Rhenium-188: Availability from the $^{188}W/^{188}Re$ Generator and Status of Current Applications

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Abstract: Rhenium-188 is one of the most readily available generator derived and useful radionuclides for therapy emitting β^- particles (2.12 MeV, 71.1% and 1.965 MeV, 25.6%) and imageable gammas (155 keV, 15.1%). The $^{188}W/^{188}Re$ generator is an ideal source for the long term (4-6 months) continuous availability of no carrier added (nca) ^{188}Re suitable for the preparation of radiopharmaceuticals for radionuclide therapy. The challenges associated with the double neutron capture route of production of the parent ^{188}W radionuclide have been a major impediment in the progress of application of ^{188}Re. Tungsten-188 of adequate specific activity can be prepared only in 2-3 of the high flux reactors operating in the World. Several useful technologies have been developed for the preparation of clinical grade $^{188}W/^{188}Re$ generators. Since the specific activity of ^{188}W used in the generator is relatively low 185 GBq(<5 Ci)/g], the eluted $^{188}ReO_4^-$ can have low radioactive concentration often insufficient for radiopharmaceutical preparation. However, several efficient post elution concentration techniques have been developed that yield clinically useful $^{188}ReO_4^-$ solutions. Rhenium-188 has been used for the preparation of therapeutic radiopharmaceuticals for the management of diseases such as bone metastasis, rheumatoid arthritis and primary cancers. Several early phase clinical studies using radiopharmaceuticals based on ^{188}Re-labeled phosphonates, antibodies, peptides, lipiodol and particulates have been reported. This article reviews the availability and use of ^{188}Re including a discussion of why broader use of ^{188}Re has not progressed as expected as a popular radionuclide for therapy.

Keywords: Rhenium-188, $^{188}W/^{188}Re$ generator, Radionuclide therapy, Bone pain palliation, hepatocarcinoma, Rheumatoid arthritis.

INTRODUCTION

Radionuclide therapy has been successfully applied for the treatment of thyroid cancer for well over 65 years and is undergoing a renaissance thanks to the demonstrated utility of β and α-emitters with potential utility in the treatment of several cancers [1-8]. One of the important factors for this new realization is the development of new targeting methodologies using novel molecules derived by taking advantage of specific biochemical reactions involving the cells. These include among others peptide-receptor, antigen-antibody and enzyme-substrate interactions. Together with the above developments is the availability of several therapeutic radionuclides [9-11] other than ^{131}I that can be bound to carrier molecules through specially designed bifunctional chelating agents (BFCAs) that are able to tightly bind the radiometal [12-16]. The large number of β^- particle emitting therapeutic radionuclides proposed in recent decades, prominently include ^{186}Re, ^{188}Re, ^{105}Rh, ^{90}Y, ^{166}Ho, ^{175}Yb, ^{177}Lu, ^{170}Tm, etc. [17-24]. While each radionuclide is proposed because of its unique properties for targeted therapy, the ultimate choice depends upon the ready availability of the radionuclide of choice in high specific activity and radiochemical concentration in the clinical setting. Most therapeutic radionuclides suggested in this context are short-lived in nature thus limiting their availability at the hospital site.

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Radionuclide generators represent convenient in-house radionuclide production systems. The availability of a daughter radionuclide that can be readily obtained from a long lived parent radionuclide greatly enhances the potential utilization of the radionuclide. In this context, ^{90}Y and ^{188}Re offer significant advantages over many other radionuclides used for therapy as they are available in pure form by adapting the radionuclide generator concept [25]. Although the development of generator technologies for both these radionuclides is feasible, each has its own specific challenges which must be addressed. Considerable progress has been made in the last couple of decades to develop therapeutically useful generators for obtaining both ^{90}Y and ^{188}Re in purity and radioactive concentration sufficient for the formulation of therapeutic radiopharmaceuticals. This review summarizes the technologies developed for the preparation of $^{188}W/^{188}Re$ generator, post elution concentration of the ^{188}Re-perrhenate eluate and a brief discussion of ^{188}Re radiopharmaceuticals.

Rhenium Radionuclides in Nuclear Medicine

There are more than 45 radionuclides reported for rhenium, of which ^{186}Re and ^{188}Re have been extensively studied for nuclear medicine applications. Table **1** summarizes the radionuclidic characteristics of these two rhenium isotopes which are used in nuclear medicine and related specialties for various therapeutic applications.

Irradiation of natural rhenium in a nuclear reactor yields a mixture of ^{186}Re and ^{188}Re [26], the proportion of each ra-

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Table 1. Decay Characteristics and Production Methods of ^{186}Re and ^{188}Re

	Decay Product	Half-life	β^- E_{max}(MeV)	γ-energy (keV)	Production
^{186}Re	^{186}W (EC, 7.47%) ^{186}Os (β^-, 92.43%)	90 h	1.069 (71.0%) 0.932 (21.54%) 0.581 (5.78%) 0.459 (1.69%)	137 (9.42%)	$^{185}Re(n,\gamma)\ ^{186}Re$
^{188}Re	^{188}Os (β-, 100%)	17 h	2.120 (71.1%) 1.965 (25.6%) 1.487 (1.65%)	155 (15.1%)	$^{188}W/^{188}Re$ generator or $^{187}Re(n,\gamma)^{188}Re$

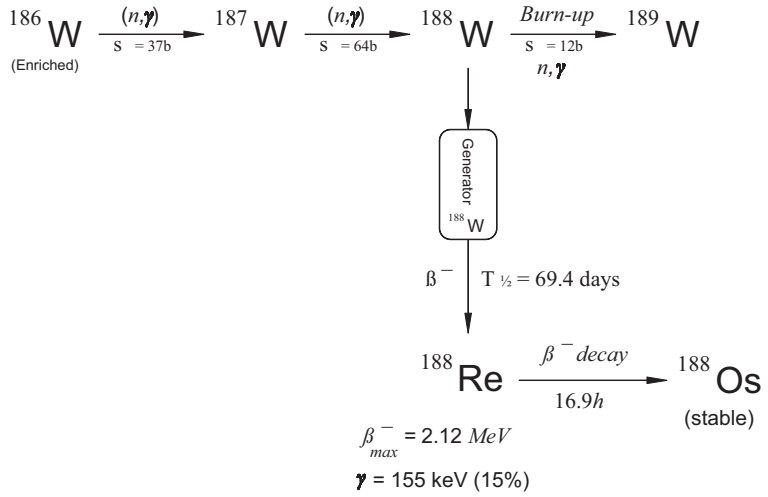

Fig. (1). Reactor Production and Decay Scheme for Tungsten-188.

dioisotope depends on the irradiation duration and post bombardment decay [27]. Radionuclidically pure ^{186}Re and ^{188}Re can be prepared by irradiating highly enriched targets, ^{185}Re and ^{187}Re, in research reactors. The corresponding nuclear reaction cross sections are fairly large (114 and 72 barns, respectively for ^{185}Re and ^{187}Re) to yield relatively large quantities of the products. Direct production using enriched targets in the reactor leads to carrier added (ca) radioisotopes having specific activities adequate for the preparation of selected radiopharmaceuticals useful for bone pain palliation therapy, hepatocarcinoma, radiosynovectomy and for intravascular radionuclide therapy (IVRNT). However, the specific activities of (n,γ) produced ^{186}Re and ^{188}Re are not adequate for radiolabelling molecules such as peptides and antibodies which seek low density targets such as receptors and tumour antigens. Generator eluted ^{188}Re offers the advantage of providing nca ^{188}Re suitable for all applications. Preparation of ^{188}Re from a $^{188}W/^{188}Re$ generator is interesting as it provides a long term source for no carrier added (nca) ^{188}Re at the nuclear medicine department.

