Continued Availability of the Tungsten-188/Rhenium-188 Generator to Enhance Therapeutic Utility of ^{188}Re

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Abstract: Rhenium-188 (^{188}Re) is a high energy beta-emitting radioisotope of widespread interest for use in nuclear medicine, oncology and other therapeutic applications. High energy beta emission (16.9 hour half-life) with E_{max} 2.12 MeV and gamma emission at 155 keV (15 %) are key factors for effective therapy and imaging for tissue kinetics and dosimetry evaluation. Moreover, on-demand availability of ^{188}Re in a highly reproducible manner from the ^{188}W/^{188}Re generator system is an important capability for installation in a hospital-based or a central radiopharmacy for cost effective availability of no-carrier-added (NCA) ^{188}Re. Because of the long 69.7 day half-life of the ^{188}W generator parent, the use of well-established post ^{188}Re elution specific volume concentration technology allow generators to have a useful/predictable operational shelf-life of a few months. This paper provides a holistic review of the development, availability and use of the ^{188}W/^{188}Re generator prototypes.

Keywords: Beta emitters, Bolus concentration, Radionuclide generator, Radionuclide therapy, Rhenium-188, Tungsten-188.

1. INTRODUCTION

The history describing the initial discovery of technetium ("masurium") and rhenium in Germany during the 1930's involved the use of minimal technical tools but great effort and impressive technical insight [1]. Rhenium (Re, element 75) was first isolated and identified by German scientists Ida Noddack-Tacke and Walter Noddack while working in Strasbourg, who named this new element after the Roman Latin designation "rhenus" for the river Rhine [1]. Of course during that time investigators had not envisaged the important future applications which technetium-99m (^{99m}Tc) and ^{188}Re would subsequently play for diagnosis and therapy in the future field of nuclear medicine.

Over the last three decades interest in the therapeutic use and development of ^{188}Re-labeled radiopharmaceuticals has persisted with broad interest on an international basis, and a number of reviews have discussed this progress [2-8]; [See Shinto and Knapp, this issue of IJNMR]. Development of high yield and easy to use ^{188}W/^{188}Re generators has provided NCA ^{188}Re to pursue new radiolabeling strategies and the development, evaluation and clinical use of a variety of therapeutic radiopharmaceuticals as described in the following paper. Although embedded in the literature and not widely known, early preliminary studies, however had actually described prototype ^{188}W/^{188}Re generators to obtain ^{188}Re for the wrong reasons, since ^{188}Re had been promoted as a diagnostic radioisotope during the period when the ^{99}Mo/^{99m}Tc generator was initially being introduced [9-11], apparently without regard to consideration of radiation dose. Initial projected studies with ^{188}Re available from an early prototype zirconium-based generator had thus been proposed use for imaging [9], although the gamma decay is accompanied by emission of high energy beta particles. Use of ^{188}Re for diagnostic applications would of course result in unacceptable radiation dose to both targeted and non-targeted tissues.

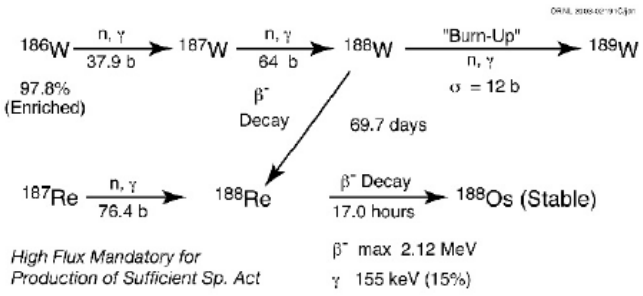

Figure 1: Tungsten-188 is reactor produced by double neutron capture on enriched ^{186}W targets. Subsequent processing provides ^{188}Re solution for preparation of the ^{188}W/^{188}Re generators.

The ^{188}W/^{188}Re "chromatographic-type" generator prototypes (Figure **1**) utilize loading of the processed ^{188}W divalent anion (WO_4^{-2}, half-life 69 days) which is obtained by reactor double neutron capture production

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on enriched ^{186}W targets [12-21]. The irradiated targets are processed and the ^{188}W tightly bound as tungstic acid to an adsorbant. The ^{188}Re (half-life 16.9 hours) generated as the perrhenate (ReO_4^{-1}) monovalent anion by beta decay of ^{188}W is not tightly bound to the adsorbant, and readily removed from the generator by elution, for instance, with physiological saline.

Because of the relative radioactive half-lives, the ^{188}Re daughter is quickly re-formed by continuous ingrowth from ^{188}W decay after elution of the bolus from the $^{188}W/^{188}Re$ equilibrium mixture (Figure **2**, left panel). On a daily 24 hour elution basis, approximately 62% of the equilibrium yield of ^{188}Re is eluted, indicating that about 600 mCi can initially be eluted from a 1 Ci $^{188}W/^{188}Re$ generator at equilibrium. Data obtained from successive elution of a 1 Ci generator [4] summarized in Figure **2** (right panel) demonstrate the reproducibly high ^{188}Re yields with low ^{188}W parent breakthrough for elution over a two month period.

