Bulk Production and Evaluation of High Specific Activity ^{186}gRe for Cancer Therapy Using Enriched $^{186}\text{WO}_3$ Targets in a Proton Beam

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Short Title: High Specific Activity ^{186}gRe from Enriched $^{186}\text{WO}_3$ Targets

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ABSTRACT

Introduction

Rhenium-186g ($t_{1/2} = 3.72$ d) is a β^- emitting isotope suitable for theranostic applications. Current production methods rely on reactor production by way of the reaction $^{185}\text{Re}(n,\gamma)^{186g}\text{Re}$, which results in low specific activities limiting its use for cancer therapy. Production via proton or deuteron activation of enriched ^{186}W results in a ^{186g}Re product with a specific activity approximately seven times higher than conventional methods, allowing it to be used more broadly for targeted radiotherapy applications.

Methods

A target consisting of highly enriched, pressed $^{186}\text{WO}_3$ was irradiated with protons at the Los Alamos National Laboratory Isotope Production Facility (LANL-IPF) to evaluate ^{186g}Re product yield and quality. LANL-IPF was operated in a dedicated nominal 40 MeV mode. Alkaline dissolution followed by anion exchange chromatography was used to isolate ^{186g}Re from the target material. Phantom and radiolabeling studies were conducted with the produced ^{186g}Re activity.

Results

A ^{186g}Re batch yield of 1.38 ± 0.09 MBq/ μAh or 384.9 ± 27.3 MBq/C was obtained after 16.5 h in a 205 μA average/230 μA maximum current proton beam. The chemical recovery yield was 93% and radiolabeling was achieved with efficiencies ranging from 60-80%. True specific activity of ^{186g}Re at EOB was determined via ICP-AES and amounted to 0.788 ± 0.089 GBq/ μg (0.146 ± 0.017 GBq/nmol). Phantom studies show similar imaging quality to the gold standard ^{99m}Tc .

Conclusions

These results demonstrate the production of high specific activity $^{186\text{g}}\text{Re}$ from enriched $^{186}\text{WO}_3$ targets with exceptional chemical recovery and radiochemical purity.

Keywords: Theranostic; $^{186\text{g}}\text{Re}$; $^{186}\text{WO}_3$ target; high specific activity; radiolabeling; SPECT phantom images

1 Introduction

Rhenium isotopes have garnered significant, recent interest given their utility in targeted cancer therapy and their chemical similarity to $^{99\text{m}}\text{Tc}$, which combines for a theranostic pair [1-3]. The two main isotopes of rhenium of interest for radiotherapy are $^{186\text{g}}\text{Re}$ and ^{188}Re . The beta-emitting isotope rhenium-186g ($t_{1/2} = 3.72$ d) [4] has been used to successfully treat bone pain in patients, where a low specific activity radiopharmaceutical was required [5-10], however, its use in radiotherapy targeting cell surface receptors on cancer cells has been limited by the specific activity achieved when it is produced via the $^{185}\text{Re}(n,\gamma)^{186\text{g}}\text{Re}$ reaction in a reactor [11, 12]. Rhenium-188 ($t_{1/2} = 17$ h) is available in high specific activity from a radionuclide generator via decay of ^{188}W ($t_{1/2} = 69.4$ d) [13], however its short half-life is problematic when using targeting agents with long biological half-lives, such as monoclonal antibodies. Owing to the longer half-life, $^{186\text{g}}\text{Re}$ is considered to be more conducive to radiolabeling procedures, which allows sufficient time for the synthesis and shipment of potential radiopharmaceuticals. Further, the most abundant beta emissions from ^{188}Re decay have very high energy ($\beta_{\text{max}} \sim 2$ MeV), which can irradiate non-target tissues while in the blood. Rhenium-186g has lower energy beta emissions ($\beta_{\text{max}} \sim 1$ MeV), making it more attractive for patient use. It also emits a low-abundance (9.47 %) 137.2 keV γ -ray, enabling in vivo tracking of radiolabeled biomolecules and dosimetry estimates via SPECT (single photon emission computed tomography).

A simplified decay scheme of ^{186g}Re is shown in Figure 1. The isotope may be produced at either a reactor or an accelerator facility. Since accelerator produced charged particle induced reactions can convert other elements in ^{186g}Re , allowing separation of that isotope from the bulk target material, this approach can yield ^{186g}Re of higher true specific activities, i.e, activity of ^{186g}Re per mass of rhenium, than the product obtained via neutron irradiation of the same element, ^{185}Re , in a nuclear reactor. Currently the true specific activity of ^{186g}Re obtained via reactor production is $\leq 0.11 \text{ GBq}/\mu\text{g}$ [14], however the theoretical maximum true specific activity achievable through proton induced reactions is $189 \text{ Ci}/\text{mg}$.

