core is made all the more attractive as a direction for further research by the observation that bis(amido)bis(phosphine) [54] and bis(thioether)-bisphosphine) [55] ligands (Figure **4**) can also stabilise the $[ReO_2]^+$ core, and the complexes are accessible directly from [^{188}Re]-perrhenate using citrate as an intermediate chelator.

An alternative to the oxo- and dioxo-ligand set providing a π-donating environment to stabilise the Re(V) core is the nitride ligand N^{3-} [56]. Invariably the $[^{188}ReN]^{2+}$ core is generated in the first step of a multi-step radiolabelling process, by reaction of [^{188}Re]perrhenate with a hydrazide derivative in the presence of a reducing agent, usually stannous chloride. A number of hydrazide derivatives have been tested as a source of the nitride ligand, including N-methyl-S-methyl dithiocarbazate (HDTCZ), [57] its pegylated derivative (HO_2C-PEG(600)-DTCZ) [58] and succinic dihydrazide, with the former preferred as the most generally useful and efficient. The reaction produces an intermediate rhenium nitride complex which is subsequently treated with a suitable ligand combination to produce the final (usually square pyramidal) complex. Ligand sets employed include a symmetrical pair of dithiocarbamates [57, 59, 60] or dithiocarboxylates, [61] or unsymmetrical combinations of aminodiphosphine (PNP) with a bidentate thiolate [58, 62] or a monodentate tertiary phosphine with a tridentate dithiolate derived from two cysteine residues appended to a peptide (Figure **5**) [63]. The bis(dithiocarbamate) is most simply used as the basis of a divalent targeting agent, such as the bis(bisphosphonate) derivatives developed as potential therapeutic radiopharmaceuticals for bone metastases [60]. Although the $[ReN]^{2+}$ system is stable and potentially versatile, the multi-step nature of the labelling process means it is unlikely to find widespread utility in its present form.

A bifunctional chelator that has been successful for ^{99m}Tc labeling of biomolecules is hydrazinonicotinamide (HYNIC) (Figure **6**). It offers probably the most efficient and highest specific activity methods for labelling peptides and proteins, but is limited by the need for a set of co-ligands to complete the ^{99m}Tc coordination sphere and the consequent problem of formation of mixtures of isomers, each with potentially different biodistribution [64]. Although usually depicted with monodentate diazenido ligands, all physical evidence, coupled with knowledge of the structure of model complexes, suggests that the HYNIC is a bidentate chelating ligand forming Tc(V) complexes (Figure **6**) [64-66]. Despite much of this structural evidence arising from analogy to known stable rhenium complexes, [64] attempts to use HYNIC as a bifunctional chelator for ^{188}Re [67] have met with failure and the conditions required to form labelled complexes with structure and stability analogous to the ^{99m}Tc-labelled HYNIC-biomolecule conjugates are yet to be discovered. Extension of HYNIC with a thioamide tethering group provides a modification that gives a

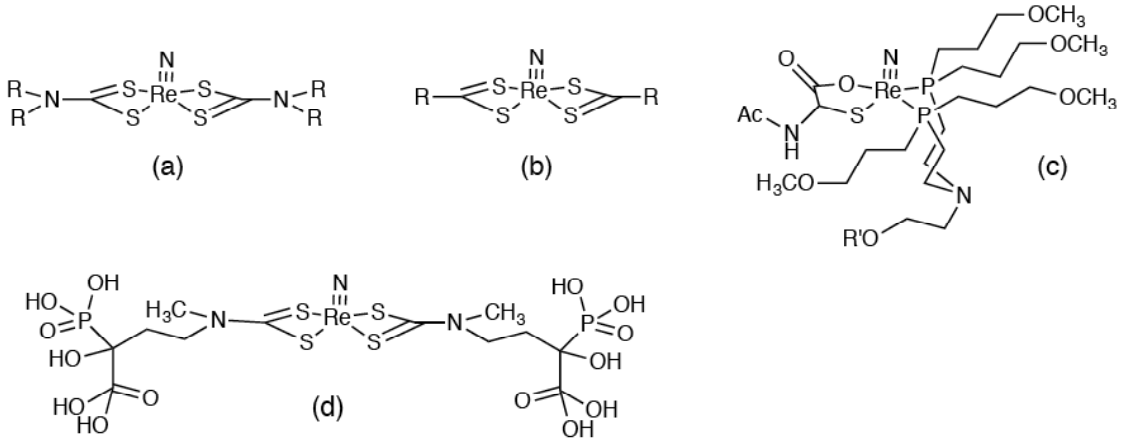

Figure 5: Complexes of the rhenium (V) nitride core. (**a**) Bis(dithiocarbamate) complexes; (**b**) bis(dithiocarboxylate) complexes; (**c**) diphosphine compexes (ref. 58); (**d**) dithiocarboxylate bisphosphonate conjugate (ref. 60).

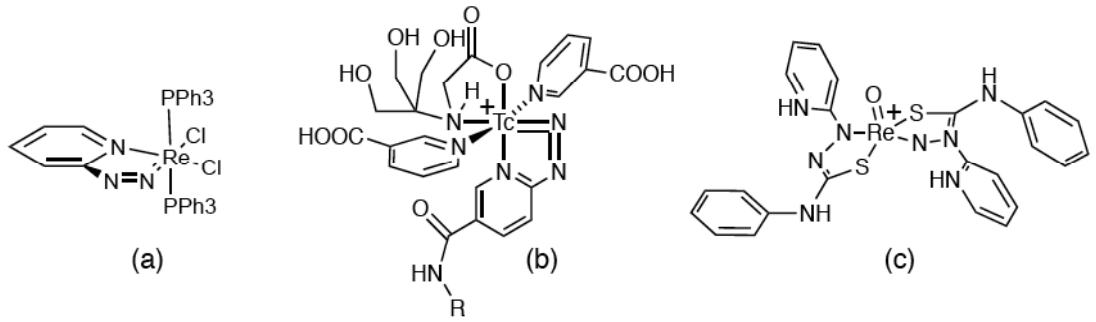

Figure 6: Complexes of HYNIC and related ligands. (**a**) structure of model rhenium complex (ref. 64); (**b**) suggested structure of Tc-HYNIC complex with tricine and nicotinic acid co-ligands, deduced from mass spectroscopy and analogy to model Re structure (**a**) (ref. 131); (**c**) $[ReO]^{3+}$ complex with HYNIC-thioamide derivative (ref. 68).

stable, well-defined chelated derivative with the square pyramidal $[ReO]^{3+}$ core [68] and can be radiolabelled with ^{188}Re in this form (Figure **6**) [69].

Rhenium (I) Complexes

The Re(I) tricarbonyl fragment $[^{188}Re(CO)_3]^+$ has proven itself as a versatile radiolabelling synthon for coupling to a range of chelators conjugated to targeting molecules, and for direct labelling of proteins (Figure **7**). The precursor used for labelling is commonly assumed to exist in the form of $[^{188}Re(CO)_3(H_2O)_3]^+$ (Figure **7a**) but in the presence of typical buffers with metal-coordinating ability, it is likely that other species are prevalent (*e.g.* incorporating coordinated phosphate ions in phosphate buffer which is typically used [70]). Unlike the kit-based preparation of the $[^{99m}Tc(CO)_3]^+$ precursor, it is prepared from perrhenate using borane-ammonia as reducing agent under a CO atmosphere [71] and often requires purification before use in labelling the bioconjugate. A simple purification method has been developed [72] but the method remains somewhat cumbersome and the $[^{188}Re(CO)_3]^+$ method is not likely to be widely adopted clinically unless a simpler, more "kit-like" method is developed. The reported mild methods for the alternative precursors $[^{188}Re(CO)_5X]$ (X = Cl, Br, I) [73] or $[Re_2(CO)_{10}]$ [74] are unlikely to meet that need.

