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Use of the Oak Ridge National Laboratory Tungsten-188/Rhenium-188 Generator for Preparation of the Rhenium-188 HDD/Lipiodol Complex for Trans-Arterial Liver Cancer Therapy

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This work describes the installation, use, and quality control (QC) of the alumina-based tungsten-188 (^{188}W)/rhenium-188 (^{188}Re) generators provided by the Oak Ridge National Laboratory (ORNL). In addition, methods used for concentration of the ^{188}Re-perrhenate bolus and preparation of ^{188}Re-labeled HDD (4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol) for trans-arterial administration for therapy of nonresectable liver cancer also are described. The ^{188}W/^{188}Re generator has a long useful shelf-life of several months and is a convenient on-site ^{188}Re production system. ^{188}Re has excellent therapeutic and imaging properties ($T_{1/2}$ 16.9 hours; $E_{\beta max}$ 2.12 MeV; 155-keV gamma ray, 15%) and is cost effectively obtained on demand by saline elution of the generator. The clinical efficacy of a variety of ^{188}Re-labeled agents has been demonstrated for several therapeutic applications. Because of the favorable physical properties of ^{188}Re, several ^{188}Re-labeled agents are being developed and evaluated for the treatment of nonresectable/refractory liver cancer. ^{188}Re-labeled HDD has been the most widely studied of these agents for this application and has been introduced into clinical trials at a number of institutions. The trans-arterial administration of ^{188}Re-labeled agents for treatment of inoperable liver cancer requires use of high-level (1-2 Ci) ^{188}W/^{188}Re generators. The handling of such high levels of ^{188}Re imposes radiological precautions normally not encountered in a radiopharmacy and adequate care and ALARA (ie, "As Low As Reasonably Achievable") principles must be followed. The ORNL generator provides consistently high ^{188}Re yields (>75%) and low ^{188}W parent breakthrough ($<10^{-3}$%) over an extended shelf-life of several months. However, the high elution volumes (20-40 mL for 1-2 Ci generators) can require concentration of the ^{188}Re bolus by postelution passage through silver cation chloride trapping columns used in the cost-effective tandem cation/anion column system. The silver column removes the high levels of chloride anion as insoluble AgCl, thus allowing subsequent specific trapping of the perrhenate anion on the small (QMA SeaPak) anion column. This method permits subsequent elution of ^{188}Re-perrhenate with a small volume of saline, providing a very high activity-concentration solution. Because the ^{188}Re-specific volume-activity concentration continually decreases with time, the tandem system is especially effective method for extending the useful generator shelf-life. Low elution flow rates (<1 mL/min) minimize any high back pressure which may be encountered during generator/tandem column elution when using tightly packed, small-particle-size commercial columns. In-house preparation of silver cation columns is recommended since the chloride trapping capacity is essentially unlimited, it is inexpensive and not limited in availability to any one supplier, and back pressure can be eliminated by the use of larger particles. Methods for the preparation of ^{188}Re-HDD have been optimized and this agent can be obtained in high yield (80%).
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The advantages of using rhenium-188 (^{188}Re) for radionuclide therapy include its convenient, inexpensive, and on-site availability from the tungsten-188 (^{188}W)/^{188}Re generator.[1-6] ^{188}Re ($T_{1/2}$ 16.9 hours) thus has the potential to fulfill the potential leading role in therapeutic nuclear medicine similar to the role technetium-99m (^{99m}Tc) plays as a diagnostic radioisotope.[2] The high energy of the beta emission of ^{188}Re ($E_{\beta max}$ 2.12 MeV) is of the same magnitude as the 2.3-MeV beta emission of yttrium-90, and is thus particularly well suited for effective penetration in solid tumors (maximal penetration 10 mm). In addition to the cost-effective on-demand availability, ^{188}Re has the added advantage of emission of a 155-keV gamma ray (15% abundance), with an energy comparable to that of ^{99m}Tc, allowing quantitative gamma camera imaging for evaluation of biokinetics and dosimetry.[7]

Although the radiation protection issues in handling high levels of ^{188}Re must be carefully considered, the much lower energy of its principal gamma emission and its shorter half-life minimize these issues compared with those encountered, for instance, with the use of iodine-131 ($T_{1/2}$ 8 days). The opportunity for outpatient therapy using ^{188}Re is thus possible. The long 69-day ^{188}W parent half-life and the ready, on-demand availability of ^{188}Re from a ^{188}W/^{188}Re generator—similar to the use of the molybdenum-99 (^{99}Mo)/^{99m}Tc generator system—ensures reliable clinical availability on a daily basis anywhere in the world. Clinical experience during a 15-year period has demonstrated that the long generator shelf-life indicates that two 1- to 2-Ci generators per year would provide sufficient ^{188}Re for preparation of a variety of useful therapeutic radiopharmaceuticals.

During the last decade, several important therapeutic applications of ^{188}Re have emerged that have demonstrated its effectiveness as an alternative to the use of more expensive and/or less readily available therapeutic radioisotopes. These clinical trials include the use of ^{188}Re-labeled agents such as hydroxyethylidenediphosphonate[8-11] and dimercaptosuccinic acid[12-14] for the treatment of metastatic bone pain; anti-CD66 antibody for conditioning of bone marrow before stem cell rescue[15,16]; evaluation of tumor-targeted peptides for cancer therapy[17-19]; and tin colloid for radionuclide synovectomy.[20,21] In the clinical arena, the use of ^{188}Re-labeled agents for the treatment of nonresectable liver cancer has received broad attention (*vide infra*), because of the cost effectiveness and availability in developing countries. Although the use of various ^{188}Re-labeled species in liquid-filled balloons demonstrated the first effective method in clinical trials for the inhibition of coronary restenosis after PTCA,[22-26] this strategy using high beta energy emitting radioisotopes paved the way as the first successful strategy to prevent arterial restenosis. More recently, this technology has been eclipsed by the use of drug eluting stents.