2. ADVANTAGES OF THERAPEUTIC USE OF RHENIUM-188

The availability of high yield NCA ^{188}Re, on demand, from the $^{188}W/^{188}Re$ radionuclide generator system was a central practical consideration which had stimulated interest in the use of ^{188}Re for a variety of therapeutic applications, which are discussed in detail in an accompanying paper in this issue of *IJNMR*. Radiopharmaceutical development beginning in the 1980's has subsequently blossomed into a variety of clinical applications. Figure **3** (left panel) further illustrates the theoretical elution characteristics and multi-cycling of the generator for four elution cycles demonstrating the slow decay of ^{188}W. The curves for ^{188}W decay, ^{188}Re in growth and 62% daily ^{188}Re elution yields are shown in Figure **3** (right panel).

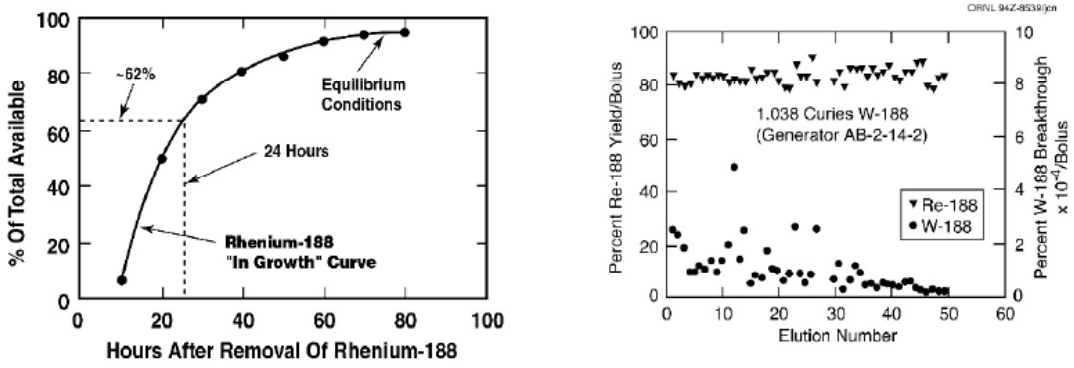

Figure 2: **Left** - A major advantage for radiopharmacy use of the $^{188}W/^{188}Re$ generator is the relatively rapid in growth of ^{188}Re from ^{188}W decay following elution which provides 62% of the maximal ^{188}Re in growth available every 24 hours. **Right** – Generator operational is consistent and predictable over a long time period with high ^{188}Re yields and low ^{188}W parent breakthrough.

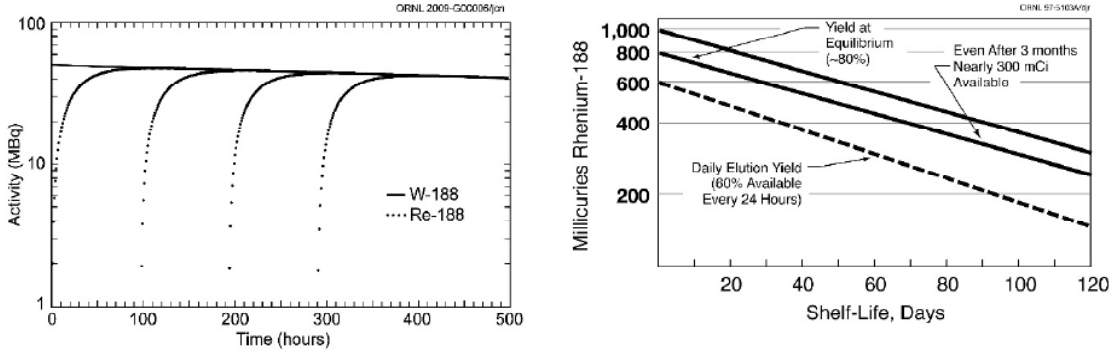

Figure 3: In growth curves for ^{188}Re generated from decay of ^{188}W. **Left** - four successive cycles following 24 elution of ^{188}Re (half-life 16.9 hours) illustrating daily in growth and availability of high daily activity levels of ^{188}Re. **Right** – The slow decay of ^{188}W (69 day half-life) will provide high daily levels of ^{188}Re. Even after four months (1.7 decay half-lives of ^{188}W) a 1 Ci generator will decay to only 300 mCi. Although the saline bolus elution volume is essentially the same for the operational shelf-life of the generator, post elution concentration can provide constant specific volume (mCi/mL) levels of ^{188}Re eluted throughout the generator shelf-life.

3. DEVELOPMENT OF THE TUNGSTEN-188/RHENIUM-188 GENERATOR

Although a variety of ^{188}W/^{188}Re generator prototypes have been described in the literature [12-49], the alumina-based generator system has been demonstrated as the most simple, reliable and is widely used to obtain ^{188}Re for clinical use [12, 22-26, 30-32]. Other variations which have been described and include ^{188}W/^{188}Re generators based on zirconium oxide/zirconia [27, 37-38, 41-42], gel-type technology [44-46], electrochemistry [43], extraction centrifuge techniques [40], thermo-chromatography, use of high capacity adsorbent-based, nanomaterial-based and solvent extraction, but apparently none of these systems have been further evaluated for routine use of ^{188}Re in a clinical setting. The first evaluation of the generator separation of no-carrier-added ^{188}Re from the ^{188}W parent using a generator-based system was explored in 1966 [9-10]. This system involved use of ^{188}W bound to the zirconium oxide adsorbant eluted with the methyl ethyl ketone (MEK) organic solvent. Apparently not further evaluated, this system was impractical for providing ^{188}Re for clinical evaluation of ^{188}Re-based therapeutic agents and further development and use did not mature. This approach was impractical, since eluant evaporation, subsequent manipulation and re-dissolution of ^{188}Re in a system to allow labeling of the desired targeting agent presented technical and quality control challenges.