The preferred binding sites of $[^{188}Re(CO)_3]^+$ in proteins are histidine residues and this has been particularly useful for labelling recombinant proteins that incorporate histidine tags (a sequence of typically six consecutive histidine residues) as a purification tool. Proteins without histidines, or with only isolated histidines, label poorly [75] whereas those with oligohistidine sequences can be labelled relatively efficiently [76]. Studies aimed at identifying optimal histidine-containing sequences for labelling with $[Re(CO)_3]^+$ have shown that as well as multiple histidines, incorporation of cysteine [77] or methionine [70, 78] residues into the sequence can enhance labeling efficiency and stability, and incorporation of positively charged amino acids (arginine, lysine) is particularly effective, with the potential to improve specific activity and avoid the need for post-labelling purification steps [78]. Although at least two histidine imidazole groups are assumed to bind to the rhenium, the full make-up of the coordination sphere when $[Re(CO)_3]^+$ is bound to histidine tags is unknown. The

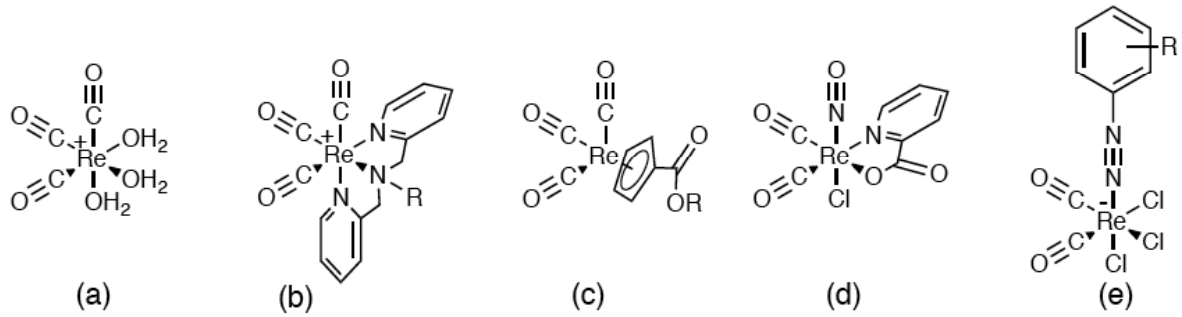

Figure 7: Rhenium(I) tricarbonyl and related complexes. (**a**) putative tris(aqua) $[Re(CO)_3]^+$ precursor; (**b**) dipyridylamine complex (R = linker to peptide etc.); (**c**) acid/ester-derivatised cyclopentadienyl complex (R = H or alkyl, ref. 93-96); (**d**) isoelectronic nitrosyl analogue with $[Re(CO)_2(NO)]^{2+}$ core (ref. 97); (**e**) isoelectronic diazenido complex (ref. 98).

amino acid preferences are the same for both $[^{188}Re(CO)_3]^+$ and $[^{99m}Tc(CO)_3]^+$, [78] supporting the therapeutic and diagnostic "matched pair" aspiration. $[^{188}Re(CO)_3]^+$ has also been used to label monoclonal antibodies after reduction of their inter-chain disulfide bonds. This experience adds weight to the suggestion that thiolate groups may play a part in binding the rhenium [79].

Several synthetic, usually tridentate, bifunctional chelators have been used to link the tricarbonyl fragment to biomolecules. Most common is dipyridyl (DPA, Figure **7b**)[51] [72, 80-82] but related structures including picolinic acid derivatives, [83, 84] tridentate pyrazolyl ligands, [85] aminodiacetate, [86] triazoles, [87-89] histidine derivatives [89-91] and pyrimidines [92] have been reported. Carboxylate and ester derivatives of the cyclopentadienyl ligand (Figure **7c**), which forms an η^5-complex with $[Re(CO)_3]^+$, have been shown to be highly stable and can be synthesised in water [93-96].

A potentially interesting variant on the $[M(CO)_3]^+$ (M = Tc or Re) core is the isoelectronic nitrosyl analogue $[M(CO)_2(NO)]^{2+}$ (Figure **7d**), which can be produced by reaction of the tricarbonyl precursor with nitrosonium salts in acetonitrile or dichloromethane [97]. There are no reports so far of actual use of this approach for ^{188}Re-labelling but the $[M(CO)_2(NO)]^{2+}$core is expected to bind to the same types of ligands as $[M(CO)_3]^+$, with subtle differences due to the increased positive charge. However, with the reported synthetic route this synthon requires an additional step, over and above the already cumbersome preparation of the $[^{188}Re(CO)_3]^+$ precursor. Similarly, in reaction of $[ReBr_3(CO)_3]^{2-}$ with diazonium salts, $^+$NNAr displaces one carbonyl ligand to yield a diazenido-complex $[ReX_3(CO)_2(NNAr)]^-$ (Figure **7e**). The diazenido ligand offers the possibility of a covalent link to targeting molecules. However, neither this possibility nor the application of this reaction to ^{188}Re-labelling have been realised [98].

Synthesis of the ^{188}Re analogue of well-known Tc(I) complex ^{99m}Tc-sestamibi ($[Tc(CNR)_6]^+$ where CNR = 2-methoxyisobutylisonitrile) has been reported but no evidence that the complex produced has the reported structure was provided [99].

Rhenium (III) Complexes

$[Re(PS)_2]^+$ (PS = 1,2-phosphinothiolate) has been identified as a stable Re(III) core, synthesised from Re(III) precursors, whose coordination sphere can be completed using a third bidentate ligand such as a dithiocarbamate (Figure **8a**), pyridine-2-thiolate or xanthate [100, 101]. The analogous technetium complexes can be made direct from pertechnetate and show some analogy to the Tc(III) complex formed by reduction of pertechnetate with water-soluble phosphines in the presence of peptides containing a reduced disulfide bond (Figure **8**) [16]. It is not yet clear whether the greater barrier to reduction of rhenium will allow $[Re(PS)_2]^+$ complexes to be accessible direct from perrhenate. Analogously, Re(III) can be

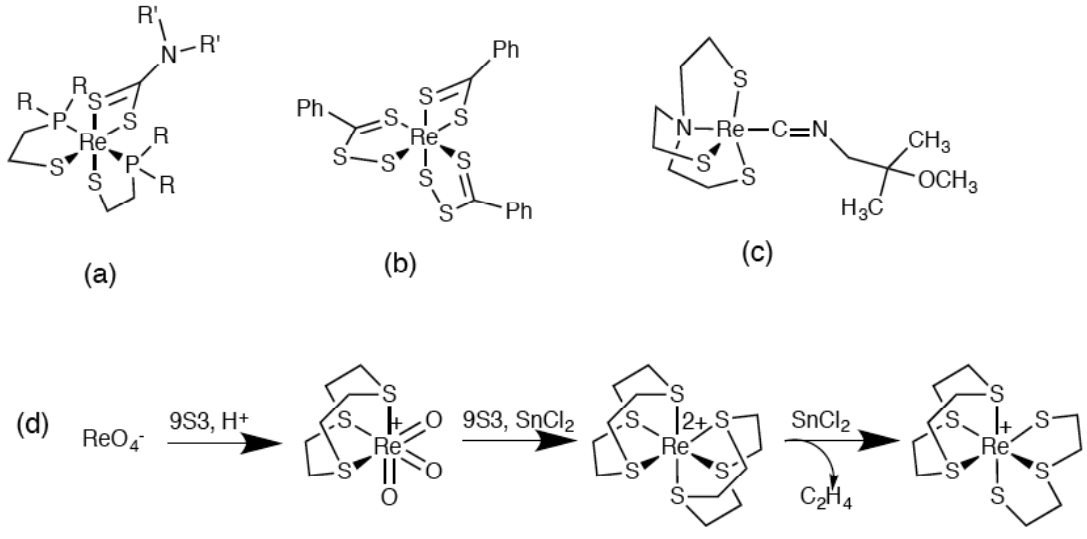

Figure 8: Rhenium(III) complexes. (**a**) $[Re(PS)_2]^+$ core (PS = 1,2-phosphinothiolate, R = alkyl/aryl, R' = alkyl)with dithiocarbamate co-ligand (ref. 100); (**b**) Re(III) bis(trithioperoxy) complex with dithiocarboxylate co-ligand (ref. 102); (**c**) trigonal bipyramidal Re(III) complex with aminothiolate ligand and isonitrile co-ligand (ref. 104); (**d**) reaction scheme showing formation of Re(III) 9S3 complex via reductive C-S bond cleavage of coordinated 9S3 (ref. 105).

coordinated by a ligand set of six sulfur atoms comprising two trithioperoxy and one dithiocarboxylate ligand (Figure **8b**) [102]. The dithiocarboxylate ligand can be replaced by dithiocarbamates to give more stable complexes containing two trithioperoxy ligands and a dithiocarbamate, which could become the basis of a bioconjugate (Figure **8**). These complexes are readily synthesised from Re(V) oxo precursors but synthesis direct from perrhenate has yet to be explored [103].