The Oak Ridge National Laboratory (ORNL) ^{188}W/^{188}Re generator prototype[2,4-6] is based on the use of an aluminum oxide (alumina) column adsorbent, analogous to the traditional ^{99}Mo/^{99m}Tc generator system, permitting elution with normal saline. Use of this generator system at multiple institutions during the last decade has demonstrated consistently high ^{188}Re yields accompanied by low ^{188}W parent breakthrough during periods of several months. Currently, ORNL is the only major source of these generators (Table 1). These are provided as a radiochemical, and the sterility and apyrogenicity of the eluate must be assessed at the clinical facility before radiopharmaceutical preparation. With the expected introduction of ORNL-mandated cGMP requirements for radiopharmaceutical preparation, it is expected that the ^{188}W/^{188}Re generator will provide an important therapeutic radionuclide for routine clinical use. The range of in-house ^{188}Re-labeled radiopharmaceuticals is essentially unlimited.

^{188}Re-Labeled Agents for Trans-Arterial Therapy of Liver Cancer

A variety of therapeutic radioisotopes are being evaluated for therapy of inoperable hepatocellular carcinoma (HCC) and metastatic cancer to the liver, and such use of ^{188}Re recently has received significant attention because of its ready availability from the ^{188}W/^{188}Re generator. Because of the cost-effectiveness resulting from the long useful shelf-life of several months, this generator is very attractive as a source of a versatile therapeutic radioisotope, especially in developing countries. ^{188}Re-labeled 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol (TDD) (Fig. 1) and other long-chain analogues were the first ^{188}Re-labeled agents developed for this application and have shown potential in animal studies for effective liver cancer therapy.[27-30]

^{188}Re-labeled DEDC/lipiodol (Fig. 1) is a promising agent that has recently entered clinical trials for liver cancer therapy.[31,32] The ^{188}Re-labeled 4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD)/lipiodol agent

Table 1 Availability of Tungsten-188/Rhenium-188 Generators (Aluminum Oxide ["Alumina"] Adsorbant)

Institution	Max. Activity	History	Comments
ORNL, TN, USA	Up to 3 Ci	>500 generators since 1986	cGMP expected in 2007
IRE, Belgium	Unknown	Clinical testing stage	Sterile cGMP system expected
ITM AG, Germany	Unknown	New	Expected in 2007
Polatom, Poland	500 mCi	Use of established ^{99}Mo/^{99m}Tc column system	Sterile cGMP system expected
Dimitrovgrad, Russia	Unknown	Occasional production since 1986	Expected to resume production
MAP, Finland	<500 mCi	Use of established ^{99}Mo/^{99m}Tc column system	Production ceased in 2002

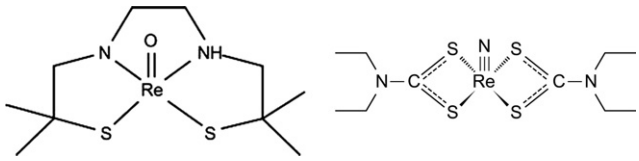

Figure 1 Chemical structure of ^{188}Re-labeled TDD (left) and DEDC (right).

(Fig. 2) is a more lipophilic analog of TDD and was selected by the International Atomic Energy Agency (IAEA) for a multicenter trial in 2002. The therapeutic efficacy of this agent was evaluated at several clinical sites throughout the world.[30-58] In addition, the preparation and animal and clinical evaluation of a variety of other ^{188}Re-labeled agents for liver cancer therapy, including very promising results with radiolabeled particles[59-64] and colloids,[65-69] also are being pursued as alternatives of lipiodol mixtures as methods of targeting liver cancer. The goal of this work is to describe in detail the use of the ^{188}W/^{188}Re generator, concentration of the ^{188}Re bolus, and subsequent use of concentrated solutions of ^{188}Re for the preparation of the HDD and acetylated HDD (AHDD) agents.

The ^{188}W/^{188}Re Generator: Setup and Daily Use

The alumina-based ^{188}W/^{188}Re generators are produced at the ORNL by adsorption of reactor-produced ^{188}W as tungstic acid on a column of alumina, with a typical maximum loading of 50 mg W per gram of alumina. The generators are slowly washed (1 mL/min) with saline (150-200 mL) after ^{188}W loading and air dried before shipment. Generators are provided with short lengths of arterial extension tubing that are coiled into recessed holes at the top inlet and bottom outlet of the lead shielding unit. To minimize exposure to personnel, after receipt and unpacking, the system is typically housed behind a leaded glass and/or polyacrylate shield. The typical generator system set-up configuration is illustrated in Figure 3, although the type and configuration of shielding is based on the facility capabilities and requirements. In some institutions the generator and associated postelution columns and valving are housed in a lead hot cell, behind polyacrylate and/or lead shields or behind leaded glass partitions. The radiological protection staff at each institution should be consulted for advice on the appropriate requirements.

The use of a polyacrylate shield between the generator and solutions of ^{188}Re and the lead shield is a convenient and cost-effective method to decrease radiation exposure by minimizing the *bremsstrahlung* from interaction of the beta particles with the lead. A short length of disposable extension tubing is attached to the lower Luer outlet connection of the generator. Inclusion of an in-line acidic alumina QMA SepPak (Waters Corp, Milford, MA) trapping column effectively removes the low levels of any ^{188}W parent breakthrough and any alumina or other particles which may be eluted from the generator. Following receipt and set-up with adequate shielding, the generators are conditioned and eluted by slow washing at less than 1 mL/min using a peristaltic or syringe pump with 100 to 200 mL of 0.9% normal saline, and are then ready for use.