Production of ^{188}W

Fig. (**1**) depicts the nuclear reactions leading to the production of ^{188}W along with its decay scheme. In the nuclear reactor, ^{186}W undergoes two consecutive neutron capture reactions to form ^{188}W. There are in fact few examples of radionuclides other than ^{188}W produced by the double neutron capture process that are in routine use. This is because the double neutron capture process is inherently inefficient since the radionuclide production yield is a function of the product of the cross section values (s_1 and s_2). Since cross sections are relatively low values (~10^{-24} cm^2), the product of the cross sections becomes much smaller and hence the production yields are low even when very high flux research reactors are used [28]. Similarly, the neutron flux is very important as the production yield is a function of the square of the flux (ϕ). Increasing the flux by only one order will make two order higher amount of activity. Hence, reactors having flux values of about <$5x10^{14}$ $n.cm^{-2}.sec^{-1}$ are not suitable for the production of ^{188}W. Fig. (**2**) represents the calculated specific activity of ^{188}W at various thermal neutron flux values.

The natural abundance of ^{186}W is 28.6% and enriched targets are essential for the production of ^{188}W sufficient for generator use. By using enriched ^{186}W targets, the specific activity of ^{188}W is correspondingly augmented. Use of an enriched targets is also important to avoid the high radiation field contributed by other radioactive isotopes of W (^{185}W, ^{187}W mainly). Otherwise, thicker shielding will be required for both transportation of ^{188}W to the generator loading facilities and for generator shielding. A specific activity of upto 185GBq(5Ci)/g can be obtained by using enriched target and following an irradiation cycle of about 20-24 days at neutron flux of ~ 10^{15} $n.cm^{-2}.sec^{-1}$. The current status of reactor production and processing of ^{188}W is summarized as a chapter of a recent book published by the International Atomic Energy Agency (IAEA) [29]. As per this report,

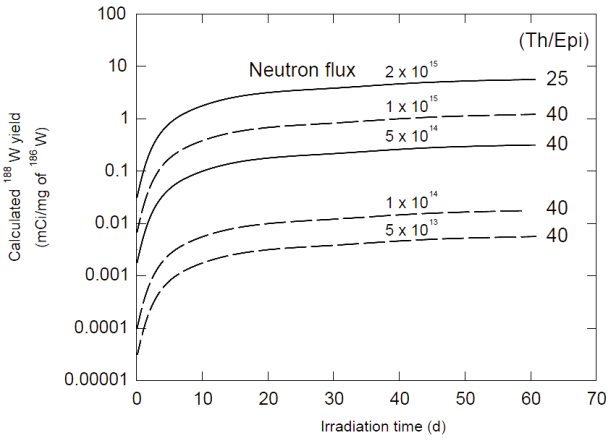

Fig. (2). Calculated Specific Activity of Reactor-produced Tungsten-188 at Various Thermal Neutron Flux.

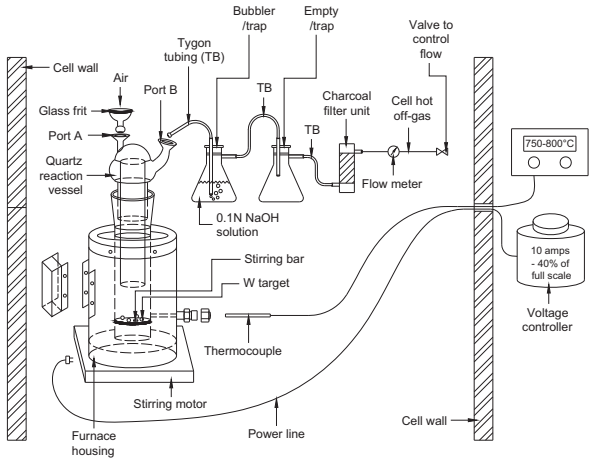

Fig. (3). Apparatus used at ORNL for Post-irradiation Conversion of Metallic Enriched ^{186}W Targets to Tungsten Oxide.

tungsten-188 having adequate specific activity suitable for the production of ^{188}W/^{188}Re generators can be accomplished in only a limited number of the research reactors i.e. SM Reactor, RIAR, Dmitrovgrad, Russian Federation; ORNL HFIR, USA and BR2 Reactor, Belgium.

Enriched ^{186}W as metal as well as oxide form is used as target for irradiation. At ORNL, 97% enriched ^{186}W as the oxide sealed in quartz tubes enclosed in aluminum capsules is irradiated for one or two cycles of 23-24 days each at a neutron flux of about 2.5×10^{15} n.cm^{-2}.s^{-1} [30]. The production yields are substantially lower than the calculated values using reported cross sections for the different reactions taking place during irradiation. The loss of ^{188}W due to neutron burn-up, ^{188}W(n, γ)^{189}W (σ = 12 barn), is one of the factors contributing to reduced production yields of ^{188}W [31]. Sodium tungstate solution required for subsequent treatment for generator loading is produced by dissolving tungsten oxide in sodium hydroxide solution with moderate heating.

Owing to the relatively low density of powder metallic targets and to ensure maximum utilization of irradiation space in the reactor, ORNL has developed a pressed enriched ^{186}W metal target configuration [32]. In this method, the metallic tungsten target, in the form of small pellets (4 mm diameter × 3 mm height) is prepared by cold pressing followed by sintering. Such targets have difficulties in dissolving post irradiation and therefore converted to tungsten oxide by heating in a stream of air in a furnace and dissolved in sodium hydroxide to obtain solutions of sodium tungstate. It is estimated that greater than 37TBq(1 kilo curie) of ^{188}W per cycle can be produced in the HFIR, ORNL using this methodology [29]. The apparatus used at ORNL for post-irradiation conversion of metallic enriched ^{186}W targets to tungsten oxide is shown schematically in Fig. (**3**).

Collaboration between ORNL and SCK.CEN in 1998 had successfully demonstrated that the BR2 reactor in Mol, Belgium can be utilized for ^{188}W production. The production of ^{188}W in the BR2 Reactor was carried out in the central beryllium plug H1 where the thermal neutron flux peaks to 1×10^{15} n.cm^{-2}.s^{-1} [33]. The high-density pressed metallic ^{186}W targets (97% enriched) made by ORNL were used for irradiation. The specific activity of BR2-produced ^{188}W was about 37GBq(1Ci) using 20+ day cycle of irradiation.

The chemical processing of the targets is accomplished by dissolution of the target in NaOH solution while using metal oxide targets. Metallic enriched targets are dissolved by high temperature oxidative processing. Post dissolution purification of the target is essential to remove radionuclidic impurities such as ^{191}Os, ^{192}Ir and other chemical impurities such as silicates coming from quartz capsules [29]. In Russia, an ion-exchange chromatography purification using Dowex-1 resin is reported [29]. After purification, the pertungstic acid solution is evaporated to dryness and taken in required quantity of sodium hydroxide and treated for the preparation of generators. At the SM reactor at Dimitrovgrad ^{188}W having specific activity >185 GBq(5 Ci)/g had been obtained by irradiating ^{186}W enriched targets in oxide form at neutron flux >1x10^{15} n.cm^{-2}.sec^{-1} and following several 'mini cycles' [29]. At present the SM reactor at Dimitrovgrad, Russian Federation is the sole source of ^{188}W suitable for the production of ^{188}W/^{188}Re generators and World's dependence on a single source for the raw material ^{188}W is a major factor affecting the progress of ^{188}Re radiopharmaceuticals in clinical medicine. Table **2** summarizes the high flux research reactors that can produce ^{188}W.