Trigonal bipyramidal Re(III) complexes with a tetradentate aminotrithiolate ligand and a π-acceptor ligand such as an isonitrile or phosphine (Figure **8c**) are accessible efficiently in a two stage process from perrhenate via a Re-EDTA complex formed by stannous reduction of perrhenate in the presence of EDTA. By incorporation of a carboxylate side chain into the tetradentate ligand (Figure **8**) synthesis of bioconjugates based on this core structure is feasible [104].

An intriguing and unusual set of complexes in a range of oxidation states is made possible by use of the 1,4,7-trithiacyclononane ligand (9S3). In acidic non-aqueous solvent (*e.g*. acetic acid) 9S3 reacts with perrhenate to form $[ReO_3(9S3)]^+$, which can be reduced with stannous ions in the presence of more 9S3 to $[Re(9S3)_2]^{2+}$, a rare example of a Re(II) complex; upon further reduction, instead of forming the Re(I) complex, the ligand undergoes C-S bond cleavage to liberate ethane, forming a stable Re(III) complex coordinated by a 9S3 ligand and a thioether-dithiolate ligand (Figure **8d**). This sequence of reactions can be performed, and the ^{188}Re product isolated, within a few minutes with ^{188}Re generator eluate, [105, 106] but has not been developed into a system for ^{188}Re-bioconjugate synthesis.

Rhenium (VII) Complexes

The possibility of finding chelators that will stabilise the Tc(VII) trioxo core $[TcO_3]^+$, such as 1,4,7-triazacyclononane [107] and 1,4,7-trithiacyclononane [105] (Figure **8d**) has been explored with some promise. Given that rhenium(VII) is expected to be more stable towards reduction than technetium(VII), it might be expected that a similar approach would be successful for ^{188}Re and indeed the feasibility to chelate $[ReO_3]^+$ with a range of tridentate ligands has been reviewed, [108] but no radiopharmaceuticals based on such Re(VII) complexes have been reported.

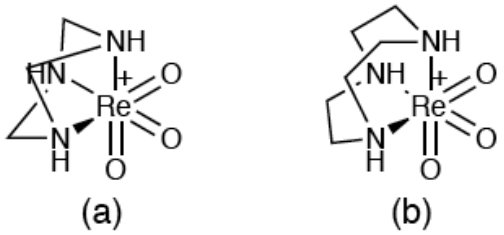

Figure 9: Re(VII) trioxo complexes. (**a**) 1,3,5-triazacyclohexane complex; (**b**) 1,4,7-triazacyclononane complex (ref. 107)

MISCELLANEOUS RHENIUM COMPLEXES WITH UNKNOWN OXIDATION STATE

A number of ligands have been "labelled" with ^{188}Re without structural characterisation or determination of stability. Although the procedures reported are sometimes convenient, these studies provide no understanding of the chemical nature or structure of the complexes formed and do not contribute to understanding of how to design chelators for ^{188}Re. They include complexes with porphyrins, [109-111] macrocyclic polyaminophosphonates for targeting bone, [112] a DTPA complex [113] and a tripodal tris(hydroxamate) ligand linked to an antibody [114].

PERRHENATE AS A THERAPEUTIC RADIOPHARMACEUTICAL

The [^{188}Re]perrhenate ion itself is a potentially useful therapeutic radiopharmaceutical, being a substrate of the sodium/iodide symporter (NIS), which is expressed in thyroid follicular cells and which has been explored as a target in breast and thyroid cancer models and gene therapy of other tumours, using [^{131}I]iodide and [^{188}]perrhenate [115-124]. Since perrhenate, like iodide, is a substrate of NIS, but unlike iodide, not of the other cellular enzyme systems required to metabolise iodide for thyroid hormone synthesis, there may be advantages in its use for cancer therapy compared to [^{131}I]iodide. In thyroid follicles it remains within the thyrocyte, whereas [^{131}I]iodide is rapidly translocated to the colloid of the follicle; hence, [^{188}Re]perrhenate irradiates NIS-expressing cells from the inside rather than the outside, and this offers a microdosimetric advantage that could result in higher cytotoxicity [125]. It may also be advantageous in non-thyroid tumours expressing NIS, because its lack of metabolism means that its retention in normal thyroid tissue will be lower and hence its availability for uptake in non-thyroidal NIS-expressing cells will be greater than that of [^{131}I]iodide.

CONCLUSION

Despite the alarm caused by ^{99m}Tc shortages in the last decade, and the fall in reporting of new ^{99m}Tc and ^{188}Re chemistry since 2000, investment in new reactor- and accelerator-based facilities for ^{99m}Tc production, coupled with a resurgence of interest in use of the ^{188}Re generator in less developed countries, should ignite a reawakening of development of new chemistry to support use of both radionuclides in the new age of molecular imaging and targeted radionuclide therapy. Current clinical use of ^{188}Re radionuclide therapy relies entirely on chemistry developed in the 1990s and earlier, and new chemistry to facilitate use of specific molecular targeted biomolecules is needed. In particular, chemistry to exploit the use of generator-produced ^{188}Re on the hospital site is needed, and this requires chemical methodology that is simple and kit-based to minimise the requirement for costly infrastructure. This in turn needs chemistry to convert ^{188}Re from perrhenate to the required radiopharmaceutical, rapidly, under mild conditions compatible with biomolecules, preferably in a single step and without need for post-labelling purification, to produce a single stable homogeneous labelled product free of isomerism. The chemistry reported in this and previous reviews does not fully meet these challenges. Chemists must be imaginative and innovative to design new chelating systems and rhenium “cores” and discover reducing agents other than stannous salts to reduce perrhenate, in order to meet these challenges in the coming years.

REFERENCES

[1] Torres Martin de Rosales R, Blower PJ. The role of ^{99m}Tc in the development of rhenium radiopharmaceuticals. In: *Technetium radiopharmaceuticals: status and prospective*. Edited by Duatti A. Vienna: IAEA; 2008. pp. 250-278.

[2] Carvalho PA, Chiu ML, Kronauge JF, Kawamura M, Jones AG, Holman BL*, et al.*Subcellular-distribution and analysis of technetium-99m-MIBI in isolated perfused rat hearts. J Nucl Med 1992; 33: 1516-1521.