The generators are eluted with physiological saline and ^{188}Re yields are generally 75% to 80% of the available ^{188}Re. Because the generator returns to 62% of equilibrium after 24 hours (Fig. 4), daily elution will provide approximately 50% of the ^{188}Re that would be available at equilibrium, illustrating the daily availability of ^{188}Re for preparation of various therapeutic agents. ^{188}W breakthrough values are typically in the 10^{-6} range, and any breakthrough can be effectively removed by subsequent postelution passage of the bolus through a small, commercially available alumina QMA SepPak column. The complete generator setup consists of attachment of 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 anion concentration system (described in detail below). A typical large clinical-scale generator loaded with greater than 1 Ci of ^{188}W provides more than 750 mCi (>75% yield) of ^{188}Re-perrhenate at equilibrium (30-35 mCi/mL) or approximately 500 mCi (20-25 mCi/mL) for sequential daily elutions (24 hour in-growth; Fig. 4). As shown in Figure 5 for a typical generator eluted for more than 2 months, consistently high ^{188}Re yields (70-80%) and low ^{188}W breakthrough (<0.0001%/bolus) are maintained during at least 60 days with the alumina-based generator ("dry storage" minimizes radiolysis).

Because of the relatively low specific activity of the reactor-produced ^{188}W, a large amount of alumina is required for the generator column, resulting in relatively high saline elution volumes and low activity concentrations (eg, in mCi/mL) of the ^{188}Re. For this reason, effective postelution concentration methods (described in "Concentration of the ^{188}Re Elutant") have been developed which provide the very high ^{188}Re con-

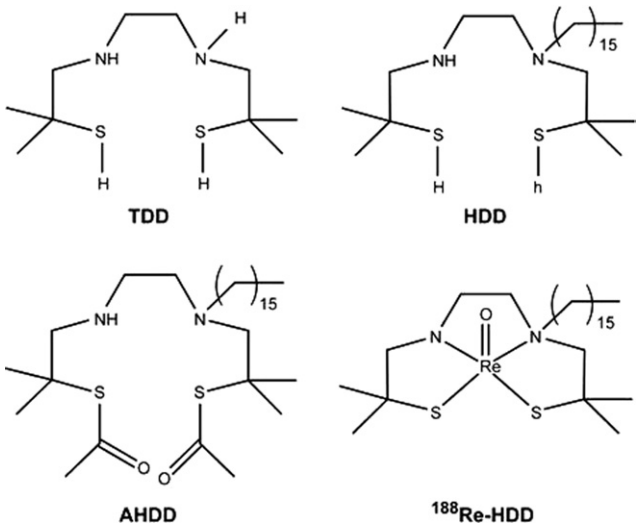

Figure 2 Structures of the HDD and AHDD analogs.

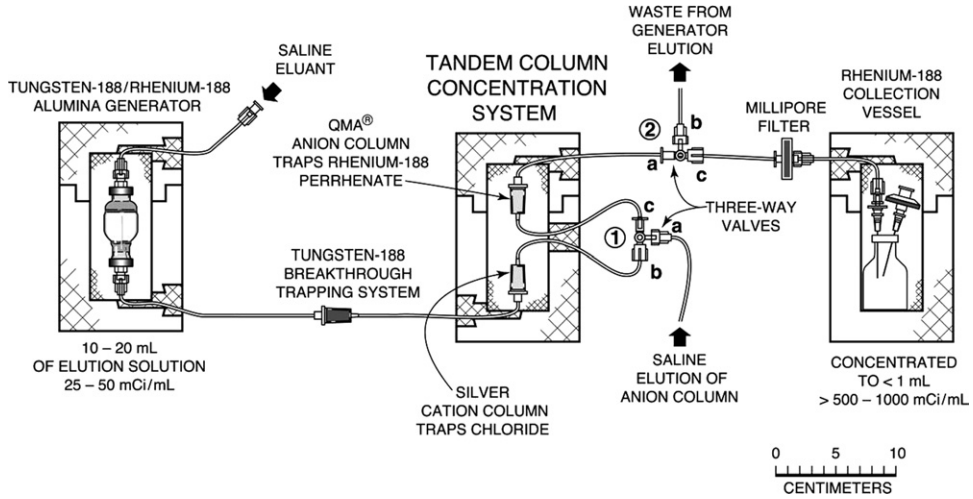

Figure 3 Schematic of typical $^{188}W/^{188}Re$ generator setup.

centrations required for typically low-volume radio-labeling methods.

Radiation Safety and Shielding Requirements

Setup and use of the $^{188}W/^{188}Re$ generator and handling of high-level (1-2 Ci) ^{188}Re solutions requires adequate attention to the pertinent radiation safety. In addition to the use of plastic shielding to minimize *bremsstrahlung* radiation and lead or leaded glass for gamma shielding, the careful monitoring of radiation levels and especially the use of ring monitors for extremity exposure are required. Further, personnel exposures may be reduced by automation or semiautomation of generator operation.[70,71]

The consequences of the high activity levels of such a high beta-energy emitting radionuclide should not be underestimated, and the radiological protection issues required to minimize radiation dose to personnel are important in using this generator system. In addition to the *bremsstrahlung* radiation from interaction with the high energy 2.12 MeV beta particle, as shown in Figure 6, there are also several high-energy gamma-rays emitted by ^{188}Re that complicate the shielding requirements for and gamma camera imaging of this isotope. It is important, therefore, that medium- or high-energy collimation be used for imaging of ^{188}Re because of the prohibitive septal penetration of these high-energy photons through low-energy collimation (ie, the type of collimation conventionally used for 155-keV photons.[7]