^{188}W/^{188}Re Generator

Hayes and Rafter in 1965 proposed the use of ^{188}Re as a possible diagnostic (not therapeutic) agent [34,35] and subsequently in 1966, Lewis and Elridge first reported the preparation of a ^{188}W/^{188}Re generator [36]. There have been several early reports subsequent to that on the development of ^{188}W/^{188}Re generator culminating in the development of clinically useful devices [37-44]. As in the case of development of ^{99}Mo/^{99m}Tc generators, all available options have also been evaluated for the preparation of ^{188}W/^{188}Re generators and the technologies used for the separation of ^{188}Re from ^{188}W are briefly discussed below.

Alumina Based ^{188}W/^{188}Re Generator

The alumina based column generator technology used for the preparation of ^{99}Mo/^{99m}Tc generators has also been widely used for the preparation of ^{188}W/^{188}Re generators. Due to the lower specific activity, a maximum of 185 GBq(5

Table 2. High Flux Research Reactors for the Production of ^{188}W

	Reactor	Institution	Reported/Projected Specific Activity (Activity of ^{188}W/g W)	Remarks
1	HFIR	ORNL, Oak Ridge,USA	148-185 GBq(4–5 Ci), one cycle 296-333 GBq(8–9 Ci), two consecutive cycle	Routine production since 1986
2	SM3	Research Institutefor Atomic Reactors (RIAR), Dimitrovgrad, Russian Federation	~ 185 GBq(5 Ci) for several 'mini-cycles'	Routine production since about 1986. Backup production for ORNL.
3	BR2	SCK•CEN, Mol, Belgium	~ 37 GBq(1 Ci), 20+ d cycle; cycle length varies	Experience since about 2001 Backup production for ORNL
4	ATR	Idaho National Laboratory (INL), Idaho Falls, USA	18.5 GBq(0.5 Ci), one cycle expected	Production not yet initiated

Table 3. The Characteristics of the Commercial $^{188}W/^{188}Re$ Generators

S. No	Institution/ Suppliers	Strength	Column Material	Specific Activity of ^{188}W	Housing	Remarks
1	ORNL, TN, USA	9.25 GBq(250 mCi) to 111 GBq(3 Ci) cGMP system	Alumina	148-185 GBq(4-5 Ci)/g	one inch lead pig with inlet/outlet holes	>500 generators since 1986.
2	Dimitrovgrad, Russia	3.7-111 GBq(0.1-3 Ci) Sterile cGMP system	Alumina	185GBq(5 Ci)/g	15 kg lead assembly	Regular production and supply.
3	IRE, Belgium	Up to 55.4 GBq(1.5 Ci)	Alumina	185 GBq(5 Ci)/g	highly shielded	Generator is available with an automatic concentration module.
4	ITM AG, Germany	Unknown	Alumina	185 GBq(5 Ci)/g	Unknown	Regular production and supply.
5	Polatom, Poland	18.5 GBq(500 mCi) cGMP system	Use of $^{99}Mo/^{99m}Tc$ column system	185 GBq(5 Ci)/g	Unknown	Regular production and supply.
6	IDB, Holand	3.7-18.5 GBq(100 - 500 mCi)	alumina	Unknown	16 kg lead assembly	Regular production and supply.
7	MAP Medical Technologies, Finland	< 18.5 GBq(500 mCi)	Use of established $^{99}Mo/^{99m}Tc$ column system	185 GBq(5 Ci)/g	Unknown	Production ceased in 2002.

Ci)/g for ^{188}W as compared to >370 TBq(10000 Ci)/g for fission produced ^{99}Mo, the eluted ^{188}Re has lower radioactive concentration. Hence, most often the ^{188}Re eluted from an alumina column chromatography generator is not suitable for the direct formulation of radiopharmaceuticals and post elution concentration of the generator eluent solution is essential to obtain $^{188}ReO_4^-$ having radioactive concentration sufficient for radiopharmaceutical formulation. Table **3** summarizes the characteristics of the commercial $^{188}W/^{188}Re$ generators available in the world market.

Extensive work started by Knapp, *et al.*, at the Oak Ridge National Laboratory (ORNL) in the mid eighties have resulted in the preparation of a $^{188}W/^{188}Re$ generator system using acidic alumina matrix analogous to the widely used $^{99}Mo/^{99m}Tc$ generator [44-46]. The alumina-based $^{188}W/^{188}Re$ generators produced at the ORNL typically contains 50 mg W per gram of alumina. Owing to the low specific activity of ^{188}W and limited binding capacity of alumina for W, a large alumina column is required for the generator column, resulting in relatively high saline elution volumes and low activity concentrations of the ^{188}Re. The generators are eluted with physiological saline and ^{188}Re yields are generally 75% to 80%. As the buildup of ^{188}Re is 62% at 24 hour post elution, daily elution provides ^{188}Re of approximately 50% of the ^{188}W activity. Tungsten-188 breakthrough values are typically in the 10^{-6} range; however, any breakthrough can be effectively removed by subsequent post elution process bypassage of the bolus through a small, commercially available alumina QMA Sep-Pak column [47]. Schematic view of a $^{188}W/^{188}Re$ generator is shown in Fig. (**4**).

The complete generator setup consists of an attachment for the generator effluent for flow through an alumina QMA SepPak, which effectively removes low levels of any ^{188}W breakthrough, and then through a tandem silver-cation/QMA

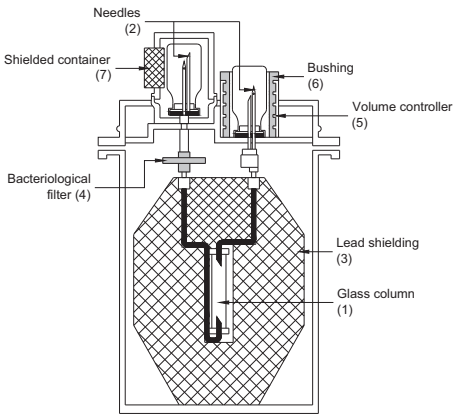

Fig. (4). Schematic view of a Typical $^{188}W/^{188}Re$ generator Set-up.

anion column for concentration of the ^{188}Re eluate to usable radioactive concentration. A clinical-scale generator loaded with greater than 37GBq(1 Ci) of ^{188}W provides more than 27.75GBq(750 mCi) (~75% yield) of ^{188}Re-perrhenate at equilibrium [1.1-1.29 GBq(30-35 mCi)/mL or approximately 18.5GBq(500 mCi) [0.74-0.925 GBq(20-25 mCi)/mL)] for sequential daily elutions.

Kodina *et al.* also reported about the same time the production of $^{188}W/^{188}Re$ generator based on acidic alumina and using the ^{188}W prepared at the SM reactor (RIAR) in Russian Federation [48]. Recently, Mikolajczak *et al.* reported the preparation of an alumina based column generator using the high specific activity ^{188}W [148 GBq(4 Ci)/g] and having a load of about 18.5 GBq(0.5 Ci) of ^{188}W. The generator had elution yield of 70-90% with good radiochemical and chemical purity and radioactive concentration sufficient to be used directly for the preparation of radiopharmaceuticals [49].