[3] Denoyer D, Perek N, Le Jeune N, Frere D, Dubois F. Evidence that Tc-99m-(V)-DMSA uptake is mediated by NaP_i cotransporter type III in tumour cell lines. Eur J Nucl Med Mol Imaging 2004; 31: 77-84. https://doi.org/10.1007/s00259-003-1334-7

[4] Blower PJ, Kettle AG, O'Doherty MJ, Coakley AJ, Knapp FF. Tc-99m(V)DMSA quantitatively predicts Re-188(V)DMSA distribution in patients with prostate cancer metastatic to bone. Eur J Nucl Med 2000; 27: 1405-1409. https://doi.org/10.1007/s002590000307

[5] Blower PJ, Lam ASK, O'Doherty MJ, Kettle AG, Coakley AJ, Knapp FF. Pentavalent rhenium-188 dimercaptosuccinic acid for targeted radiotherapy: synthesis and preliminary animal and human studies. Eur J Nucl Med 1998; 25: 613-621. https://doi.org/10.1007/s002590050263

[6] Bisunadan M, Blower PJ, Clarke SEM, Singh J, Went MJ. Synthesis and characterisation of [^{186}Re]rhenium(V) dimercaptosuccinic acid: a possible tumour radiotherapy agent. Appl Radiat Isot 1991; 42: 167-171. https://doi.org/10.1016/0883-2889(91)90068-C

[7] Singh J, Reghebi K, Lazarus CR, Clarke SEM, Callahan AP, Knapp FFJ*, et al.* Studies on the preparation and isomeric composition of [^{186}Re]- and [^{188}Re]-pentavalent rhenium dimercaptosuccinic acid complex. Nucl Med Commun 1993; 14: 197-203. https://doi.org/10.1097/00006231-199303000-00009

[8] Hang CL, Hsieh BT, Wu CJ, Yip HK, Yang CH, Chen SM*, et al.*Six-year clinical follow-up after treatment of diffuse in-stent restenosis with cutting balloon angioplasty followed by intracoronary brachytherapy with liquid rhenium-188-filled balloon via transradial approach. Circ J 2011; 75: 113-120. https://doi.org/10.1253/circj.CJ-10-0054

[9] Paez D, Becic T, Bhonsle U, Jalilian AR, Nunez-Miller R, Osso JA. Current status of nuclear medicine practice in the middle east. Sem Nucl Med 2016; 46: 265-272. https://doi.org/10.1053/j.semnuclmed.2016.01.005

[10] Knapp FF, Pillai MRA, Osso JA, Dash A. Re-emergence of the important role of radionuclide generators to provide diagnostic and therapeutic radionuclides to meet future research and clinical demands. J Radioanal Nucl Chemy 2014; 302: 1053-1068. https://doi.org/10.1007/s10967-014-3642-8

[11] Prakash SD, Blower PJ. The chemistry of rhenium in nuclear medicine In: *Perspectives on Bioinorganic Chemistry*. Edited by Hay R, Dilworth JR, Nolan KB. Connecticut: JAI Press; 1999. pp. 91-143.

[12] Bolzati C, Carta D, Salvarese N, Refosco F. Chelating Systems for Tc-99m/Re-188 in the Development of Radiolabeled Peptide Pharmaceuticals. Anti-Cancer Agents Med Chem 2012; 12: 428-461. https://doi.org/10.2174/187152012800617821

[13] Liu GZ, Hnatowich DJ. Labeling biomolecules with radiorhenium - a review of the bifunctional chelators. Anti-Cancer Agents Med Chem 2007; 7: 367-377. https://doi.org/10.2174/187152007780618144

[14] Mindt T, Struthers H, Garcia-Garayoa E, Desbouis D, Schibli R. Strategies for the development of novel tumor targeting technetium and rhenium radiopharmaceuticals. Chimia 2007; 61: 725-731. https://doi.org/10.2533/chimia.2007.725

[15] Molina-Trinidad EM, de Murphy CA, Jung-Cook H, Stack EM, Pedraza-Lopez M, Morales-Marquez JL*, et al.* Therapeutic Re-188-lanreotide: determination of radiopharmacokinetic parameters in rats. J Pharm Pharmacol 2010; 62: 456-461. https://doi.org/10.1211/jpp.62.04.0007

[16] Greenland WEP, Blower PJ. Water-soluble phosphines for direct labeling of peptides with technetium and rhenium: Insights from electrospray mass spectrometry. Bioconjugate Chem 2005; 16: 939-948. https://doi.org/10.1021/bc0500600

[17] Nelson CA, Azure MT, Adams CT, Zinn KR. The somatostatin analog Re-188-P2045 inhibits the growth of AR42J pancreatic tumor xenografts. J Nucl Med 2014; 55: 2020-2025. https://doi.org/10.2967/jnumed.114.140780

[18] Li YW, Ma LX, Gaddam V, Gallazzi F, Hennkens HM, Harmata M*, et al.* Synthesis, characterization, and *in vitro* evaluation of new Tc-99m/Re(V)-Cyclized octreotide analogues: an experimental and computational approach. Inorg Chem 2016; 55: 1124-1133. https://doi.org/10.1021/acs.inorgchem.5b02306

[19] Cantorias MV, Howell RC, Todaro L, Cyr JE, Berndorff D, Rogers RD*, et al.* MO tripeptide diastereomers (M=Tc-99/99m, Re): Models to identify the structure of Tc-99m

peptide targeted radiopharmaceuticals. Inorg Chem 2007; 46: 7326-7340.
https://doi.org/10.1021/ic070077p

[20] Su ZF, Xu Y. Possible mechanisms of controlling the configuration, stability, and lipophilicity of (TcO)-Tc-99m N3S and ReO N3S chelates. J Labelled Compd Radiopharm 2008; 51: 93-100.
https://doi.org/10.1002/jlcr.1487

[21] Jeong JM, Kim YJ, Lee YS, Ko JI, Son M, Lee DS*, et al.* Lipiodol solution of a lipophilic agent, Re-188-TDD, for the treatment of liver cancer. Nucl Med Biol2001; 28: 197-204.
https://doi.org/10.1016/S0969-8051(00)00208-0

[22] Guhlke S, Schaffland A, Zamora PO, Sartor J, Diekmann D, Bender H*, et al.* Re-188- and Tc-99m-MAG_3 as prosthetic groups for labeling amines and peptides: Approaches with pre- and postconjugate labeling. Nucl Med Biology 1998; 25: 621-631.
https://doi.org/10.1016/S0969-8051(98)00025-0

[23] Altai M, Honarvar H, Wallberg H, Strand J, Varasteh Z, Rosestedt M*, et al.* Selection of an optimal cysteine-containing peptide-based chelator for labeling of affibody molecules with Re-188. Eur J Med Chem 2014; 87: 519-528.
https://doi.org/10.1016/j.ejmech.2014.09.082

[24] Altai M, Wallberg H, Honarvar H, Strand J, Orlova A, Varasteh Z*, et al.* Re-188-Z(HER2:V2), a promising affibody-based targeting agent against HER2-expressing tumors: preclinical assessment. J Nucl Med 2014; 55: 1842-1848.
https://doi.org/10.2967/jnumed.114.140194

[25] Banka VK, Moon SH, Jeong JM, Seelam SR, Lee YS, Kim YJ*, et al.* Development of 4-hexadecyl-4,7-diaza-1,10-decanedithiol (HDD) kit for the preparation of the liver cancer therapeutic agent Re-188-HDD/lipiodol. Nucl Med Biol 2015; 42: 317-322.
https://doi.org/10.1016/j.nucmedbio.2014.11.013

[26] Lee YS, Jeong JM, Kim YJ, Chung JW, Park JH, Suh YG*, et al.* Synthesis of Re-188-labelled long chain alkyl diaminedithiol for therapy of liver cancer. Nucl Med Commun 2002; 23: 237-242.
https://doi.org/10.1097/00006231-200203000-00006

[27] Cui LY, Liu ZF, Jin XN, Jia B, Li F, Wang F. Evaluation of Re-188-MAG_2-RGD-bombesin for potential prostate cancer therapy. Nucl Med Biol 2013; 40: 182-189.
https://doi.org/10.1016/j.nucmedbio.2012.11.002

[28] Yu F, Lv ML, Cai HD, Li D, Yuan XY, Lv ZW. Therapeutic effect of ^{188}Re-MAG3-depreotide on non-small cell lung cancer *in vivo* and *in vitro*. Int J Clin Exp Pathol 2013; 6: 421-430.