Concentration of the ^{188}Re Elutant

As discussed previously, high activity-concentration ^{188}Re is necessary for the preparation of ^{188}Re-labeled HDD. The approaches that have been developed at ORNL for effective concentration of the larger elutant volumes obtained with the ORNL generator are based on a unique concept of postgenerator elution concentration of the ^{188}Re elutant.[4-6,12-14,72-74] Several other groups have subsequently evaluated various technical modifications for postelution concentration.[75-78] The activity concentration (mCi ^{188}Re/mL) is thus increased

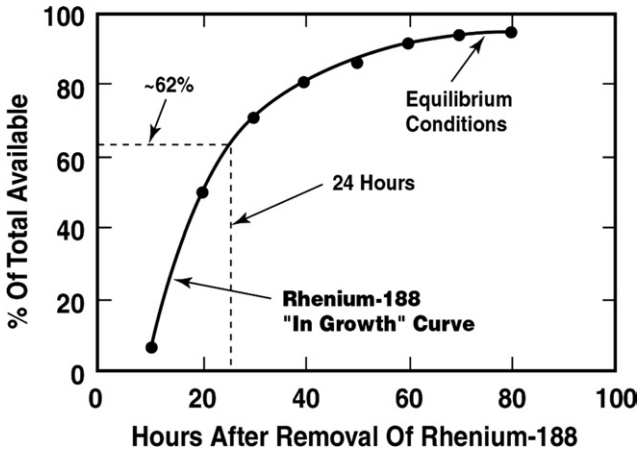

Figure 4 In-growth and elution yields of ^{188}Re in the $^{188}W/^{188}Re$ generator.

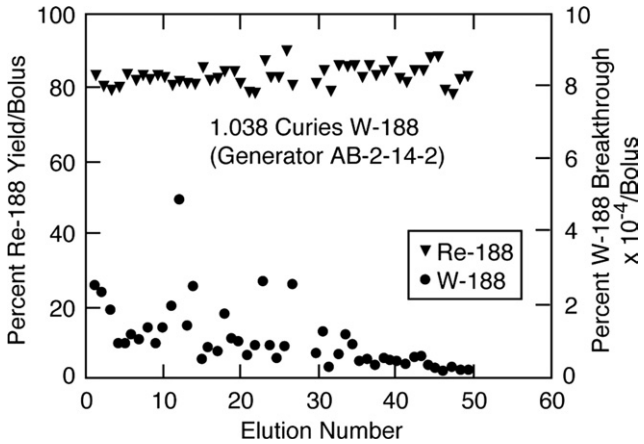

Figure 5 High ^{188}Re yields and low ^{188}W breakthrough are maintained consistently for several months.

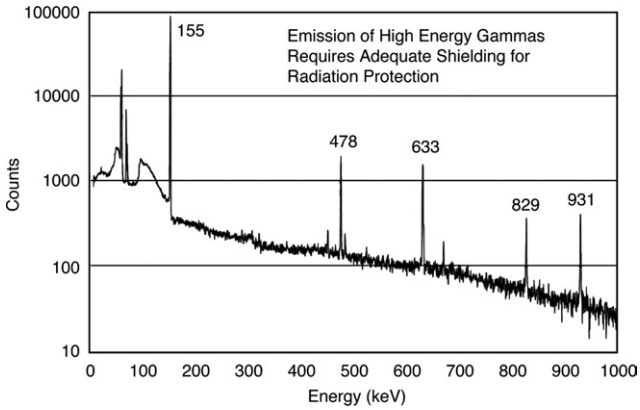

Figure 6 Gamma spectrum (HPGe) of ^{188}he, illustrating the relatively high abundance of several high-energy gamma-rays (478-931 keV) in addition to its image-able 155-keV gamma-ray.

considerably by subsequent elution of the ^{188}Re generator bolus through a tandem silver-impregnated cation/anion exchange column system to provide perrhenic acid solutions. The silver cation columns (1.4-2 mEq silver/column) are commercially available (eg, Alltech, Inc or Dionix, Inc). The availability of practical elutant concentration methods can allow the use in radiochemistry of low-specific activity ^{188}W produced in lower-flux nuclear research reactors. Although the commercially available columns have been used to obtain the required activity concentrations, high elution pressures and significant back pressure during generator/concentrator elution can be encountered. This appears to result from the properties of particular batches of commercial columns. Potentially high back pressure can thus be overcome by the in-house preparation of silver cation trapping columns (as described in the following paragraph).

The alumina trapping column is a safety measure that is highly recommended for use with the ORNL generator. Fabrication of the ORNL generator is based on a conservative tungsten/alumina loading capacity of <50 mg W/gm alumina to overcome any potential risk of increasing ^{188}W breakthrough with long-term use. However, the disadvantage of this lower generator-loading capacity is that the elution volumes (20-40 mL) are much larger than those for high-capacity generators. Extensive performance data collected with more than 500 ORNL generators over the last 20 years have clearly demonstrated that significant ^{188}W breakthrough is not encountered with high-level (1-3 Ci) generators over the useful generator shelf-life (>3 months). Use of an alumina trapping column, while minimizing the possibility of significant levels of ^{188}W, can cause increased back pressure during positive elution. After QMA SeaPak anion column trapping and subsequent elution with saline, very high purity solutions of ^{188}Re are obtained (Fig. 7).