Gel Generator

Malyshev and Smimov reported the preparation of a $^{188}W/^{188}Re$ generator using hydrated zirconium oxide [41]. The $^{188}W/^{188}Re$ gel generator system developed by Erhardt *et al.* at the Missouri University Research Reactor (MURR) in conjunction with Neorex, Inc. (Seattle, Washington) was a zirconium oxide gel system [43, 50, 51]. The gel was prepared by the reaction of sodium tungstate (^{188}W) with zirconyl nitrate in acid solution with careful pH control to precipitate zirconyl tungstate. The precipitate was washed successively with water, organic solvents and air dried to form a free flowing powder which was then packed in the generator columns. Elution of the generator with normal saline provides ^{188}Re as sodium perrhenate in yields of 50-70%. Analysis by HPLC demonstrated that the ^{188}Re eluate was > 99% perrhenate. Prototype generators having a maximum activity upto 8.325 GBq(225 mCi) of ^{188}W had been prepared and evaluated. The ^{188}Re yields were consistently high for several months with ^{188}W breakthrough <1 ppm. The reported advantages of this system were as the ability to use low specific activity ^{188}W prepared at the Missouri University Research Reactor (MURR) and providing relatively small bolus volumes of sodium perrhenate of about 3 mL. Despite the good reported procedure, this generator was not evaluated further.

Dadachova and coworkers reported the preparation of titanium-tungstate gel using natural tungsten followed by neutron irradiation of the preformed gel in a moderate flux reactor [52-54]. The reported results suggest that ^{188}Re elution performance and elution yields were very close to those of conventional alumina $^{188}W/^{188}Re$ generator. Although the reported method obviously held promise as an alternative approach, GBq(curie)-level ^{185}W formed as a result of neutron activation of natural tungsten pose a major challenge during processing of the target material and during generator preparation and subsequent elution of the generator. This generator was not further evaluated; however, the method is expected to be readily adapted with ^{188}W prepared using enriched ^{186}W target.

Iller *et al.* studied the feasibility of using zirconium tungstate gels (composites of WO_3-ZrO_2) synthesized by sol-gel process for the production of $^{188}W/^{188}Re$ generators using tungsten of natural isotopic abundance irradiated in a moderate flux nuclear reactor [55]. Rhenium-188 as perrhenate was eluted using 0.9% NaCl solution. Long term use of a clinical scale generator made by this route is, however, yet to be assessed.

Thermo-chromatographic Separation

A thermo-chromatographic process has also been reported for separating ^{188}Re from ^{188}W based on the volatility of $HReO_4$. In this process, the irradiated target (^{188}W) is heated to about 900 to 1000 °C to volatilize the Re containing species, which is carried to a colder region in a stream of moist air with a yield of 65% [32, 56]. The main advantage of this method is that the enriched ^{186}W target used for activation could be recovered and recycled more easily. The major disadvantage of this process is the requirement of high temperature operations which results in a slow start up and requires significant thermal shielding to retain heat. The high operating temperature can also potentially volatilize other undesirable materials out of the target as well and contaminate the ^{188}Re. Like the $^{99}Mo/^{99m}Tc$ generator based on sublimation technology, this method was not further evaluated. The requirement of high temperature operations, typically several hundred degrees centigrade on a very regular basis poses many challenges that limit its utility.

Chromatographic Generators Using High Capacity Adsorbents

Development of high capacity adsorbents for the preparation of adsorption/chromatography column generators using low specific activity ^{99}Mo as well as ^{188}W is an interesting proposition and ongoing research. In this connection, the pioneering work of Matsuoka *et al.* on the preparation of poly zirconium compound (PZC) that showed ^{99}Mo capacity several times higher than the conventional acidic alumina is an important step [57]. Van So *et al.* prepared polymeric titanium oxychloride sorbent as column matrix for the development of both $^{99}Mo/^{99m}Tc$ and $^{188}W/^{188}Re$ generators [58]. Adsorption capacities of up to 520 mg of tungsten per gram of PZC and 515 mg of tungsten per gram of PTC were reported [59]. Elution yields greater than 80% were achieved with both the PZC and the PTC sorbents. These sorbents are yet to be tested at high activity level operations and other harsh conditions typically encountered in making clinical scale generators.

Polyethylene glycol (PEG)-based aqueous biphasic systems (ABS) and the analogous aqueous biphasic extraction chromatographic (ABEC) resins have also been evaluated for the separation of ^{188}Re from tungstate ^{188}W in alkaline tungstate media [60,61]. The reported studies indicated that $^{188}Re/^{188}W$ separation is possible, however, follow up and demonstration of the utility of these techniques still remains. Other reports include the use of hydroxyapatite particles as column matrix, however, with limited success [62]. A synthetic alumina functionalized with a sulfate moiety has been developed by sol-gel process to be used as a column matrix [63]. The maximum capacity of the adsorbent for tungsten is reported to be higher than 450 mg/g. The efficacy of the sorbent was demonstrated by developing a 37 GBq(1 Ci) $^{188}W/^{188}Re$ generator. Elution efficiency of ^{188}Re was 70-90% by using 5 mL of the saline solution. The ratio of $^{188}W/^{188}Re$ in the eluted solution is 0.002-0.003%. Rhenium-188 obtained from this generator required purification to reduce the ^{188}W level. The feasibility of this concept is yet to be evaluated under high activity loading typically used in the preparation of clinical sacle generator.

Nanomaterial Based Adsorbents

Owing to the high surface area and intrinsic surface reactivity, nanomaterial based sorbents has higher sorption capacity and selectivity compared to the conventional adsorbents such as alumina and similar oxide species. The high surface area is advantageous for realizing high capacity facilitating enhanced loading of ^{188}W and allowing the use of low specific activity ^{188}W. Chakraborty *et al*. have successfully exploited three different nanomaterial based sorbents such as polymer embedded nanocrystalline titania (TiP), nanocrystalline zirconia and nanocrystalline γ-Al_2O_3 for the preparation of radionuclide generators [64-66]. The high sorption properties coupled with their relatively easy synthesis and exceptional acid base stability have rendered these nanocrystalline metal oxides well suited for the preparation of $^{188}W/^{188}Re$ generators. The surface acid-base properties of nanocrystalline metal oxides are inherent and are primarily responsible for the retention of ^{188}W. Interfacial chemistry of the nanocrystalline metal oxides allows for selective sequestration of negatively charged poly tungstate anions. Apart from improving sorption capacity, the rigid, open pore structure of these nanomaterial based sorbents facilitate poly tungstate anions to reach binding sites of sorbent for rapid and efficient sorption kinetics. The decay of ^{188}W to ^{188}Re is not accompanied by any serious disruption of chemical bonds. As the tungstate ions begin transformation into perrhenate ion $(^{188}ReO_4)^-$ which has -1 charge, the binding would become weaker and easy displacement of $^{188}ReO_4^-$ is expected with facile elution with normal 0.9% saline. From the perspective of the end-user, the reported procedure retains the simple-to-operate qualities of the chromatographic generator. The radioactive concentration of ^{188}Re availed from this generator is adequate for radiolabelling studies. The scope of using nanomaterial based adsorbents is relatively more appealing, especially if engineering efforts for the development of a closed shielded generator assembly system containing sterile column are given. This is a realizable proposition that is less demanding and can contribute to regional needs in the near future.