[29] Pervez S, Mushtaq A, Arif M. Formulation of a freeze-dried kit for Re-188-MAG_3 and its quality control. J Radioanal Nucl Chem 2003; 257: 421-424.
https://doi.org/10.1023/A:1024764703623

[30] Zhang XL, Wang YX, Li JL, Yin DZ. An improved synthesis of S-benzoyl mercaptoacetyltriglycine as BFCA and the labeling of IgG with carrier-free Re-188. J Radioanal Nucl Chem 2003; 256: 339-343.
https://doi.org/10.1023/A:1024532723304

[31] Crudo JL, Edreira MM, Obenaus ER, Chinol M, Paganelli G, de Castiglia SG. Optimization of antibody labeling with rhenium-188 using a prelabeled MAG_3 chelate. Int J Pharmaceutics 2002; 248: 173-182.
https://doi.org/10.1016/S0378-5173(02)00434-9

[32] Ferro-Flores G, Ramirez FD, Martinez-Mendoza MG, de Murphy CA, Pedraza-Lopez M, Garcia-Salinas L. Peptide labeling using Re-188,Re-188-MAG_3 and Sm-153-H(1)ETA: A comparison on their *in vitro* lipophilicity. J Radioanal Nucl Chem 2002; 251: 7-13.
https://doi.org/10.1023/A:1015077707567

[33] Das T, Banerjee S, Samuel G, Sarma HD, Ramamoorthy N, Pillai MRA. Re-188-ethylene dicysteine: a novel agent for possible use in endovascular radiation therapy. Nucl Med Commun 2000; 21: 939-945.
https://doi.org/10.1097/00006231-200010000-00008

[34] Das T, Banerjee S, Samuel G, Kothari K, Unni PR, Sarma HD*, et al*. Re-186/188 rhenium-ethylene dicysteine (Re-Ec): Preparation and evaluation for possible use in endovascular brachytherapy. Nucl Med Biol 2000; 27: 189-197.
https://doi.org/10.1016/S0969-8051(99)00097-9

[35] Singh J, Powell AK, Clarke SEM, Blower PJ. Crystal structure and isomerism of a tumour targetting radiopharmaceutical: $[ReO(dmsa)_2]^-$ (H_2dmsa = meso-2,3-demercaptosuccinic acid). J Chem Soc, Chem Commun 1991: 1115-1117.
https://doi.org/10.1039/C39910001115

[36] Blower PJ, Singh J, Clarke SEM. The chemical indentity of pentavalent technetium-99m-DMSA. J Nucl Med 1991; 32: 845-849.

[37] Pirmettis I, Limouris GS, Bouziotis P, Papadopoulos M, Knapp FF, Chiotellis E. Pentavalent rhenium-188 dimercaptosuccinic acid: a new kit formulation and its initial evaluation in mice. Radiochim Acta 2001; 89: 115-118.
https://doi.org/10.1524/ract.2001.89.2.115

[38] Bolzati C, Boschi A, Uccelli L, Duatti A, Franceschini R, Piffanelli A. An alternative approach to the preparation of Re-188 radiopharmaceuticals from generator produced $(ReO_4)^-$ Re-188 (-): Efficient synthesis of Re-188(V)-meso-2,3-dimercaptosuccinic acid. Nucl Med Biol 2000; 27: 309-314.
https://doi.org/10.1016/S0969-8051(00)00079-2

[39] Nogawa N, Momose S, Miyazawa K, Makide Y, Oohashi K, Hashimoto K, *et al.* Synthesis of Re-186-DMSA and its biodistributions in mice. J Radioanal Nucl Chem 1999; 239: 385-389.
https://doi.org/10.1007/BF02349517

[40] Dadachova E, Chapman J. Re-188(V)-DMSA revisited: Preparation and biodistribution of a potential radiotherapeutic agent with low kidney uptake. Nucl Med Commun 1998; 19: 173-181.
https://doi.org/10.1097/00006231-199802000-00012

[41] Garcia-Salinas L, Ferro-Flores G, Arteaga-Murphy C, Pedraza-Lopez M, Hernandez-Gutierrez S, Azorin-Nieto J. Uptake of the ^{188}Re(V)-DMSA complex by cervical carcinoma cells in nude mice: pharmacokinetics and dosimetry. Appl Radiat Isot 2001; 54: 413-418.
https://doi.org/10.1016/S0969-8043(00)00278-5

[42] Guhlke S, Scheithauer S, Oetjen K, Sartor J, Bender H, Biersack HJ. Re-188(V)-DMSA: in-vitro and in-vivo studies on the individual stereo isomers. Radiochim Acta 2004; 92: 277-283.
https://doi.org/10.1524/ract.92.4.277.35610

[43] Blower PJ. unpublished.

[44] Park JY, Lee TS, Choi TH, Cheon GJ, Choi CW, Awh OD. A comparative study of Re-188(V)-meso-DMSA and Re-188(V)-rac-DMSA: preparation and *in vivo* evaluation in nude mice xenografted. Nuclear Medicine and Biology 2007; 34: 1029-1036.
https://doi.org/10.1016/j.nucmedbio.2007.06.016

[45] Seifert S, Syhre R, Spies H, Johannsen B. Novel tumortropic ester derivatives of Tc-99m(V) mesodimercaptosuccinic acid with low affinity for bone tissue. Nucl Med Commun 2003; 24: 1175-1183.
https://doi.org/10.1097/00006231-200311000-00008

[46] Choudhry U, Greenland WEP, Goddard WA, Maclennan TAJ, Teat SJ, Blower PJ. New routes to bioconjugates of rhenium using the oxobis(dithiolato)rhenate(v) core. Dalton Trans 2003: 311-317.
https://doi.org/10.1039/b209820b

[47] Seifert S, Heinrich T, Jentschel C, Smuda C, Bergmann R, Pietzsch HJ. Preparation and biological characterization of isomeric Re-188(V) oxocomplexes with tetradentate S-4

ligands derived from meso-dimercaptosuccinic acid for labeling of biomolecules. Bioconjugate Chem 2006; 17: 1601-1606.
https://doi.org/10.1021/bc0602331

[48] Seifert S, Jentschel C, Bergmann R, Pietzsch HJ, Wunderlich G, Kotzerke J*, et al.* Very stable Re-188-S-4 chelates for labelling biomolecules. Nuklearmedizin-Nucl Med 2007; 46: 181-184.

[49] Kramer A, Alberto R, Egli A, Novak-Hofer I, Hegetschweiler K, Abram U*, et al.* Derivatives of 1,3,5-triamino-1,3,5-trideoxy-cis-inositas versatile pentadentate ligands for protein labeling with Re-186/188. Prelabeling, biodistribution, and X-ray structural studies. Bioconjugate Chem 1998; 9: 691-702.
https://doi.org/10.1021/bc980014i

[50] Wagner T, Zeglis BM, Groveman S, Hille C, Pothig A, Francesconi LC*, et al.* Synthesis of the first radiolabeled Re-188 N-heterocyclic carbene complex and initial studies on its potential use in radiopharmaceutical applications. J Labelled Compd Radiopharm 2014; 57: 441-447.
https://doi.org/10.1002/jlcr.3203

[51] Prakash S, Went MJ, Blower PJ. Cyclic and acyclic polyamines as chelators of rhenium-186 and rhenium-188 for therapeutic use. Nucl Med Biol 1996; 23: 543-549.
https://doi.org/10.1016/0969-8051(96)00038-8

[52] Kremer C, Dominguez S, PerezSanchez M, Mederos A, Kremer E. Comparative electrochemistry of technetium(V) and rhenium(V) dioxo complexes. J Radioanal Nucl Chem-Lett 1996; 213: 263-274.
https://doi.org/10.1007/BF02163572

[53] Abiraj K, Mansi R, Tamma ML, Forrer F, Cescato R, Reubi JC*, et al.* Tetraamine-derived bifunctional chelators for technetium-99m labelling: synthesis, bioconjugation and evaluation as targeted SPECT imaging probes for GRP-receptor-positive tumours. Chem Eur J 2010; 16: 2115-2124.
https://doi.org/10.1002/chem.200902011

[54] Kothari KK, Gali H, Prabhu KR, Pillarsetty N, Owen NK, Katti KV*, et al.* Synthesis and characterization of Tc-99m- and Re-188-complexes with a diamido-dihydroxymethylenephosphine-based bifunctional chelating agent (N2P2-BFCA). Nucl Med Biol 2002; 29: 83-89.
https://doi.org/10.1016/S0969-8051(01)00280-3

[55] Gali H, Hoffman TJ, Sieckman GL, Owen NK, Katti KV, Volkert WA. Synthesis, characterization, and labeling with Tc-99m/Re-188 of peptide conjugates containing a dithia-bisphosphine chelating agent. Bioconjugate Chem 2001; 12: 354-363.
https://doi.org/10.1021/bc000077c

[56] Boschi A, Duatti A, Uccelli L. Development of technetium-99m and rhenium-188 radiopharmaceuticals containing a terminal metal-nitrido multiple bond for diagnosis and therapy. In: *Contrast Agents III: Radiopharmaceuticals - from Diagnostics to Therapeutics*. Edited by Krause W; 2005. pp. 85-115.