In addition to the alumina-based systems, one area of ^{188}W/^{188}Re generator development which had been of extensive earlier interest involved the use of "gels," which consist of homogeneous admixture of ^{188}W with the chromatographic adsorbent prior to generator column loading, as opposed to the adsorptive binding of ^{188}W with the initial volume of the alumina adsorbent [41, 44-46]. The "gel" technology allows the use of low specific ^{188}W - or in the case of the ^{99}Mo/^{99m}Tc generator – low specific activity ^{99}Mo produced by irradiation of enriched ^{98}Mo [*i.e.* ^{98}Mo(n,γ)^{99}Mo]. Although significant research efforts had been reported evaluating this technology, the challenges associated with reproducible generator fabrication and performance, and other technical issues, resulted in no further broader evaluation and clinical introduction of this type of generator. In the same context, an alternative technology focused on the liquid extraction [47-48] and subsequent radiolabeling use of ^{188}Re from ^{188}W/^{188}Re mixtures has only evidently been evaluated in a cursory manner [9-10].

The most practical strategy then focused on further development of the acidic alumina-based generator system similar to the ^{99}Mo/^{99m}Tc generator, allowing generator elution with saline which would represent a medium for subsequent substrate radiolabeling, also representing a physiologically compatible medium for intravenous administration. Subsequently, our ORNL program and other investigators focused on the use of an alumina-based generator system with saline elution, which provided a convenient approach to obtain ^{188}Re-perrhenate directly from generator elution without subsequent complex eluent manipulation, similar to the elution of ^{99m}Tc from the alumina-based ^{99}Mo/^{99m}Tc generator system. However, an important difference for the ^{188}W/^{188}Re alumina-based generator is the requirement for much larger amounts of the alumina adsorbent, which is required for binding of the much lower specific activity ^{188}W, reactor produced by neutron irradiation of enriched ^{186}W targets, compared with ^{99}Mo, available NCA from isolation from ^{235}U fission product mixtures. This necessity for the use of large amounts of the alumina adsorbant for ^{188}W binding results in the requirement for higher eluant and thus bolus volumes, as discussed in more detail below, ideally requiring the use of technologies for post elution concentration of the ^{188}Re generator bolus. These post elution concentration technologies described later are also useful for concentration of the high saline volume ^{99m}Tc boluses obtained from ^{99}Mo/^{99m}Tc generators prepared from (n,γ) ^{99}Mo.

4. IMPORTANCE OF AVAILABILITY OF TUNGSTEN-188

In contrast to the availability of very high specific activity microscopic levels of ^{99}Mo produced at about 6% yield *via* nuclear fission of uranium-235 (^{235}U), ^{188}W is produced by neutron capture on macroscopic levels of enriched ^{186}W (Figure **1**). Since the ^{188}W product and ^{186}W target atoms cannot be separated by any cost effective/practical strategy, the specific activity of ^{188}W is significantly lower (about 10^4) than ^{99}Mo due to fission mixture contamination with other Mo isotopes. Although the specific activity is also affected by the irradiation period, post irradiation decay and the ^{235}U enrichment, values are still very high at levels estimated to be > 2 x 10^4 Ci/gram Mo, compared to a maximum of about only about 10 Ci/gram W, based on the ^{186}W target contamination. One unfortunate, yet established certainty, is that only a limited number of high flux reactors are available for production of ^{188}W

with specific activity value approaching the maximum expected of approximately 10 Ci/gram ^{186}W (ORNL High Flux Isotope Reactor, Oak Ridge, TN USA; SM-3 Reactor, Dimitrovgrad, Russian Federation; BR2 Reactor, Mol, Belgium). However, because of the long useful $^{188}W/^{188}Re$ generator shelf-life and availability, and post irradiation recovery possibilities for enriched ^{186}W for re-use as irradiation targets, experience over the last two decades has demonstrated that sufficient ^{188}W can be produced to meet the expected international clinical demands [19-20, 23]. Because of the relatively low ^{188}W specific activity, relatively large amounts of the alumina column adsorbant are required for adequate generator loading/binding of the processed ^{188}W tungstic acid. The $^{188}W/^{188}Re$ generator thus requires much higher alumina levels than required for clinical scale multi-Ci ^{99}Mo generators. This necessity results in much higher generator void volumes, resulting in significantly higher saline elution volumes and lower specific volume (activity/volume) of ^{188}Re eluants.