Solvent Extraction Generator

In the quest for an effective method to obtain ^{188}Re using LSA ^{188}W, attention had been focused towards the use of solvent extraction technique with methylethyl ketone (MEK) as used for $^{99}Mo/^{99m}Tc$ generator systems owing to their similar chemical properties. A $^{188}W/^{188}Re$ solvent extraction generator using methylethyl ketone (MEK) to separate $^{188}ReO_4^-$ was reported from the V.G. Khlopin Radium Institute, Russia for medical purposes [67]. The main advantage of such a generator is the possibility to use low specific activity ^{188}W. The parent and daughter radionuclides were separated on centrifugal semicounter-current extractor in which ^{188}Re was extracted by MEK from alkaline solution (2.5 M KOH + 2.5 M K_2CO_3) containing up to 200 g/L of W. Subsequently MEK layer is evaporated to dryness and the residue is dissolved in isotonic solution of NaCl. The yield was about 89 % and the radiochemical purity of $^{188}ReO_4^-$ solution was ~ 97 %. The current status of this generator system is unknown.

Electrochemical Generator

Electrochemical separation technologies have many advantages and was first reported for making a $^{90}Sr/^{90}Y$ generator yielding clinically useful ^{90}Y [68]. This work was then extended to the electrochemical separation of ^{188}Re from ^{188}W [69]. In the technology developed, the separation of ^{188}Re from $^{188}W/^{188}Re$ mixture was realized in an oxalate bath. Controlled electrolysis carried out at pH 1-2 at a constant potential of -7 V and for sixty minute duration, about 85% of the ^{188}Re could be deposited on the platinum cathode. The ^{188}W contamination was between 0.05 - 0.1 % which was removed by passing through a small column containing 200 mg of acidic alumina which reduced the level to below 10^{-3} % in different batches. The radiochemical purity of $^{188}ReO_4^-$ eluate varied from 95-98 %. The main advantages of the electrochemical separation is that the radiolytic damage as seen in a column generator is avoided as the ^{188}W after electrolysis is stored in solution form. This technology is effective with low specific activity ^{188}W. The electrochemical separation by itself acts as a concentration step and hence there is no need for post elution concentration of $^{188}ReO_4^-$. The electrochemical generator technology is an open technology without any intellectual property right (IPR) issues and hence can be universally adapted.

Post- elution Concentration of ^{188}Re

A major challenge in the successful development of $^{188}W/^{188}Re$ generators for clinical application is the low radioactive concentration of the eluted $^{188}ReO_4^-$ solution which is often encountered for the commonly used adsorptive type column generator, this results from the large alumina columns needed for adsorbing sufficient quantity of the invariably low specific activity ^{188}W. A radioactive concentration 740 MBq (20 mCi)/mL is desirable for most radiolabelling studies which can be achieved by having a post elution concentration step. The long half-life of the parent radioisotope (69 d) allows the generator to be used for 2-3 half-lives, that is for at least 4-6 months provided the generator is integrated with a post elution concentration system.

Table 4. Characteristics of ^{188}Re

Characteristics	Assessment
Energy of β^- radiation	2.12 MeV (79%) 1.96 MeV (20%)
Energy of γ radiation	155 keV (10%)
Availability	^{188}W/^{188}Re generator
Specific activity	Carrier-free [6.8 TBq (184 Ci)/μmol]
Half-life	16.7 hour
Chemistry	VII B transition metal, chemistry is similar to technetium.

The concept of post elution concentration of generator eluates was first developed at the ORNL, USA [70]. Several methods have been subsequently reported for the post elution concentration of perrhenate eluate. The use of evaporation as a concentrating procedure is precluded owing to its complexity in the radiopharmacy and the potential presence of macroscopic levels of NaCl present which will also get concentrated to unacceptable levels for radiolabeling as well as injection into patients.

The ORNL method for ^{188}Re concentration utilizes the sequential trapping of the macroscopic levels of the chloride anion on a silver impregnated cation column followed by selective trapping of perrhenate on a QMA anion column [71]. After washing with water, perrhenate ions can be eluted in saline. The volume of saline required and thus the final radioactive concentration of ^{188}Re solution is a function of the QMA column void volume. Jaeckel *et al.* reported a semi-automated system for elution and concentration of the ^{188}Re-eluate from 111 GBq (3 Ci) ^{188}W/^{188}Re-generators to provide high ^{188}Re-activity per unit volume [72]. By using ion exchange cartridges, small eluate volumes (2-3 ml) of maximum 37 GBq (1 Ci) of ^{188}Re/mL activity concentration were routinely prepared. Luo *et al.* designed an automated system comprised of a concentrator, a control box and a computer to control the process [73]. A column of cation-exchange resin in Ag^+ form and an anion-exchange column in series were used in the concentration procedure. Mushtaq reported a method based on generator elution with a mixture of 0.7 M acetic acid and 0.0225 M sodium chloride instead of physiological saline [74]. The passage of the bolus through an amine-type (Accell Plus QMA Sep-Pak) anion exchange cartridge results in trapping of the microscopic levels of the perrhenate. Subsequent elution of the anion exchange cartridge with 2 mL of saline provides solutions with high radioactive concentration of ^{188}Re. Sarkar *et al.* described two methods using (i) a single diethyl aminoethyl (DEAE) cellulose anion exchanger column and (ii) a combination of Dowex-1× 8 and AgCl columns to concentrate ^{188}Re availed from an alumina column [75].

Mushtaq described a method which is based on generator elution with acetone followed by evaporation and dissolution in saline to obtain sodium perrhenate solution [76]. Mushtaq *et al.* have also proposed a method which is based on the extraction of ^{188}Re-perrhenate in methyl ethyl ketone for concentration purposes [77]. The electrochemical separation by Chakravarty *et al.* was also extended for the post elution concentration of generator eluted sodium perrhenate [78]. Several concentration systems were also developed as part of an IAEA coordinated research project on the development of generator technologies for therapeutic radionuclides [25].

The availability of ^{188}W/^{188}Re generator has been one of the major challenges since there were very limited suppliers for the generators on an international basis. Initially, their generator production and supply was provided by ORNL and later a Finnish company called MAP Technologies entered into the manufacturing of the generators. The production of generators by both the above organization has been discontinued. Currently Polatom, Poland; ITM Isotopen Technologien, München AG, Germany and IDB Holland are the known suppliers of ^{188}W/^{188}Re generators.

Rhenium Chemistry

Rhenium is a transition metal and the last element having a stable isotope to be discovered in the year 1925 and is named after the river Rhine. Rhenium is a third-row transition metal in group 7 after manganese and technetium with an atomic number of 75. Chemically, rhenium resembles to manganese and technetium [79,80]. The ground state electronic configuration of rhenium is $4f^{14}$, $5d^5$, $6s^2$. The ability of rhenium to complex with a variety of ligands and bifunctional chelating agents is a key factor in the successful development of rhenium radiopharmaceuticals for targeted therapy. Rhenium complexes exist in nine oxidation states ranging from −1, 0 to +7 and having coordination numbers upto nine. Three distinct approaches have been adapted for the preparation of rhenium radiopharmaceuticals which include complexation of the targeting molecule, complexing rhenium to a prosthetic bifunctional chelating agent (BFCA) attached to the targeting molecule or making rhenium as an integral part of a molecule which by itself is expected to work as the targeting molecule [81]. The nuclear and chemical characteristics of ^{188}Re are depicted in Table **4**.