[57] Boschi A, Bolzati C, Uccelli L, Duatti A. High-yield synthesis of the terminal Re-188 N multiple bond from generator-produced $(ReO_4)^-$Re-188 (-). Nucl Med Biol 2003; 30: 381-387.
https://doi.org/10.1016/S0969-8051(03)00002-7

[58] Boschi A, Massi A, Uccelli L, Pasquali M, Duatti A. PEGylated N-methyl-S-methyl dithiocarbazate as a new reagent for the high-yield preparation of nitrido Tc-99m and Re-188 radiopharmaceuticals. Nucl Med Biol 2010; 37: 927-934.
https://doi.org/10.1016/j.nucmedbio.2010.05.008

[59] Demaimay F, Dazord L, Roucoux A, Noiret N, Patin H, Moisan A. Rhenium-188 and technetium-99m nitridobis(N-ethoxy-N-ethyldithiocarbamate) leucocyte labelling radiopharmaceuticals: Re-188;$N(NOET)_2$ and Tc-99m;$N(NOET)_2$, NOET=Et(EtO)NCS_2: Their *in vitro* localization and chemical behaviour. Nucl Med Biol 1997; 24: 701-705.
https://doi.org/10.1016/S0969-8051(97)00096-6

[60] Bordoloi JK, Berry D, Khan IU, Sunassee K, de Rosales RTM, Shanahan C*, et al.* Technetium-99m and rhenium-188 complexes with one and two pendant bisphosphonate groups for imaging arterial calcification. Dalton Trans 2015; 44: 4963-4975.
https://doi.org/10.1039/C4DT02965H

[61] Demaimay F, Roucoux A, Dazord L, Noiret N, Moisan A, Patin H. Studies of technetium-99m nitridobisdithiocarboxylate leucocyte specific radiopharmaceutical: (TcN)-Tc-99m$(DTCX)_2$, DTCX = $CH_3(CH_2)(8)CS_2$. The cellular and subcellular distribution in human blood cells, and chemical behaviour. Synthesis of the analogous rhenium-188 radiopharmaceutical. Nucl Med Biol 1999; 26: 225-231.
https://doi.org/10.1016/S0969-8051(98)00082-1

[62] Carta D, Jentschel C, Thieme S, Salvarese N, Morellato N, Refosco F*, et al.* Assessment of the best N^{3-} donors in preparation of M(N)(PNP) -based (M=Tc-99m-; Re-188) target-specific radiopharmaceuticals: Comparison among succinic dihydrazide (SDH), N-methyl-S-methyl dithiocarbazate (HDTCZ) and PEGylated N-methyl-S-methyl dithiocarbazate (HO_2C-PEG(600)-DTCZ). Nucl Med Biology 2014; 41: 570-581.
https://doi.org/10.1016/j.nucmedbio.2014.04.126

[63] Smilkov K, Janevik E, Guerrini R, Pasquali M, Boschi A, Uccelli L*, et al.* Preparation and first biological evaluation of novel Re-188/Tc-99m peptide conjugates with substance-P. Appl Radiat Isot 2014; 92: 25-31.
https://doi.org/10.1016/j.apradiso.2014.06.003

[64] Meszaros LK, Dose A, Biagini SC, Blower PJ. Hydrazinonicotinic acid (HYNIC) - coordination chemistry and applications in radiopharmaceutical chemistry. Inorg Chim Acta 2010; 363: 1059-1069.
https://doi.org/10.1016/j.ica.2010.01.009

[65] Surfraz MB, King R, Mather SJ, Biagini S, Blower PJ. Technetium-binding in labelled HYNIC-peptide conjugates: Role of coordinating amino acids. J Inorg Biochem 2009; 103: 971-977.
https://doi.org/10.1016/j.jinorgbio.2009.04.007

[66] King RC, Surfraz MB, Biagini SC, Blower PJ, Mather SJ. How do HYNIC-conjugated peptides bind technetium? Insights from LC-MS and stability studies. Dalton Trans 2007: 4998-5007.
https://doi.org/10.1039/b705111e

[67] Luo TY, Cheng PC, Chiang PF, Chuang TW, Yeh CH, Lin WJ. Re-188-HYNIC-trastuzumab enhances the effect of apoptosis induced by trastuzumab in HER2-overexpressing breast cancer cells. Annals Nucl Med 2015; 29: 52-62.
https://doi.org/10.1007/s12149-014-0908-8

[68] Clarke C, Cowley AR, Dilworth JR, Donnelly PS. Pyridylthiocarbazide complexes of rhenium with potential radiopharmaceutical applications. Dalton Trans 2004: 2402-2403.
https://doi.org/10.1039/b406439a

[69] North AJ, Karas JA, Ma MT, Blower PJ, Ackermann U, White JM*, et al.* Rhenium and technetium-oxo complexes conjugated to the tumour avid peptides octreotate and cyclic-RGDfK. submitted.

[70] Williams JD. PhD thesis. King's College London; 2013.

[71] Schibli R, Schwarzbach R, Alberto R, Ortner K, Schmalle H, Dumas C*, et al.* Steps toward high specific activity labeling of biomolecules for therapeutic application: Preparation of precursor Re-188$(H_2O)_3(CO)_3^+$ and synthesis of tailor-made bifunctional ligand systems. Bioconjugate Chem 2002; 13: 750-756.
https://doi.org/10.1021/bc015568r

[72] de Rosales RTM, Finucane C, Foster J, Mather SJ, Blower PJ. Re-188$(CO)_3$-dipicolylamine-alendronate: a new bisphosphonate conjugate for the radiotherapy of bone metastases. Bioconjugate Chem 2010; 21: 811-815. https://doi.org/10.1021/bc100071k

[73] Miroslavov AE, Alekseev IE, Tyupina MY, Lumpov AA, Stepanova ES, Kol'tsov VV, *et al.* Synthesis of (ReX)-Re-188$(CO)_5$ (X = Cl, Br, and I). J Radioanal Nucl Chem 2016; 308: 1039-1042. https://doi.org/10.1007/s10967-015-4558-7

[74] Top S, Morel P, Pankowski H, Jaouen G. Rapid and mild synthesis of $Re_2(CO)_{10}$ by reduction of NH_4 ReO_4 at atmospheric CO pressure. J Chem Soc Dalton Trans 1996: 3611-3612. https://doi.org/10.1039/dt9960003611

[75] Ogawa K, Kawashima H, Kinuya S, Shiba K, Onoguchi M, Kimura H, *et al.* Preparation and evaluation of Re-186/188-labeled antibody (A7) for radioimmunotherapy with rhenium(I) tricarbonyl core as a chelate site. Annals Nucl Med 2009; 23: 843-848. https://doi.org/10.1007/s12149-009-0319-4

[76] Guo R, Ma Y, Zhang R, Liang S, Shen H, Xu H, *et al.* Rhenium-188 labeled recombinant human plasminogen kringle5 (rhk5) and preliminary biodistribution evaluation in mice bearing A549 tumours. Nuklearmedizin-Nucl Med 2011; 50: 234-239. https://doi.org/10.3413/Nukmed-0349-10-09

[77] Tavare R, Williams J, Howland K, Blower PJ, Mullen GED. $[Re(CO)_3]^+$ labelling of a novel cysteine/hexahistidine tag: insights into binding mode by liquid chromatography-mass spectrometry. J Inorg Biochem 2012; 114: 24-27. https://doi.org/10.1016/j.jinorgbio.2012.04.006

[78] Blower PJ. A nuclear chocolate box: the periodic table of nuclear medicine. Dalton Trans 2015; 44: 4819-4844. https://doi.org/10.1039/C4DT02846E