5. AVAILABILITY OF TUNGSTEN-188 AND W-188/RE-188 GENERATORS

For the expanded clinical utilization of ^{188}Re a crucial issue which must be addressed is the dependable, routine availability of GMP-produced $^{188}W/^{188}Re$ generators. Table **1** summarizes information for $^{188}W/^{188}Re$ generators which are currently, or which have been previously, available. All of these generator prototypes are alumina-based systems and eluted with physiological saline, with reported high ^{188}Re yields of 90-95% and with low ^{188}W parent breakthrough of 10^{-4}-10^{-3} %/bolus. Information included in this summary is based on data available *via* the Internet. All these generator systems are alumina-based, have reproducible high ^{188}Re yields, low ^{188}W parent breakthrough/bolus and long useful half-lives. The $^{188}W/^{188}Re$ generators are available in high activity levels from the three manufacturers described in Table **1**. Although these three prototypes are manufactured under quality conditions, only the Rhein Eo generator equipped with the post elution ^{188}Re concentration cassettes from IRE-Elit in Belgium, is

Table 1: Principal Suppliers of Tungsten-188/Rhenium-188 Generators

Institution/ Organization	Generator Designation	Activity Levels	Comment/Special Features, Web Page Contacts
Examples of Currently Available W-188/Re-188 Generators			
IRE-Elit, Fleurus, Belgium	Rheni Eo	0.5-1.5 Ci	*Sterile GMP system.* Active pharmaceutical product (API). Fully automated system available with convenient plug-in cassette unit for post elution ^{188}Re concentration 6 month shelf-life. *http://www.ire.eu/ouractivities/radiopharmaceutical-products.* Also reported to be distributed by Iso Solutions and Radio Medix Inc.
Isotope Technologies Munich (ITM),Germany	$^{188}W/^{188}Re$ Generator	2.7 Ci	*Non-sterile system.* < 10 mL elution volume, >135/mL. Several month shelf-life. For laboratory research purposes only. Reported that post concentration of ^{188}Re not required. *<http://www.isotope-technolgies-munich.com/products/radionuclides/188w188re-generator/>*
JSC "SSC RF-IPPE, Obninsk, Russian Federation	GREN-1	<1.0 Ci	*Non-sterile system.* Registration certificate No. FS, 02032006/5395-06 issued by the Ministry of Health of the Russian Federation. Process regulation PR No. 35.92-3/61-01 for the production of generators *<http://www.ippe.ru/prod/isotope/isot-1-3en.php>*
Key Examples of Previously Available W-188/Re-188 Generators			
Oak Ridge National Laboratory (ORNL), Oak Ridge, TN, USA	$^{188}W/^{188}Re$ Generator	Up to 3 Ci	*May still be available non GMP on special order* >500 generators provided internationally during the 1986-2011 period. Bolus concentration technology provided. Non-sterile GMP production under FDA Drug Master. File #22577 (Type 2). Active pharmaceutical ingredient (API). Indefinite useful shelf-life of several months. ORNL Isotope Business Office, Oak Ridge, TN. Tel. 1-(865) 574-6984; FAX 1-(865) 574-6986
Polatom, Otwock, Poland		0.100-0.810 Ci	*No longer available since about 2005.* Generator was fitted with bacteriological filter. At least 6 month shelf-life
MAP Medical Technologies, Tikkakoski, Finland		0.5-1.0 Ci	*No longer available since about 2003.* Produced for IAEA-funded projects in conjunction with Mol Reactor and ORNL

apparently the only system available as a sterile GMP device approved for clinical use. The other generators are evaluated in house prior to acceptance for human use. The non-sterile GMP generators previously supplied from ORNL are evidently no longer available (Table **1**), since the manufacturing facility is no longer in operation. The sterile, pyrogen-free GMP manufactured generators which had been previously manufactured at POLATOM, are also no longer available. Evidently the high production and delivery costs of processed ^{188}W from the Dimitrovgrad facility and the less than expected modest generator sales are factors which resulted in removal of this generator from the POLATOM product line.

Although availability of high specific activity ^{188}Re from the ^{188}W/^{188}Re generator is the preferred cost-effective route, it is surprising that the well-established "direct" reactor production and facile post irradiation processing and dispensing of high specific activity ^{188}Re by irradiation of enriched ^{187}Re [^{187}Re (n,γ)^{188}Re] (Figure **1**) has not been pursued for availability of this therapeutic radionuclide for radiopharmaceutical preparation for clinical applications. There are many research reactors throughout the world, including many developing countries, which have sufficient thermal neutron flux for production of ^{188}Re with sufficient specific activity by this route. Target preparation, processing and ^{188}Re product dispensing are straight forward and the 16.9 hour half-life of ^{188}Re would allow delivery even beyond local sites. All of the alumina-based generators summarized in Table **1** have been reported – primarily in promotional product information available on the Internet – to have predictable operation with "long" useful shelf-lives to provide ^{188}Re in about 95% yield and with low ^{188}W breakthrough values of < 10^{-3} %/^{188}Re bolus.