Reactor production of ^{188}W requires a route (double neutron capture by ^{186}W) that produces only low specific activity ^{188}W, requiring a much larger generator alumina bed per unit of activity compared with the amount of alumina used for ^{99}Mo/^{99m}Tc generators fabricated from fission-produced ^{99}Mo. This is why high elution volumes require postelution concentration. Elution of carrier-free ^{188}Re from a clinical-scale ^{188}W/^{188}Re generator thus requires an elution volume as large as 20 to 40 mL for a 1- to 2-Ci generator, and the resulting activity concentration is often too low for the "kit" labeling of radiopharmaceuticals such as HDD and AHDD and other radiolabeling applications. Although the generator void volume can be discarded and only the principal elution peak collected, the initially high activity concentration of eluant of course decreases with time as the ^{188}W (69-day half-life) decays. Because the long useful shelf-life is an important aspect of this generator system, the availability of simple, efficient methods for concentration of the generator eluant and maintenance of the activity concentration in the elutant as the ^{188}W decays are important.

As a cost-effective strategy to increase the ^{188}Re activity concentration to acceptable levels, use of the ^{188}W/^{188}Re generator has been optimized for routine clinical use by incorporating disposable tandem cation-exchange/anion-exchange columns to provide high activity-concentration solutions of ^{188}Re required for preparation of various therapeutic agents.[4-5,12-14,72-74] The combined elution and concentration of the ^{188}Re generator bolus can be performed in 5 to 10 minutes, which makes routine use of this system practical in the radio pharmacy laboratory. The use of the inexpensive disposable tandem concentration units is simple and yields reproducible solutions of ^{188}Re. The postelution bolus concentration system is illustrated in Figure 8.

As shown in Fig. 3, the tandem cation/anion concentration system is installed in the center lead shield and consists of a commercially available silver cation exchange cartridge with a capacity of 2 to 4 mEq attached to a three-way stopcock connected at the outlet to the QMA SepPak anion-exchange column. Alternatively, the system including the valves can be installed in a thick polyacrylate shield with remote operation of the valves, as has previously described.[2] Another length of extension tubing then connects the outlet of the anion exchange column to the ^{188}Re collection vessel which is housed in a lead shield. The concentration methods make the availability of high activity-concentration solutions of carrier-free ^{188}Re feasible and extend the generator shelf-life to several months. Detailed studies have demonstrated that concentra-

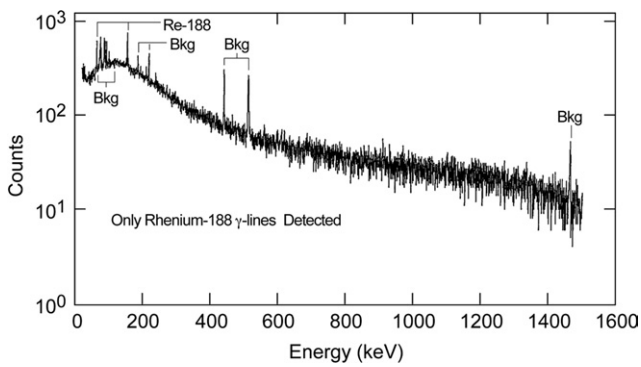

Figure 7 Gamma spectrum illustrating the high radioisotopic purity of ^{188}Re obtained after passage through the tandem cation/anion and alumina column system.

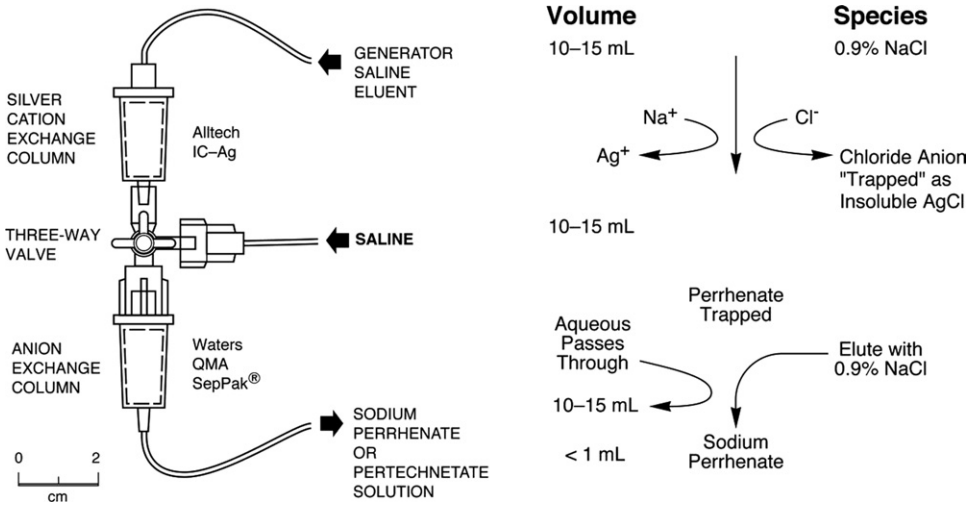

Figure 8 Tandem column system for removal of chloride anions and specific trapping and subsequent saline elution of ^{188}Re.