[79] Dias CR, Jeger S, Osso JA, Mueller C, De Pasquale C, Hohn A, *et al.* Radiolabeling of rituximab with Re-188 and Tc-99m using the tricarbonyl technology. Nucl Med Biol 2011; 38: 19-28. https://doi.org/10.1016/j.nucmedbio.2010.05.010

[80] Xia JY, Long S, Yu JF, Wang YX, Cao Z. Pyridyl derivatives provide new pathways for labeling protein with fac- Re-188$(CO)_3(H_2O)_3^+$. J Radioanal Nucl Chem 2009; 281: 493-499. https://doi.org/10.1007/s10967-009-0025-7

[81] Xia JY, Wang YX, Li GC, Yu JF, Yin DZ. Synthesis of pyridyl derivatives for the future functionalization of biomolecules labeled with the fac- Re-188$(CO)_3(H_2O)_3^+$ precursor. J Radioanal Nucl Chem 2009; 279: 245-252. https://doi.org/10.1007/s10967-007-7145-8

[82] Bartholoma M, Valliant J, Maresca KP, Babich J, Zubieta J. Single amino acid chelates (SAAC): a strategy for the design of technetium and rhenium radiopharmaceuticals. Chem Commun 2009: 493-512. https://doi.org/10.1039/B814903H

[83] Tzanopoulou S, Pirmettis IC, Patsis G, Paravatou-Petsotas M, Livaniou E, Papadopoulos M, *et al.* Synthesis, characterization, and biological evaluation of M(I)$(CO)_3$(NNO) complexes (M = Re, Tc-99m) conjugated to 2-(4-aminophenyl)benzothiazole as potential breast cancer radiopharmaceuticals. J Med Chem 2006; 49: 5408-5410. https://doi.org/10.1021/jm0606387

[84] Muller C, Schubiger PA, Schibli R. Isostructural folate conjugates radiolabeled with the matched pair Tc-99m/Re-188: a potential strategy for diagnosis and therapy of folate receptor-positive tumors. Nucl Med Biol 2007; 34: 595-601. https://doi.org/10.1016/j.nucmedbio.2007.05.011

[85] Fernandes C, Monteiro S, Mendes P, Gano L, Marques F, Casimiro S, *et al.* Biological assessment of novel bisphosphonate-containing Tc-99m/Re-organometallic complexes. J Organomet Chem 2014; 760: 197-204. https://doi.org/10.1016/j.jorganchem.2013.10.038

[86] Lee BC, Moon BS, Kim JS, Jung JH, Park HS, Katzenellenbogen JA, *et al.* Synthesis and biological evaluation of RGD peptides with the Tc-99m/Re-188 chelated iminodiacetate core: highly enhanced uptake and excretion kinetics of theranostics against tumor angiogenesis. RSC Advances 2013; 3: 782-792. https://doi.org/10.1039/C2RA22460G

[87] Wang C, Yin JL, Zhou W, Zhang L, Zhou Z. Study on radiolabeling of 1,2,3-triazole analogs with fac- Re-188$(CO)_3(H_2O)_3^+$ via click chemistry. Nucl SciTech 2013; 24.

[88] Wang C, Zhou W, Yu JF, Zhang L, Wang N. A study of the radiosynthesis of fac- Re-188$(CO)_3(H_2O)_3^+$ and its application in labeling 1,2,3-triazole analogs obtained by click chemistry. Nucl Med Commun 2012; 33: 84-89. https://doi.org/10.1097/MNM.0b013e32834d3ba7

[89] Mindt TL, Muller C, Melis M, de Jong M, Schibli R. "Click-to-Chelate": *In vitro* and *in vivo* comparison of a Tc-99m$(CO)_3$-labeled N(tau)-histidine folate derivative with its isostructural, clicked 1,2,3-triazole analogue. Bioconjugate Chem 2008; 19: 1689-1695. https://doi.org/10.1021/bc800183r

[90] Papagiannopoulou D, Tsoukalas C, Makris G, Raptopoulou CP, Psycharis V, Leondiadis L, *et al.* Histidine derivatives as tridentate chelators for the fac- M-I$(CO)_3$ (Re, Tc-99m, Re-188) core: Synthesis, structural characterization, radiochemistry and stability. Inorg Chim Acta 2011; 378: 333-337. https://doi.org/10.1016/j.ica.2011.08.062

[91] Sparr C, Michel U, Marti RE, Muller C, Schibli R, Moser R, *et al.* Synthesis of a novel gamma-folic acid-N-tau-histidine conjugate suitable for labeling with Tc-99m and Re-188. Synthesis-Stuttgart 2009: 787-792.

[92] Zobi F, Spingler B, Fox T, Alberto R. Toward novel DNA binding metal complexes: Structure and basic kinetic data of M(9MeG)$_2$$(CH_3OH)(CO)_3^+$ (M=Tc-99, Re). Inorg Chem 2003; 42: 2818-2820. https://doi.org/10.1021/ic030028m

[93] Ursillo S, Can D, N'Dongo HWP, Schmutz P, Spingler B, Alberto R. Cyclopentadienyl chemistry in water: synthesis and properties of bifunctionalized (eta^5-C_5H_3{COOR}$_2$)M$(CO)_3$ (M = Re and Tc-99m) complexes. Organometallics 2014; 33: 6945-6952. https://doi.org/10.1021/om501029e

[94] Uehara T, Koike M, Nakata H, Hanaoka H, Iida Y, Hashimoto K, *et al.* Design, synthesis, and evaluation of Re-188 organorhenium-labeled antibody fragments with renal enzyme-cleavable linkage for low renal radioactivity levels. Bioconjugate Chem 2007; 18: 190-198. https://doi.org/10.1021/bc0602329

[95] Uehara T, Koike M, Nakata H, Miyamoto S, Motoishi S, Hashimoto K, *et al. In vivo* recognition of cyclopentadienyltricarbonylrhenium (CpTR) derivatives. Nucl Med Biol 2003; 30: 327-334. https://doi.org/10.1016/S0969-8051(02)00437-7

[96] Le Bideau F, Salmain M, Top S, Jaouen G. New and efficient routes to biomolecules substituted with cyclopentadienyltricarbonylrhenium and -technetium derivatives. Chem Eur J 2001; 7: 2289-2294. https://doi.org/10.1002/1521-3765(20010601)7:11<2289::AID-CHEM22890>3.0.CO;2-R

[97] Rattat D, Schubiger PA, Berke HG, Schmalle H, Alberto R. Dicarbonyl-nitrosyl-complexes of rhenium (Re) and technetium (Tc), a potentially new class of compounds for the direct radiolabeling of biomolecules. Cancer Biother Radiopharm 2001; 16: 339-343. https://doi.org/10.1089/108497801753131426

[98] Alberto R, Cowley AR, Dilworth JR, Donnelly PS, Pratt J. Diazenide and hydrazide(2-) derivatives of the Re$(CO)_3^+$

core. Dalton Trans 2004: 2610-2611.
https://doi.org/10.1039/B407708C

[99] Talaat HM, El-Mohty AA. Preparation of Re-186-MIBI complex for myocardial perfusion imaging as potential replacement of analogues Tc-99m-MIBI complex. J Radioanal Nucl Chem 2013; 295: 233-237.
https://doi.org/10.1007/s10967-012-2105-3

[100] Salvarese N, Dolmella A, Refosco F, Bolzati C. Reactivity of the $M(PS)_2^+$building block (M = Re-III and Tc-99m(III); PS = phosphinothiolate) toward isopropylxanthate and pyridine-2-thiolate. Inorg Chem 2015; 54: 1634-1644.
https://doi.org/10.1021/ic502632h

[101] Salvarese N, Morellato N, Venzo A, Refosco F, Dolmella A, Bozati C. Synthesis and characterization of M-III$(PS)_2$(L) Mixed-Ligand Compounds (M = Re, Tc-99; PS = phosphinothiolate; L = dithiocarbamate) as potential models for the development of new agents for SPECT imaging and radiotherapy. Inorg Chem 2013; 52: 6365-6377.
https://doi.org/10.1021/ic400094s