6. ISSUES ASSOCIATED WITH AVAILABILITY AND UTILIZATION OF THE W-188/RE-188 GENERATOR IN THE RADIOPHARMACY

Because of the low specific activity of ^{188}W, the ^{188}W/^{188}Re generators must be eluted with relatively high saline volumes which results in lower per volume bolus activity (lower activity/bolus volume) compared to ^{99m}Tc available from the ^{99}Mo/^{99m}Tc generator system. For this reason the useful elution shelf life for generator use can be limited – if the ^{188}Re specific volume is a key issue - and much shorter than the demonstrated prolonged time period for generator performance of several months, unless post elution ^{188}Re bolus concentration methods are used. Important technologies which make routine availability of ^{188}Re possible include GMP generator production, automated systems for generator elution and ^{188}Re bolus concentration, effective chemical strategies for attachment of ^{188}Re to targeting molecules and the increasing availability of radiolabeling "kits" for radiopharmacy preparation of targeted ^{188}Re radiopharmaceuticals. Obviously, in addition to GMP manufacture of the ^{188}W/^{188}Re generators, the same quality programs are required for production of the concentration units and "kits" which would result in significantly higher costs to the expanded clinical introduction of specific^{188}Re-labeled therapeutic agents.

6.1. Post Elution Rhenium-188 Bolus Concentration Using Tandem Cation/Anion Columns

Although apparently only one commercially available ^{188}W/^{188}Re generators apparently is provided with post elution concentration units/cassettes (Table **1**; IRE-Elit) to obtain ^{188}Re of sufficient specific volume for radiopharmaceutical radiolabeling, the use of such technologies is widely felt to be very effective in considerably extending the generator shelf-life and to reduce unit ^{188}Re dose costs [50]. These systems are readily prepared, easy to use and are very efficient and effective in concentrating ^{188}Re eluants when a higher specific volume is required (Figure **4**). Our ORNL technology using a tandem silver nitrate/QMA system had first been reported [4, 50-57] for isolation of the ^{188}Re-perrhenate anion from the high volume generator eluant. Several alternate post elution approaches/ systems had subsequently been reported in the literature using various perrhenate trapping cartridge systems [58-63], but it is unclear, however, which of these systems have been routinely used for clinical application. Use of the tandem silver impregnated chloride trapping/perrhenate trapping column system represents effective access to high specific volume^{188}Re solutions which has been used for a number of years to obtain high specific volume ^{188}Re for a variety of clinical applications, including single center and IAEA-sponsored programs for vascular therapy describe here later, and for liver cancer therapy. Use of such disposable ^{188}Re bolus concentration cartridge units using readily available and inexpensive components is well described [4, 53-57], is well established and disposable ^{188}Re bolus concentration systems can be provided as disposable packaged cassette systems with commercial generators [Rheni Eo, IRE Elit, Table **1**].

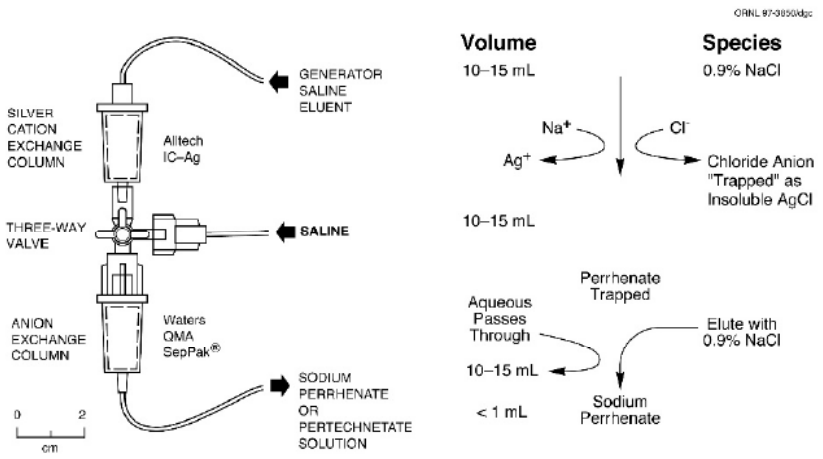

Figure 4: Schematic illustrating the basis of the tandem silver nitrate imbedded adsorbant-based silver-chloride trapping system for subsequent anion column trapping of the ^{188}Re-perrhente anion for elution with low saline volume.

This silver chloride trapping-based ^{188}Re concentration system is simple, cost effective method based on the concept for post elution trapping of the macroscopic levels of the chloride anion from the saline as insoluble silver chloride in the silver-cation column. Subsequent trapping of microscopic levels of the $^{188}ReO_4^-$ [1]perrhenate anion then occurs on the small QMA anion trapping column. Water washing followed by isotonic saline elution of the QMA anion column then provides highly concentrated levels of sodium ^{188}Re-perrhenate. This simple flow through method using inexpensive disposable components provides high specific volume solutions of ^{188}Re sodium perrhenate over the generator shelf-life [4-5].