tion using the disposable tandem cation/anion systems is readily feasible for the multiple elutions of clinical-scale ^{188}W/^{188}Re generators (>1 Ci) on a routine basis, and the column concentrator units are inexpensive and disposable following each use. This method is based on the concept that the macroscopic levels of the chloride anion are trapped as insoluble silver chloride. In this manner, all the chloride anions are removed from the solution and will not compete with specific binding of the perrhenate anion to the QMA SeaPak anion column. Subsequent elution through the anion column thus specifically traps the microscopic levels of the perrhenate anions and this initial eluant collected from the QMA SeaPak column contains only low levels of radioactivity and is discarded as waste. After adjustment of the intermediary three-way valve, the QMA SeaPak anion column is subsequently washed with sterile water using a syringe attached to the side port, and the ^{188}Re perrhenate is then eluted from the anion column in <1 mL of isotonic saline. This inexpensive, straightforward method provides high activity concentration solutions of ^{188}Re sodium perrhenate over several months. Automation, semiautomation, or the remote operation of syringes and valve actuators can reduce operator radiation exposure. Any back pressure may also result from use of the alumina trapping column in conjunction with the silver cation/anion tandem columns. While commercially available silver cation columns are now used for this purpose, the small particle size, lack of Luer-lock connectors, possible high pressure encountered with their use, and simple inexpensive in-house preparation of chloride trapping columns using readily available and disposable components (*vide ante*) has been shown to overcome these problems.

A less expensive alternative than the purchase of commercially available silver-cation columns that results in less back pressure during elution involves in-house fabrication of the silver cation columns. Commercially available columns, such as the Bio-Rad #737 to 15-12 Econo-Column (1.5 cm o.d. × 10 cm length) fitted with Luer Lock fittings, can be used for this purpose. The degree of chloride trapping capacity is determined by the amount of silver bound to the cation resin, and larger columns can be used if increased chloride trapping capacity is required. These glass columns have a glass frit at the bottom and the top is a plastic pressure fit Luer assembly. The AG 50-X4 sulfonic acid resin, with 200 to 400 Mesh, for instance, can be used. This size column holds about 8 g of the resin (dry weight) that should be wet thoroughly with distilled water. The top of the column can then be packed with a fine glass wool plug. A solution of 1 N silver nitrate solution (14-15 mL) is added to the column which is then washed with distilled water. If quantification is required, a sample of the total eluant/wash can be titrated with chloride solution to determine how much silver ion was present and thus how much is bound to the resin. Approximately 50 to 55 mL of 0.9% normal saline can be passed through a column prepared in this manner, before the chloride anion is detected by elution into a silver nitrate solution. In this way a single silver/cation column can be prepared which can trap any volume of saline. Since the cation resin is not tightly packed as in the commercial columns, the generator/tandem-trapping system should be eluted at a low flow rate (0.25-0.30 mL per minute). Lower flow rates will also minimize backpressure from the complete system. Addition of ^{188}Re tracer to the saline solution permits evaluation of saline elution through the Ag-cation column until the conditions are optimized for use with the generator. If the silver-cation columns are thoroughly washed after use and allowed to decay for several days (>10 half lives), the packing can be carefully removed and discarded and the column packed again for re-use.

Preparation and QC of ^{188}Re-HDD

Lipiodol is an iodinated and esterified lipid of poppy seed oil that has been used for many years as a radiological radiograph contrast agent for detection and treatment of liver can-

cer. Trans-arterial administration of the viscous lipiodol results not only in embolization of the microvasculature but also phagocytosis by liver cells. To couple the tumor-localizing properties of lipiodol with the therapeutic potential of ^{188}Re's high-energy beta particles and thus optimize its therapeutic efficacy, the lipophilic 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol substrate was developed for preparation of the ^{188}Re-labeled Re(V)-oxo agent for treatment of liver cancer.[27] To increase cancer cell retention, the more lipophilic HDD was then developed[30] (Fig. 2), and in both preclinical and subsequent clinical trials, the^{188}Re-HDD showed good localization in and by liver cancer sites accessible by trans-arterial administration.

A radiolabeling method was developed and established for the preparation of ^{188}Re-HDD and formulation into a kit form was successfully performed. However, improvements of the radiolabeling yield were an important factor to insure optimal incorporation of the available 4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol and delivery of sufficient radioactivity to the cancer foci. Initially, HDD was radiolabeled with ^{188}Re and extracted into lipiodol at neutral pH. However, this initial method did not optimize radio-labeling yields because the highest labeling efficiency is obtained at acidic pH (pH = 1~2). Moreover, instability of HDD was often observed during kit formulation. To evaluate analogues which would overcome these problems, more recently an AHDD kit in which highly reactive and unstable thiol groups of HDD were protected by acetylation, was developed. The acetate protecting groups can easily then be de-protected during the radiolabeling procedure.[33]

HDD and AHDD Kit Preparation

Two types of aseptic and apyrogenic kits have thus been developed and formulated for preparation of ^{188}Re-HDD- and AHDD-lipiodol, respectively. The HDD kits are composed of two vials, containing HDD and phosphate buffer, respectively. The advantage for preparation of AHDD kits is that only one vial is required. The ingredients of the HDD and AHDD kits, which are prepared under aseptic condition using aseptic and apyrogenic materials and vials, are described to follow.

HDD Kit Preparation

Vial 1: Freeze-dried with each 10-mL vial containing a sterile, nonpyrogenic, lyophilized mixture of HDD, 1 mg; L(+)-Tartaric acid ($C_4H_6O_6$, M.W. 150.1), 40 mg; Tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$, M.W. 225.6), 10 mg; and D-Mannitol ($C_6H_{14}O_6$, M.W. 182.2), 20 mg. Before lyophilization the pH is ~1.9. The contents of the vial are lyophilized and stored under nitrogen. The vial should be stored in a refrigerator at a temperature <5°C and protected from light. Vial 2: Each 5-mL vial contains sodium phosphate tribasic dodecahydrate ($Na_3PO_4{\cdot}12H_2O$) 330 mg in 2 mL of water. The pH of the solution in Vial 2 is 12.