The initial developments of rhenium radiopharmaceuticals have been based on the experience gained with ^{99m}Tc radiopharmaceuticals [82] and most labelling methods have been very similar to those used for the preparation of ^{99m}Tc radiopharmaceuticals. However, as the work progressed significant differences in the chemistry between the two elements were noticed necessitating more fundamental work for the development of rhenium chemistry applicable for the preparation of radiopharmaceuticals. The overall conclusion is that rhenium chemistry at the tracer level (nca) is much more difficult than ^{99m}Tc chemistry. At macroscopic levels, the complexes formed with technetium and rheniums with different ligands could have identical structures, despite following different routes of synthesis [83, 84]. The chemistry between ^{186}Re and ^{188}Re is expected to be similar as the difference in mass number is too small to show any isotopic effect. However, ^{188}Re eluted from the generator often needs addition of carrier rhenium to make stable complexes (i.e.for HEDPpreparation).

REVIEW OF RHENIUM RADIOPHARMACEUTICALS

Rhenium-188 is one of the early radionuclides proposed for radionuclide therapy and there have been several active groups working on the development of therapeutic radio-

pharmaceuticals with ^{188}Re, eluted from the $^{188}W/^{188}Re$ generator. A variety of therapeutic radiopharmaceuticals with ^{188}Re are reported and several of these have progressed into human studies. A brief review of the preparation and clinical use of ^{188}Re radiopharmaceuticals is given below.

^{188}Re-DMSA for the Treatment of Medullary Carcinoma

^{188}Re-DMSA (dimercaptosuccinic acid) is a true 'matched pair' of ^{99m}Tc and $^{186/188}Re$ and one of the earliest radiorhenium radiopharmaceuticals to be developed [85]. $^{99m}Tc(V)DMSA$ is useful for imaging medullary carcinoma of thyroid, head and neck tumors and metastasis from breast carcinoma to liver, brain and skeleton [86]. ^{188}Re-DMSA was envisaged to be useful for the treatment of the above cancers. Blower *et al.* reported clinical studies in patients with ^{188}Re-DMSA and found that the radiopharmaceutical is particularly taken up by metastatic bone cancer originating from prostatic carcinoma [87]. The authors concluded that ^{188}Re-DMSA could be a good agent for metastatic bone pain palliation.

However, one of the problems associated with the preparation of $^{188/186}Re$-DMSA was the high renal uptake of the product as compared to $^{99m}Tc(V)$-DMSA. Unlike the $^{99m}Tc(V)$-DMSA complex, increasing the pH to higher values did not result in the reduction of renal uptake presumably irrespective of the pH, Re forms complex at +5 oxidation state [88]. Singh *et al.* performed thorough detailed HPLC studies confirmed that ^{188}Re-DMSA complex exists in multiple isomeric forms [89]. Dadachova *et al.* reported the synthesis of $^{188}Re(V)$-DMSA by using sodium metabisulfite instead of stannous ions as the reducing agent and the complex showed less renal uptake [90]. Similar results were obtained by Kothari *et al.* who demonstrated by detailed HPLC analysis that the complexes formed with stannous ions and metabisulfite (MBS) have varying amounts of the different isomers which could explain the difference in the *in vivo* uptake values of the two products [91]. Their studies also showed that while there is no difference in the blood clearance pattern between the two complexes, the kidney retention of Re(V)-DMSA(MBS) was significantly lower (0.68 ± 0.06%) as compared to 2.93±0.93% for Re(V)DMSA ($SnCl_2$). Another interesting observation was that the bone uptake and retention of the complex prepared with $SnCl_2$ was much higher as compared to the complex prepared with metabisulfite. Apparently despite the promising results of Blower and others, the clinical use of ^{188}Re-DMSA has not progressed further.

Bone Pain Palliation Agents

Among the two radionuclides of rhenium, ^{186}Re-HEDP was initiatially explored and may be is preferred as a radionuclide for bone pain palliation due to the lower energy β^- particles emitted and correspondingly by the possible lower myelotoxicity. Nevertheless, the ready availability of ^{188}Re from the generator is an operational convenience which led to the research towards the development of ^{188}Re based bone pain palliation agents. Published work includes the preparation and evaluation of ^{188}Re complexes of several bisphosphonate ligands such as hydroxyethylidene diphosphonate (HEDP) [92], ethylenediamine-N,N,N′,N′-tetrakis (methylene phosphonic acid [93], 2-sulfonato-1,1-ethylidine bisphosphonic acid (SEDP) [94] and dipicolymine-alendronate [95]. There are several reports on the clinical use of ^{188}Re-HEDP in patients suffering from metastatic bone pain [96-100]. In one of the early reports, 61 patients suffering from bone metastases due to lung, breast, prostate, renal, and bladder cancers were treated with 1.147-6.956 GBq(31-188 mCi) of activity [97]. The patients were followed up for a period of one year and 80% overall pain relief was seen in patients and with no severe side effects or hematopoietic toxicity demonstrating the efficacy of the radiopharmaceutical. Liepe *et al.* studied ^{188}Re-HEDP in 27 patients with hormone refractory prostate cancer and the patients showed a response rate of 76% [96]. Palmedo *et al.* reported the administration of ^{188}Re-HEDP in 64 patients either as single dose or repetitive dose and the latter showing slightly better pain relief and more importantly, exhibited an apperent therapeutic effect [98]. In a recent report of the use of ^{188}Re-HEDP combined with capacitabine in hormone refractory prostate cancer patients with bone metastasis treated with 37 MBq (1 mCi)/kg no toxicity was seen [101]. A phase II clinical trial for finding the efficacy is reported to be in the planning stage. The clinical experience thus far suggests that ^{188}Re-HEDP has similar clinical efficacy profile as other bone pain palliating agents. Despite the demonstrated success of the therapy with ^{188}Re-HEDP, the radiopharmaceutical is not yet widely used.

^{188}Re Labeled Antibodies

The 16.9 h half life of ^{188}Re is relatively short as compared to the relatively long biokinetics of antibodies thereby making ^{188}Re not an ideal choice for raiolabelling monoclonal antibodies. However, ^{188}Re being eluted from the generator is no carrier added (nca) and the short half life make it one of the highest specific activity radionuclides among the currently used β^- emitting radionuclides for therapy. Rhenium-188 can be incorporated in the antibody either directly after the reduction of the disulphide bridges [102-104] or through bifunctional chelating agents [105,106]. Very recently a Re-tricarbonyl core has been used for radiolabelling of monoclonal antibodies for developing radiopharmaceuticals [107,108].

There are several reports on the use of ^{188}Re labeled monoclonal antibodies in patients. Juweid *et al.* reported the biodistribution, pharmacokinetics and dosimetry of ^{188}Re labeled MN-14, an anti carcinoembryionic antigen (CEA) monoclonal antibody injected in 11 patients having advanced gastrointestinal cancer [109]. The administered dose ranged from 0.758 GBq-5.957 TBq (20.5 mCi to 161 Ci) and red marrow suppression was the only dose limiting toxicity (DLT) seen in the patients. Buchman *et al.* studied the biodistribution, radiation adsorbed organ doses, toxicity and outcome of myeloablative radioimmunotherapy of ^{188}Re-labelled anti CD-66 monoclonal antibody in 20 high risk patients prior to stem cell transplantation [110,111]. The authors concluded that myeloabalative radioimmunotherapy with ^{188}Re monoclonal antibody is a promising approach for the improvement of conventional conditioning of high risk leukemia patients prior to stem cell transplantation. Koenecke *et al.* also had a similar report on the use of ^{188}Re la-

beled anti CD66 in the conditioning of allogenic stem cell transplantation for acute myeloid leukemia [112]. Torres-Garcia *et al.* reported the biokinetics and dosimetry using ^{188}Re-anti-CD20 [4.81-8.696 GBq (130-235 mCi)] in patients with Non-Hodgkin's lymphoma [113]. They achieved a whole body dose rate of 0.75 Gy which corresponds to the dose recommended for NHL therapy. Torres *et al*. reported the locoregional administration of ^{188}Re-labelled humanized anti-epidermal growth factor receptor monoclonal antibody, nimotuzumab, for the treatment of malignant gliomas [114]. The authors concluded that a single dose of 370 MBq (10 mCi) labeled antibody could be used safely in patients suffering from high grade gliomas and the clinical efficacy was good as seen from the delayed survival of the patients. A phase II clinical trial is apparently planned in this case to assess the efficacy of the treatment, however, the study was considerably delayed due to the non-availability of the generator.