For more cost effective extension of the useful shelf-life, the use of such effective concentration strategies is required, because of the high ^{188}Re bolus volumes which are obtained from generators fabricated with the relatively low specific activity ^{188}W. The high amounts of alumina required to bind the low specific activity ^{188}W parent results in high elution volumes and low specific volume solutions of ^{188}Re, because of the double neutron capture process and only modest thermal neutron cross section values - as compared with the very high specific activity fission-produced ^{99}Mo generally used for fabrication of the ^{99}Mo/^{99m} Tc generators. Only low levels of alumina are required to bind carrier-free fission-produced ^{99}Mo for the commercially available ^{99}Mo/^{99m}Tc generators, which permits low volume saline elution of the ^{99m}Tc bolus, thus providing high specific volume ^{99m}Tc solutions. For the ORNL alumina generator prototype, the ^{188}W loading capacity is limited to < 50 mg W/gram alumina, minimizing^{188}W parent breakthrough through repeated use. The ^{188}Re specific volume (mCi/ml) eluted from a typical 1 Ci^{188}W/^{188}Re generator (14 gram alumina) requires a saline bolus volume of 12-15 ml. These values of course decrease with time (^{188}W decay), providing specific volume solutions which may not be sufficient for "kit" labeling of tissue-specific radiopharmaceuticals. For this reason, post elution ^{188}Re concentration offers a convenient cost effective strategy for providing higher specific volume ^{188}Re unit doses.

Since the long useful shelf-life is an important aspect for use of this generator system, the availability of simple, efficient methods for concentration of the generator eluant is intuitively an important capability. The availability of these methods also extends the useful shelf-life of the generator since the specific volume (mCi/mL) of the generator eluate deceases as a result of the radioactive decay of the ^{188}W parent. Use of the^{188}W/^{188}Re generators can be optimized for routine clinical use by incorporating disposable tandem silver cation-chloride trapping/anion-exchange columns to provide high specific volume ^{188}Re solutions. The combined reproducible elution/concentration of ^{188}Re is rapidly conducted making routine radiopharmacy use of a concentration system practical.

Post elution concentration of the ^{188}Re generator eluant can have important benefits since the useful ^{188}W/^{188}Re generator shelf-life can be significantly extended to a few months (Figure **3**). The possible benefits of post elution eluant depend on a number of economic and technical factors. For instance, if adsorption of upfront generator cost is not a major factor and/or if patient throughout and thus reimbursement are high, then the generator can be used during a shelf-life which is limited by the ^{188}Re

eluant specific volume (mCI/mL) required. However, other factors which may have to be considered include the high cost of generator purchase and importation and recruitment of minimal patients for ^{188}Re therapy. Other cost saving generator use optimization approaches which we have suggested when cost is a major factor also include the tandem connection of new generators with used generators for combined bolus collection and concentration in order to optimize the availability of ^{188}Re. Another important issue is the bolus saline specific volume (mCi ^{188}Re/mL) requirements for targeting agent radiolabeling or post elution use of ^{188}Re. For instance, in the case of balloon inflation with ^{188}Re solutions (*vide infra*), the specific volume must be very high (> 100 mCi ^{188}Re/mL), which generally would always require bolus concentration. If a large patient population can be treated with ^{188}Re over a short time and costs can be amortized in a short time period, than *in extenso* generator shelf-life and the need for post elution concentration may not be major issues. All of these factors must be evaluated and considered for each facility, but in the final analysis, it has been demonstrated by use at many radiopharmacy/clinical sites that post elution concentration of ^{188}Re is an effective strategy to optimize ^{188}W/^{188}Re generator use and cost.

6.2. Availability of Chemical Strategies for Attachment of Rhenium-188 to Targeting Agents

The evaluation of various useful Re oxidation states for radiolabeling has been evaluated and reviewed [62-64]. Because of relative stability and facile availability, Re(I) (*i.e*. as the tricarbonyl, $Re(CO)_3$,) [65], Re(V) (*i.e*. as DEDC) and ^{188}Re(III)-SSS-lipiodol {SSS = $(S_2CPh)(S_3CPh)_2$}) [63-66-67] and Re(V) (from facile reduction of Re(VII) with stannous ion, etc.) [62, 64] are the forms of ^{188}Re obtained from chemical transformation of generator-derived ^{188}Re-perhenate for which many other approaches have been developed for introduction into therapeutic targeting agents [68-71; See Shinto and Knapp]. The chemistry of the perrhenate obtained from the ^{188}W/^{188}Re generator is similar to pertechnetate, and similar targeted agent chemical strategies can be used, and many advances have been reported. However, in comparison with the well-established and very facile and usually simple attachment of $^{+3}$Y and radioactive trivalent lanthanides to both acyclic, and especially cyclic polyamines such as DOTA, attachment of ^{188}Re generally requires less straight forward and more complex radiochemistry.

6.3. Availability of Preformed "Kits" for Radiopharmacy Preparation of ^{188}Re-Targeting Agents

In addition to the availability of sufficiently high specific activity reactor-produced ^{188}W and GMP manufactured generators, another challenge has been developing/optimizing the required radiochemistry for stable attachment/introduction of ^{188}Re to targeting molecules. For the ease and dependable routine preparation of radiopharmaceuticals the use of sterile/pyrogen-free substrate/radiolabeling mixtures ("kits") offers many advantages for quality, dependable and easy preparation. In the context of this issue of IJNMR, several useful "kits" have been recently developed for preparation of ^{188}Re-labeled radiopharmaceuticals, and include kits for radiopharmacy preparation of HEDP for bone pain palliation [72-76], and Lipiodol analogues (DEDC, Re-SSS) for treatment of inoperable hepatic carcinoma [77-78]. It would be expected that further development of new "kits" will be reported if the expected expanded clinical use of other attractive ^{188}Re radiopharmaceuticals progresses. A major practical advantage for clinical use of ^{188}Re is the potential, but low, non-target tissue toxicity of ^{188}Re-perrehnate, since decomposition and any release of ^{188}Re from the targeting molecules results *in vivo* re-oxidation to perrhenate, which is rapidly excreted *via* the urinary bladder. If necessary, either Lugol's or perchlorate can be administered for thyroid blocking. Later in this issue the details, advantages and various methods for attachment of^{188}Re to radiopharmaceuticals are described in more detail.