AHDD Kit Preparation

Vial 1 (freeze-dried): Each 10-mL vial contains a sterile, nonpyrogenic, lyophilized mixture of AHDD, 1 mg; L(+)-Tartaric acid ($C_4H_6O_6$, M.W. 150.1), 40 mg; Tin(II) chloride dihydrate ($SnCl_2{\cdot}2H_2O$, M.W. 225.6), 10 mg; and D-Mannitol ($C_6H_{14}O_6$, M.W. 182.2), 20 mg. Before lyophilization the pH is ~1.9. The contents of the vial are lyophilized and stored under nitrogen. The vial should be stored in a refrigerator at a temperature <5°C and protected from light.

Radiolabeling

Method A: Radiolabeling Using a HDD Kit

A total of 6 mL of ^{188}W/^{188}Re-generator-eluted ^{188}Re-perrhenate is added to Vial 1 of the HDD kit and shaken well. After addition of 1 mL of phosphate buffer from Vial 2, Vial 1 is shaken well. Air should be withdrawn from Vial 1 using a syringe to prevent any build-up of pressure during the boiling procedure. The solution may be turbid due to formation of emulsion. The vial is heated in a boiling water bath (100°C) for 1 hour and then cooled to room temperature. If the water bath is not vigorously boiling, the radiolabeling efficiency will not be optimal. After addition of 3 mL of lipiodol the vial is shaken vigorously. Use of a vortexer is recommended for extraction. The Vial is then centrifuged for 10 minutes at 3,000 rpm to separate the water and lipiodol phases. After insertion of a venting needle, the lower lipiodol phase is carefully withdrawn using a syringe equipped with a long needle (Fig. 9).

Method B: Radiolabeling Using an AHDD Kit

After addition of 6 mL of the ^{188}W/^{188}Re-generator-eluted ^{188}Re-perrhenate to Vial 1 of AHDD kit, the vial is shaken well. Air should be withdrawn out of Vial 1 with a syringe to prevent possible pressure build up in the boiling procedure. The solution might be turbid due to formation of emulsion. After heating in a boiling water bath (100°C) for 1 hour, the vial is cooled to room temperature. If the water bath is not vigorously boiling, the radio-labeling efficiency will be reduced. A total of 3 mL of lipiodol is added and the vial then shaken vigorously. Use of a vortexer is recommended. The vial is then centrifuged for 10 minute at 3,000 rpm to separate the water and lipiodol phases. After inserting a venting needle, the upper aqueous phase is carefully removed with a syringe equipped with a long needle. The lower Lipiodol and emulsion phases are then recovered for QC analysis. The residual lipiodol activity remaining in the vial can be recovered by rinsing with a small amount of lipiodol.

Quality Control of Re-188-HDD

A 2-strip method using instant thin layer chromatography silica gel (ITLC-SG) plates (1 × 10 cm) is used for evaluation of radiochemical purity. Two TLC chambers (eg, test tubes) containing acetone and normal saline, respectively, are prepared, each solvent poured to a depth of 3 to 4 mm and the chambers then covered and allowed to equilibrate for about 10 minutes. Using a syringe and 22- to 26-gauge syringe needle or pipette, a small aliquot of ^{188}Re-HDD-lipiodol solution is applied at 1.5

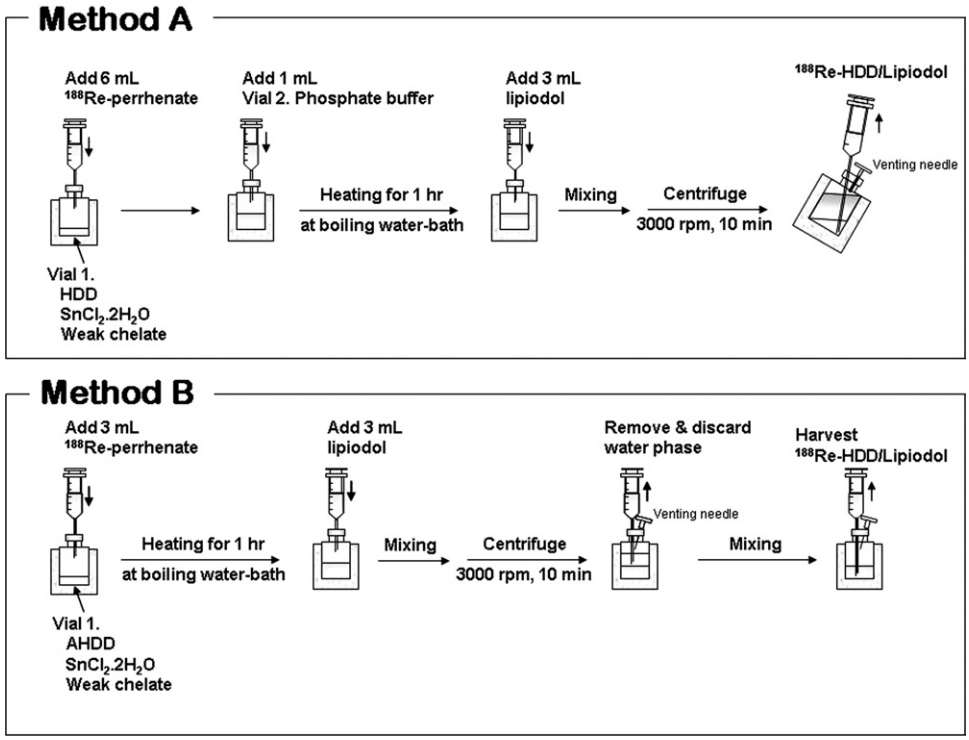

Figure 9 Formation and lipiodol extraction of ^{188}Re-HDD agent.

cm from the bottom of each plate. The plates are developed in the covered TLC chambers for a solvent-front migration distance of 8 cm from the origin. The ITLC plates are cut into 5-cm lengths from the bottom and the ^{188}Re activities in the segments are measured using an appropriate radiation detector. The radiochemical purity is then calculated as follows: Colloid % = μCi bottom segment (acetone)/μCi both segments (acetone) × 100%; Perrhenate % = μCi upper segment (saline)/μCi both segments (saline) × 100%; Purity % = 100 − Colloid % − Perrhenate %. Typical radiochromatograms from analysis of ^{188}Re-HDD are shown in Fig. 10.