Rhenium Labeled Peptides

The high specific activity ^{188}Re obtained from ^{188}W/^{188}Re generator is ideally suitable for radiolabeling peptides as the carrier vector is present at sub-micromolar levels in peptide receptor radionuclide therapy (PRRNT). Radiolabeling of several peptides with ^{188}Re is reported and many of them are analogs of the hormone somatostatin [115-121] and targeting the different subtypes of somatostatin receptors. Most of these peptides have a disulphide bridge linking the two cysteines in the structure which can be reduced and used for complexing with ^{188}Re. Early on, Zamora *et al.* reported the labeling of RC-160, a cyclic octapeptide with ^{188}Re by the direct method and the resultant radiolabelled product showed specific binding to NC1-H69 which expresses somatostatin receptors [115]. The radiolabelled product also showed specific uptake in nude mice bearing xenograofts of human prostate adenocarcinoma [116,117]. Guhlke *et al.* modified this work by radiolabelling RC-160 by using MAG_3 as a prosthetic group for chelating ^{188}Re [118]. Molina-Trinidad *et al.* reported the direct radiolabelling of lanreotide with ^{188}Re and the labeled product was injected in athymic mice implanted with different human cancer tumours and showed good uptake characteristics [119]. They further extended the work by injecting ^{188}Re-lanreotide in rats implanted with hepatocarcinoma. Injection of the products through tail vein of the rats showed that the beta elimination time is longer [120]. Cyr *et al.* studied the radiolabeling of P2045 which is an 11 amino acid somatostatin analog with ^{188}Re and ^{99m}Tc [121] targeted to small and non-small cell lung cancer. *In vivo* studies in AR42J xenograft mice model showed significant tumor uptake. A Phase I dose escalation study was done with ^{188}Re-P2045 in 15 patients having SSTR positive lung cancer [122]. The patients were treated with upto 3.33 GBq(90 mCi)/m^2 of the radiotracer. Despite the fact that most patients were pretreated, the patients showed slight improvement in their survival. Other peptides labeled with ^{188}Re include α-melanocyte stimulating hormone (α-MSH) [123,124], RGD [125], VEGF [126], and neurotensin (NT) [127].

In spite of these promising studies with ^{188}Re, currently much of the peptide radiolabelling work is done with ^{90}Y and ^{177}Lu. The main reasons for this shift in focus are the better availability of these radionuclides and the relatively easy +3 chemistry of the latter radionuclides thereby exhibiting better *in vitro* and *in vivo* stability.

^{188}Re-lipiodol for Hepatic Carcinoma (HCC)

Hepatic carcinoma is widely prevalent cancer and hence the development of therapeutic radiopharmaceuticals for its management if intercepted early, is an active area of radiopharmaceuticals research. Iodine-131 labelled lipiodol is a tradiational agent which is widely used radiopharmaceutical for the treatment of hepatocarcinoma [128]. Lipiodol or ethiodized oil, contains iodine combined with ethylesters of fatty acids and is used as a contrast agent in myelography. The inactive iodines of lipiodol are exchanged with ^{131}I, followed by solvent extraction of the labeled product for preparation of the radiopharmaceutical.

There are several reports describing the preparation of ^{188}Re lipiodol starting with Kim *et al.* suspending ^{188}Re-sulphur colloid in lipiodol [129]. Dissolution of a lipophilic complex ^{188}Re-HDD(4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol) in lipiodol was first first reported by Lee *et al*. [130] using a lipiodol solution of ^{188}Re-TDD (2,2,9,9-tetramethyl-4,7-diaza-1,10-decane dithiol). Luo *et al.* used ECD as a chelating agent to prepare a lipophilic complex of ^{188}Re for dissolution in lipiodol [131]. Ruyck *et al.* conducted a comparative evaluation of ^{188}Re-4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD)/lipiodol with ^{131}I-lipodol in patients suffering from inoperable HCC [132]. Data analysis showed that ^{188}Re-HDD/lipiodol yielded smaller cytotoxic effect and a lower radiation exposure for an expected higher tumor-killing effect. Kumar *et al.* used ^{188}Re-HDD-lipiodol in a patient with unresectable hepatocellular carcinoma to study the dosimetry aspects [133,134]. The maximum tolerated activity to be safely injected in the patient was calculated to be about 8.325 GBq(225 mCi) with the lungs being the dose limiting organ. Two doses of the radiopharmaceutical resulted in the complete disappearance of a large volume tumor and the patient was disease free for 18 months. Kumar *et al.* also reported a large scale clinical trial involving 93 patients in India and Vietnam using ^{188}Re-HDD-lipiodol [135]. Lambert *et al.* reported 35 treatments in 28 patients with ^{188}Re-HDD-lipiodol activity ranging from 4.81-7.03 GBq(130-190 mCi) [136,137]. The studies confirmed that the patients tolerated the dose and no severe complications were reported. Response assessment showed partial response in 1, stable disease in 28 and disease progression in 2 treatments. There was a significant reduction in AFP levels measured in patients six weeks after treatment. Garin *et al.* reported the preparation of ^{188}Re(III)-SSS-lipiodol [SSS = $(S_2CPh)(S_3CPh)_2$] by dissolving the highly lipophilic complex ^{188}Re(III)-SSS in lipiodol followed by injection to the hepatic artery of healthy pigs [138]. A comparative evaluation of ^{188}Re-SSS-lipodol with ^{131}I-lipiodol in rats bearing hepatocarcionoma, the authors concluded that in small tumours the latter is more efficacious [139]. However, this may not be extendable to HCC in humans as the tumors are fairly large. The International Atomic Energy Agency (IAEA) conducted a multi-country Phase I/II clinical trial

involving 185 patients in eight countries using ^{188}Re-HDD-Lipiodol in which three complete responses and 19 partial responses were reported [140-143].

The overall results of the clinical studies with ^{188}Re-lipiodol demonstrated that it is a clinically useful agent. However, potential liver leakage of activity has been a concern and there are further developments to improve the radiolabelling yields and the *in vivo* stability of the injected radiopharmaceutical. Radiolabeling yields have been considerably improved by labeling lipiodol through rhenium(V) nitrido bis(diethylthiocarbamate) (DEDC) complex [144]. The Re(V) nitrido precursor was prepared in high yields using a lyophilized kit formulation and the resultant complex being highly lipophilic is quantitatively extracted into lipiodol. The results of the studies with ^{188}ReN-DEDC-lipiodol suggest that the radiopharmaceutical is stable *in vivo* and selectively gets accumulated in the tumour with high target to non-target ratios [145]. The results of the initial clinical trials showed that this could be a useful radiopharmaceutical for the therapy of unresectable hepatocellular carcinoma. Uccelli *et al*. recently reported an automated synthesis of ^{188}Re-lipodol [146]. Thieme *et al.* had reported the synthesis, characterization and biological evaluation of a ^{188}Re(N)(cys)(PNP) mixed ligand complex for the preparation of ^{188}Re lipiodol [147]. The continued developments in the preparation of ^{188}Re-lipiodol show the interest in this product as it addresses the management of a widely prevalent cancer.