6.4. Use of the ^{188}W/^{188}Re Generator System in the Radiopharmacy

One of the most efficient models would be installation of the ^{188}W/^{188}Re and an automated handling system in a centralized specialized facility for patient referral from local institutions. Because patient throughput for ^{188}Re therapy is generally limited, use of the ^{188}W/^{188}Re generators is rarely optimized, and for this reason unit dose costs of ^{188}Re are generally much higher than would be expected if the generators were efficiently used in large institutions or localized for multi institutional distribution of ^{188}Re.

6.5. Automated Elution/Concentration Systems to Ensure Consistency of Generator Performance and Reduced Staff Radiation Exposure

The development of both in house constructed and commercially available automated systems for

synthesis, purification and dispensing of radiopharmaceuticals was initially most aggressively pursued and developed for routine high yield and reproducible GMP preparation of agents radiolabeled with positron-emitting radioisotopes. Recently, these systems have been more recently widely available commercially and can be readily adapted for preparation of a wide range of radiopharmaceuticals and have been demonstrated to be particularly well suited for preparation of therapeutic agents where the same issues of reproducibility, quality (GMP) and dose reduction of technical staff are key considerations. Since the ^{188}W product specific activity cannot be increased beyond about 10 Ci/gram W [13-18], as described earlier, the availability of effective and inexpensive post elution ^{188}Re bolus concentration methods allow a significant increase in generator useful shelf life. Use of the post elution concentration technology is well entrenched in the literature, well suited for automation and is straight forward and well established. The concentration units also require GMP manufacture and assembly and packaging. Generator and radiolabeling operation in hospital-based or for centralized radiopharmacy offers the opportunity for on demand availability of ^{188}Re for various therapeutic applications. Such automated systems have been described for preparation/ concentration of the ^{188}Re-perrhenate precursor [79-81], ^{188}Re-MAG3 [82-87] and ^{188}Re-Lipiodol-based agents for liver cancer therapy [88-89]. Figure **5** illustrates a TADDEO automated system which is in use for the preparation of the ^{188}Re-SSS-Lipiodol agent.

6.6. Generator Manufacture under Good Manufacturing Process (GMP) Conditions

For routine use of ^{188}Re in the clinical arena the ^{188}W/^{188}Re generators must be manufactured under GMP conditions, which of course requires the availability of a sophisticated quality production facility and capabilities. Although, in addition to insuring patient safety, the generator production costs are high.

DISCUSSION

The routine commercial availability of ^{188}W/^{188}Re generators in Europe, India and elsewhere, is an important issue which will hopefully catalyze expanded clinical introduction of ^{188}Re-labeled radiopharmaceuticals in other countries. It is clear that all the “infrastructure” factors and associated required technologies are now available to offer revitalization for expanded use of ^{188}Re-labeled radiopharmaceuticals for routine clinical use. In addition to the attractive radionuclidic and chemical properties and relatively low and generally accepted ^{188}Re perrhenate radiotoxicity to non-target organs, one of the principal factors which has stimulated interest in the therapeutic applications of ^{188}Re is the routine, on demand availability from ^{188}W/^{188}Re generators available in hospital-based or centralized radiopharmacies. However, to date apparent non-optimization of generator use – as illustrated by IAEA-sponsored clinical programs with ^{188}Re therapy for treatment of inoperable liver cancer and for inhibition of coronary restenotic hyperplasia after PTCA - has been a recurring factor. Two key challenges which must be overcome for more cost

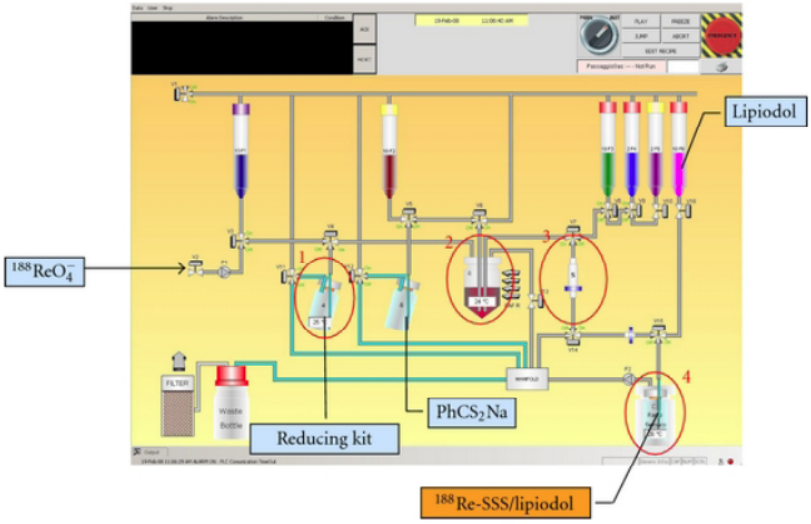

Figure 5: Flowchart of the TADDEO module for the preparation of ^{188}Re-SSS/Lipiodol. Courtesy of N. Lepareur, Rennes, France.