[102] Garin E, Noiret N, Malbert C, Lepareur N, Roucoux A, Caulet-Maugendre S, *et al.* Development and biodistribution of Re-188-SSS lipiodol following injection into the hepatic artery of healthy pigs. Eur J Nucl Med Mol Imaging 2004; 31: 542-546.
https://doi.org/10.1007/s00259-003-1402-z

[103] Lepareur N, Mevellec F, Noiret N, Refosco F, Tisato F, Porchia M, *et al.* Syntheses and reactivity of 'sulfur rich' Re(III) and Tc(III) complexes containing trithioperoxybenzoate, dithiobenzoate and dithiocarbamate ligands. Dalton Trans 2005: 2866-2875.
https://doi.org/10.1039/b503938j

[104] Pietzsch HJ, Gupta A, Syhre R, Leibnitz P, Spies H. Mixed-ligand technetium(III) complexes with tetradendate/monodendate NS3/isocyanide coordination: a new nonpolar technetium chelate system for the design of neutral and lipophilic complexes stable *in vivo*. Bioconjugate Chem 2001; 12: 538-544.
https://doi.org/10.1021/bc0001591

[105] Mullen GED, Blower PJ, Price DJ, Powell AK, Howard MJ, Went MJ. Trithiacyclononane as a ligand for potential technetium and rhenium radiopharmaceuticals: Synthesis of M(9S3)$(SC_2H_4SC_2H_4S)$ BF_4 (M=Tc-99, Re,Re-188) via C-S bond cleavage. Inorg Chem 2000; 39: 4093-4098.
https://doi.org/10.1021/ic991240m

[106] Mullen GED, Went MJ, Wocadlo S, Powell AK, Blower PJ. Electron transfer induced C-S bond cleavage in rhenium and technetium thioether complexes: Structural and chemical evidence for pi back-donation to C-S sigma* orbitals. Angew ChemInt Ed Engl 1997; 36: 1205-1207.
https://doi.org/10.1002/anie.199712051

[107] Braband H, Benz M, Tooyama Y, Alberto R. Activation of (TcO_4)-Tc-99(m)$^-$ by phosphonium cations. Chem Commun 2014; 50: 4126-4129.
https://doi.org/10.1039/c4cc00718b

[108] [108]Hahn EM, Casini A, Kuhn FE. Re(VII) and Tc(VII) trioxo complexes stabilized by tridentate ligands and their potential use as radiopharmaceuticals. Coord Chem Rev 2014; 276: 97-111.
https://doi.org/10.1016/j.ccr.2014.05.021

[109] [109] Sarma HD, Das T, Banerjee S, Venkatesh M, Vidyasagar PB, Mishra KP. Biologic evaluation of a novel Re-188-labeled porphyrin in mice tumor model. Cancer Biother Radiopharm 2010; 25: 47-54.
https://doi.org/10.1089/cbr.2009.0675

[110] Jia ZY, Deng HF, Pu MF, Luo SZ. Rhenium-188 labelled meso-tetrakis 3,4-bis (carboxymethyleneoxy) phenyl porphyrin for targeted radiotherapy: preliminary biological evaluation in mice. Eur J Nucl Med Mol Imaging 2008; 35: 734-742.
https://doi.org/10.1007/s00259-007-0682-0

[111] Jia ZY, Deng HF, Pu MF. Synthesis and preliminary biological studies of the novel conjugate Re-188-labeled meso-tetrakis(4-sulfophenyl)porphyrin in mice. Nucl Med Biol 2007; 34: 643-649.
https://doi.org/10.1016/j.nucmedbio.2007.05.006

[112] Nassar MY, El-Kolaly MT, Mahran MRH. Synthesis of a Re-188-DTPMP complex using carrier-free Re-188 and study of its stability. J Radioanal Nucl Chem 2011; 287: 779-785.
https://doi.org/10.1007/s10967-010-0933-6

[113] Paeng JC, Lee DS, Kang WJ, Yang HM, Chung JK, Jeong JM, *et al.* Dosimetry in leakage of Re-188-DTPA during intracoronary balloon brachytherapy. Eur J Nucl Med Mol Imaging 2003; 30: 1263-1265.
https://doi.org/10.1007/s00259-003-1235-9

[114] Safavy A, Sanders A, Qin HY, Buchsbaum DJ. Conjugation of unprotected trisuccin, N- tris 2- (N-hydroxyamino)carbonyl ethyl methyl succinamic acid, to monoclonal antibody CC49 by an improved active ester protocol. Bioconjugate Chem 1997; 8: 766-771.
https://doi.org/10.1021/bc970127m

[115] Zhang M, Shi S, Guo R, Miao Y, Li B. Use of rhenium-188 for *in vivo* imaging and treatment of human cervical cancer cells transfected with lentivirus expressing sodium iodide symporter. OncolRep 2016; 36: 2289-2297.
https://doi.org/10.3892/or.2016.5034

[116] Runge R, Oehme L, Kotzerke J, Freudenberg R. The effect of dimethyl sulfoxide on the induction of DNA strand breaks in plasmid DNA and colony formation of PC Cl3 mammalian cells by alpha-, beta-, and Auger electron emitters Ra-223, Re-188, and Tc-99m. Eur J Nucl Med Mol Imaging Res 2016; 6.

[117] Guo R, Zhang M, Xi Y, Ma YF, Liang S, Shi S, *et al.* Theranostic studies of human sodium iodide symporter imaging and therapy using Re-188: A human glioma study in mice. PLOS One 2014; 9.

[118] Freudenberg R, Wendisch M, Runge R, Wunderlich G, Kotzerke J. Reduction in clonogenic survival of sodium-iodide symporter (NIS)-positive cells following intracellular uptake of Tc-99m versus Re-188. Int J Radiat Biol 2012; 88: 991-997.
https://doi.org/10.3109/09553002.2012.728303

[119] Klutz K, Willhauck MJ, Wunderlich N, Zach C, Anton M, Senekowitsch-Schmidtke R, *et al.* Sodium iodide symporter (NIS)-mediated radionuclide (I-131, Re-188) therapy of liver cancer after transcriptionally targeted intratumoral *in vivo* NIS gene delivery. Human Gene Ther 2011; 22: 1403-1412.
https://doi.org/10.1089/hum.2010.158

[120] Weeks AJ, Jauregui-Osoro M, Cleij M, Blower JE, Ballinger JR, Blower PJ. Evaluation of F-18 -tetrafluoroborate as a potential PET imaging agent for the human sodium/iodide symporter in a new colon carcinoma cell line, HCT116, expressing hNIS. Nucl Med Commun 2011; 32: 98-105.
https://doi.org/10.1097/MNM.0b013e3283419540

[121] Torres-Garcia E, Carrillo-Cazares TA. Specific energy from Auger and conversion electrons of ^{131}I, ^{188}Re-anti-CD20 to a lymphocyte's nucleus. Radiat Effects Defects Solids 2011; 166: 40-43.
https://doi.org/10.1080/10420150.2010.488692

[122] Dadachova E, Bouzhzah B, Zuckier LS, Pestell RG. Rhenium-188 as an alternative to iodine-131 for treatment of breast tumors expressing the sodium/iodide symporter (NIS). Nucl Med Biol 2002; 29: 13-18.
https://doi.org/10.1016/S0969-8051(01)00279-7

[123] Zuckier LS, Dohan O, Li Y, Chang CJ, Carrasco N, Dadachova E. Kinetics of perrhenate uptake and comparative biodistribution of perrhenate, pertechnetate, and iodide by NaI symporter-expressing tissues *in vivo*. J Nucl Med 2004; 45: 500-507.

[124] Dadachova E, Carrasco N. The Na^+/I^- symporter (NIS): Imaging and therapeutic applications. Sem Nucl Med 2004;

34: 23-31.
https://doi.org/10.1053/j.semnuclmed.2003.09.004

[125] Chuamssaamarkkee K. PhD thesis King's College London; 2016.

Received on 25-04-2017 Accepted on 28-04-2017 Published on 31-07-2017

http://dx.doi.org/10.15379/2408-9788.2017.04