^{188}Re-colloids for Radiosynovectomy

Radiosynovectomy is one of the early clinical applications using ^{188}Re since the high energy β^- particles are especially useful for treating large joints. Several biodegradable particulates have been developed for this purpose which includes polypeptide colloids [148], hydroxyapatite particles [149,150], rhenium colloids [151] and microspheres [152,153]. Most of the particles are reported to have suitable biological properties for application in radiosynovectomy as seen in animal experiments. Several patient studies are also reported [154-156].

^{188}Re for Intravascular Radionuclide Therapy (IVRNT)

Percutaneous transluminal coronary angioplasty (PTCA) is a mode of treatment of patients suffering from artherosclerotic coronary artery disease. Restenosis occurs in 30–50% of the patients post angioplasty. Radioisotopes such as ^{32}P coated on stents or the use of a liquid-filled balloon containing a β− emitting radioisotope were proposed for use to prevent angioplasty restenosis [157]. This technique is called intravascular radionuclide therapy (IVRNT). Radionuclides with moderate half-life of 1-2 days and having particulate emissions close to 2 MeV are preferred for this purpose. Rhenium-188 as perrhenate was first successfully evaluated for this application [158]. Although, accidental rupture of the balloon may lead to high uptake of perrhenate ions in the thyroid gland, detailed pre and post thyroid blocking studies successfully demonstrated that perhenate uptake could be blocked or displaced. Another approach was to use ^{188}Re-complexes that have high renal clearance and several hydrophilic complexes have been reported to be prepared and clinically evaluated for this purpose [159-160].

In one IVRNT clinical trial encompassing 225 patients, 113 patients received 22.5 Gy intravascular beta-irradiation using ^{188}Re post angioplasty [163]. After 6 months, the target vessel revascularization rate was significantly lower in patients who received radiation as against the control group of 112 patients [164]. In another report of a six-year clinical follow-up after treatment with ^{188}Re filled balloon showed that the restenosis was lower in the case of ^{188}Re patients as compared to the controls [165]. However, the number of patients was too small for a meaningful comparison. IVRNT never developed to the promise that it offered due to the availability of drug coated stents which are much easier used [166].

^{188}Re Patches for Therapy of Skin Cancer

Skin cancer is one of the most common types of malignancy and although not fatal in many cases, untreated skin cancer could result in metastatic disease. Brachytherapy or external beam therapy using gamma rays X-rays or electrons are common procedures involved in radiation therapy. The use of radioactive patches to irradiate skin cancer is a simpler and non-invasive mode of treatment for those patients where tradiationally therapeutic modalities would lead to scarring and disfigurement. Isotopes such as ^{90}Y, ^{32}P, ^{166}Ho, ^{188}Re etc. could be used in the patch preparation. Preparation of ^{188}Re patches and its use in the treatment of melanoma induced in mice is reported [167]. Superficial tumors were induced in C57BL/6 mice and the ^{188}Re bandage was applied on palpable tumors. Regression and delay of tumor growth was observed in all treated animals to varying extent depending upon the radiation dose and the treatment regimen followed. ^{188}Re-labeled paper was prepared and the feasibility of its use for treating skin cancer was demonstrated by successful treatment of mouse skin cancer and mouse sarcoma [168].

STATUS OF CURRENT CLINICAL USE OF ^{188}Re RADIOPHARMACEUTICALS

Rhenium radiopharmaceutical chemistry and development is one of the widely researched areas in nuclear medicine. Despite the large quantum of work done in this field, the authors are unaware of any large scale late stage clinical studies being conducted with ^{188}Re. The main reason for the lack of clinical interest for rhenium radiopharmaceuticals appears to be the availability of other radionuclides such as ^{90}Y and ^{177}Lu for developing equivalent products.

Initially, clinicians were highly enthused by the idea of using a generator eluted ^{188}Re for making 'matched pair' of therapeutic products similar to the ^{99m}Tc eluted from the ^{99}Mo/^{99m}Tc generator. The potential availability of freeze-dried kits for this purpose was yet another factor which appealed. Together with the generator and kits, it offered the possibility of diagnosis and therapy to be done at ease ensuring the comfort of the clinicians as well as patients.

The initial developments of the generator came from Oak Ridge National Laboratory (ORNL) which has the high flux reactor capable of making adequate quantities of ^{188}W required for production of generators for the initial studies.

Other institutions having access to a research reactor were enthusiastic to produce ^{188}W; however, they soon realized that the production of ^{188}W will be the privilege of only those who have access to reactors having flux $>10^{15}$ n.cm^{-2}.sec^{-1}. Hence, despite the great interest in the work, the production of ^{188}W was confined to three high flux research reactors, HFIR at Oakridge in the USA; SM reactor at Dimitrovgrad in the Russian Federation and BR2 reactor in Belgium.

In the late nineties, the International Atomic Energy Agency established several programs to promote the use of ^{188}Re radiopharmaceuticals through a specially deviced mechanism known as 'Doctoral Coordinated Research Project (CRP)' in which large resources from the Technical Cooperation Department was also pooled to support research and development in participating member states. The project provided free generators as well as research funds to the participating groups to develop and implement therapy with ^{188}Re radiopharmaceuticals. Clinically useful work on hepatocarcinoma and radiosynovectomy were performed by the participants during the project time (140-143). However, most participating laboratories could not sustain the program post completion of the IAEA CRP, because of the apparently high cost and limited availability of ^{188}W/^{188}Re generator which came in the way of the continuation of the program.

In absolute terms the cost per Bq or mCi of eluted ^{188}Re can still be very cost effective per unit dose as the usable life of an ^{188}W/^{188}Re generator is for several months. Conservative estimate shows that 1.85-2.59 TBq(50-70 Ci) of ^{188}Re can be eluted from a 37 GBq(1 Ci) generator when used over a period of six months. However, in order to optimally use the available ^{188}Re, nuclear medicine departments need to pursue multiple applications such as targeted therapy of cancer, bone pain palliation and radiation synovectomy etc. In most cases this was never realized and the generator had limited use thereby making per patient cost high.

CONCLUSIONS

Generator produced ^{188}Re offered great promise for development of therapeutic radiopharmaceuticals and a large volume of research in the development and clinical use of ^{188}Re radiopharmaceuticals has been accomplished [169-173]. The technology for preparation of clinically useful ^{188}Re from the ^{188}W/^{188}Re generator with or without the need for post elution concentration methods is also available [25,174]. From our perception, the limited production capability of the ^{188}W parent radionuclide is the major factor which precluded the widespread use of this radionuclide. The availability of other more easily produced competing radionuclides such as ^{177}Lu and ^{90}Y increased interest in their use. Most similar studies with β^--emitting radionuclides are currently focussed on the use of these two radionuclides. The rhenium isotopes especially ^{188}Re could still have a place in providing certain unique products for e.g. ^{188}Re-DMSA as an equivalent of it could not be made using other isotopes. Just like ^{188}Re-DMSA there could be other situations, especially labelling of small molecules where conjugating DOTA or similar ligands will dramatically change the pharmacokinetic characteristics of the small molecules. The development and use for ^{188}Re radiolabeling of novel cores such as nitrido and carbonyl could yield high specific activity products with more favourable biokinetics that may not be possible with competing radionuclides.

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CONFLICT OF INTEREST

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