effective clinical use of ^{188}Re thus include significant increase in single- and multi-institutional generator use for reduction of the resulting much higher unit dose costs, which are inconsistent taking into consideration of the long useful generator shelf-life of several months (*i.e.* ^{188}W half-life = 69 days). Nearly all the reported single and multi-institutional clinical studies have not optimized ^{188}W/^{188}Re generator use, presumably because of the low patient trial recruitment and minimal referrals from local institutions. Since all the radiopharmacy issues for automation, ^{188}Re bolus concentration, quality control, etc., have been developed and are widely available, it may be expected that much greater interest in the utility and therapeutic benefits of ^{188}Re for targeted therapy would greatly increase if the generators were efficiently used and the unit dose costs would substantially decrease. In the opinion of this author, the most cost effective use of the ^{188}W/^{188}Re generator to provide ^{188}Re for clinical use would involve generator installation in a hospital-based or centralized radiopharmacy with the capability for ^{188}Re bolus concentration which would significantly extend the useful generator shelf-life and reduce ^{188}Re unit dose cost. From a clinical use perspective, centralized units should focus on multiple therapeutic applications of ^{188}Re instead of single use studies, since this would accelerate generator use. Also, to insure adequate patient throughput for therapeutic use of ^{188}Re, referral of patients to such a centralized site would enhance generator utilization and reduce the high costs currently encountered with use of this generator system. The advantages for clinical applications of ^{188}Re-labeled therapeutic agents have been recognized and are in progress in Europe and many countries in the Indian sub-continent and Asia, and hopefully this interest will expand and even be introduced into the U.S. and elsewhere.

The progress and improvements which have been made in ^{188}Re radiopharmaceutical development, important clinical applications in nuclear medicine and oncology, automation and bolus concentration would be expected to re-stimulate production, distribution and use of the ^{188}W/^{188}Re generator. While 4-5 institutions/ commercial entities had produced and distributed these generators several years ago, apparently only 2-3 manufacturers now provide the ^{188}W/^{188}Re generators (Table **1**). As well established in both the radiopharmaceutical and clinical literature, although ^{188}Re has excellent radionuclidic properties and routine availability from a long shelf life generator, the cost and availability of the ^{188}W/^{188}Re generators are two issues which have apparently limited the expected further widespread clinical introduction of ^{188}Re. In addition, one may argue that another issue associated with the under-utilization of ^{188}Re may be the chemical challenges for facile introduction of ^{188}Re into ^{188}Re-targeting molecules. The transition metal chemistry of NCA perrhenate is similar to the well described chemistry for pertechnetate [62-64], but there are distinct differences, which include the requirement for stronger reducing conditions for the conversion of perrhenate [Re(VII)] to Re(V). In addition, care that must be taken to avoid re-oxidation of Re(V) by the use of inert conditions and often by introduction of various antioxidant agents during the radiolabeling procedures (gentissic acid, etc.). Chemical attachment of ^{188}Re in comparison with other therapeutic radionuclides, moreover, requires reaction conditions which are much more facile for radiolabeling acyclic chelators and cyclic multi-dentate chelators such as DOTA with trivalent M^{+3} metals, for instance, such as ^{177}Lu [91]. Radiolabeling with ^{177}Lu generally involves simple combination of the radioisotope and chelator solutions with perhaps some heating which is sufficient for high yield formation of the desired targeting agents. These techniques are much easier, facile and straight forward than the general radiolabeling conditions required for introduction of^{188}Re into radiopharmaceuticals. Although ^{188}Re may represent in some sense a “poor man’s ^{90}Y” [91], from many perspectives use of ^{188}Re has many advantages in comparison to the use of ^{90}Y for many therapeutic applications, because of its potential expected cost effective availability from an in house generator and the emission of gamma photons for imaging, which would certainly be accepted as important in the evolving arena of personalized medicine. Because of safety and quality concerns, ^{90}Y is evidently only generally available from ^{90}Sr/^{90}Y generators installed at central manufacturing sites, thus imposing logistics and scheduling challenges as well as high unit dose costs, for instance, for HCC treatment. Since the commercial manufacturing of ^{188}W/^{188}Re generators would be expected to be readily expanded, the major challenges for broader routine reimbursed clinical use of ^{188}Re-labeled radiopharmaceuticals will of course now be dependent on major investments required for development, regulatory approval and introduction of new ^{188}Re-labeled therapeutic agents.

CONCLUSIONS

In spite of these challenges, interest in the use of ^{188}Re continues on an international basis and continued important advances are being reported for ^{188}Re radiopharmaceutical targeting strategies and for

substrate radiolabeling. These advances and important descriptions of the excellent clinical outcomes using ^{188}Re-labeled radiopharmaceuticals for liver cancer therapy, bone pain palliation and other therapeutic applications are described in this issue of the *International Journal of Nuclear Medicine and Research*, and underline the importance of continuation of studies focused on the development and evaluation of ^{188}Re-labeled agents.

AUTHOR'S STATEMENT

The author declares no conflict of interest.

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