The pH values are different for radiolabeling and extraction methods A and B. Although method A is conducted at neutral pH, method B uses an acidic pH. Comparison of these 2 methods has demonstrated that greater radiolabeling and extraction efficiencies are obtained under acidic conditions. Radiolabeling yields of greater than 90% were obtained by method B, whereas average yields of 70% were obtained by method A. Although emulsion formation was often observed after extraction under acidic conditions, such emulsions do not significantly affect the biodistribution results observed in animal studies after intravenous administration, because the aqueous phase does not contain significant radioactivity. Significant radioactivity was also observed to remain in the vial following preparation of ^{188}Re-HDD. It adheres to the glass surfaces, probably because of hydrophobic interaction and/or colloid formation, although the relative contributions from these two hypothesized processes have not been assessed.

The residual levels of radioactivity caused by hydrophobic interaction could be minimized by using glass vials with hydrophilic surfaces. Several types of glass vials were evaluated in an attempt to minimize adherence to the glass surfaces. The current kit vial is obtained from Dongsung Company (Seoul, Korea). We also found that some silanized vials exhibited adherence of high levels of radioactivity, presumably due to hydrophobic interaction. On the other hand, adher-

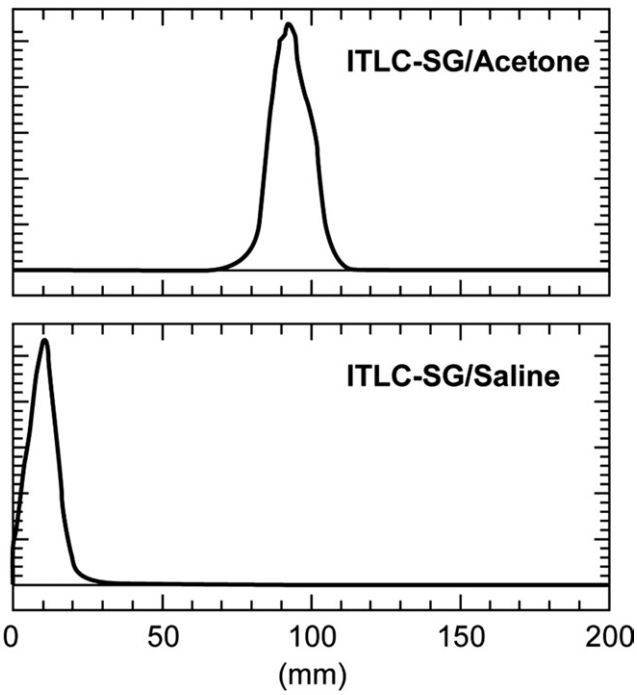

Figure 10 Radiotraces of ITLCs of ^{188}Re-labeled HDD.

ence to the glass surface resulting from a colloid formation could not be reduced by using hydrophilic surface glass vials. One strategy would be to reduce the formation of colloid, resulting from the use of high concentrations of tin(IV). The current kit used for preparation of ^{188}Re-HDD has thus been optimized for radiolabeling using 6 mL of ^{188}Re-perrhenate. Because formation of the colloid is increased if the added volume of perrhenate is less then 6 mL, normal saline should be added as necessary to bring the volume of ^{188}Re-perrhenate to this value.

Summary

The preparation of ^{188}Re-HDD has been optimized, providing a radiopharmaceuticals which is straightforward to prepare and potentially efficacious for the treatment of nonresectable liver cancer. The collective experience of the international nuclear medicine community has demonstrated that the ORNL ^{188}W/^{188}Re generator provides a cost-effective and reliable source of ^{188}Re for preparation of a variety of therapeutic radiopharmaceuticals. This generator has the potential to significantly advance the practice of therapeutic nuclear medicine—in much the same way that the ^{99}Mo/^{99m}Tc generator established diagnostic nuclear medicine as a widely accepted specialty. Although the possibility of obtaining greater ^{188}Re elution yields would presumably be translated into reduced costs per ^{188}Re dose, this possibility has yet to be demonstrated at most centers using the ^{188}W/^{188}Re generators, because the routine use of the generator has not yet been optimized.

The long useful life of the ^{188}W/^{188}Re generator is a major reason for the cost effectiveness of ^{188}Re radiopharmaceuticals. Two 1.5-Ci generators can provide sufficient activity for therapeutic administrations of ^{188}Re radiopharmaceuticals during a period of 1 year. Costs of transport of the generator and of consumable supplies are modest even if column concentration of eluates is necessary for ^{188}Re radiopharmaceutical preparation. The cost of a 1.5-Ci ^{188}W/^{188}Re generator is, in fact, less than that of a single patient dose of the commercially available yttrium-90 ibritumormab tiuxetan, Zevalin (Biogen Idec). A potentially important strategy to provide even wider availability of ^{188}Re radiopharmaceuticals for routine use in therapeutic clinical applications would be to supply ^{188}W/^{188}Re generators to centralized radiopharmacies.

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