[Figure 1]

There are multiple possible routes to produce ^{186g}Re with an accelerator, either from an isotopically enriched target of tungsten via the $^{186}\text{W}(\text{p}, \text{n})^{186g}\text{Re}$ or $^{186}\text{W}(\text{d}, 2\text{n})^{186g}\text{Re}$ reactions, or from isotopically enriched targets of osmium via the $^{189}\text{Os}(\text{p}, \alpha)^{186g}\text{Re}$ or $^{192}\text{Os}(\text{p}, \alpha 3\text{n})^{186g}\text{Re}$ reactions [15]. Compared to proton activation, deuteron activation via $^{186}\text{W}(\text{d}, 2\text{n})^{186g}\text{Re}$ has advantages in terms of higher reaction cross sections and less isotopic impurities [16]. A critical review of the two reactions was performed [17], and an upper proton energy limit for the (p,n) reaction of 18 MeV was identified. Radiorhenium formed in matrices of either W metal or WO_3 may be chemically separated via dry distillation [18-20], liquid-liquid extraction [21] or anion-exchange controlled liquid-solid sorption [22-24] from aqueous target solutions prepared from either the metal (requiring oxidizer and base) or the trioxide (requiring base only).

In a previous study [25], we reported the proton irradiation of targets consisting of $^{\text{nat}}\text{WO}_3$ powder at the Los Alamos National Laboratory Isotope Production Facility (LANL-IPF, 100 MeV mode) to evaluate radionuclide product yields, impurities, irradiation parameters and wet chemical rhenium recovery for a bulk production. We also conducted an exhaustive investigation

of rhenium and tungsten sorption behavior on a strongly basic anion exchange resin [26]. It was demonstrated that radorhenium can be isolated in 97% yield from irradiated $^{nat}\text{WO}_3$ targets within 12 h of end of bombardment (EOB) via an alkaline dissolution followed by anion exchange sorption and HNO_3 elution. Tungsten (VI) oxide could easily be recovered from the eluted tungstate solution via acidification and filtration. We recently reported the accelerator based production of ^{186g}Re using metal disulfide (MS_2 where $\text{M} = \text{Mo}, \text{W}, \text{Os}$) targets [27, 28] and the deuteron induced production of ^{186g}Re using tungsten metal and tungsten oxide targets [29], however, a high beam current evaluation of sulfide targets is still outstanding. Tungsten oxide targets, on the other hand, exhibited sufficient thermal stability to endure multiple hours of proton irradiation in a $>200\text{ }\mu\text{A}$ beam in test experiments at Los Alamos. This production study was thus carried out using enriched $^{186}\text{WO}_3$ targets that allow for easy chemical processing, ^{186g}Re isolation and enriched target material recovery. Isolated ^{186g}Re product was used for the synthesis and preliminary *in vivo* evaluation of ^{186g}Re -monooxorhenium(V) complexes, which was published as well [30].

As ^{186}W is 28.43% abundant in nature, isotopically enriched targets would give optimal yields for the production of ^{186g}Re . Isotopically enriched targets would also significantly reduce the production of undesired, long-lived rhenium isotopes that can negatively affect the purity and use of ^{186g}Re as a therapeutic isotope. Here we report for the first time the accelerator production of ^{186g}Re by proton irradiation of 99.9% enriched $^{186}\text{WO}_3$ targets.

2 Materials and Methods

2.1 Target Preparation and Irradiation

A target consisting of niobium-encapsulated pressed, enriched $^{186}\text{WO}_3$ powder (Isoflex, USA; $9.68 \pm .02\text{ g}$, pressed at 111.21 kN for 1 min) was irradiated with 230 μA of protons for 16.5

hours at LANL-IPF in a proton beam. The ^{186}W enrichment was 99.9 ± 0.1 %. Isotopic impurities included ^{184}W (0.10 ± 0.05 m-%) and $^{180,182,183}\text{W}$ (<0.01 m-%). LANL-IPF was operated in a 40 MeV dedicated mode.

The incident proton energy was measured via time-of-flight (TOF), i.e., the time that elapses as the beam travels a known distance between two beam position monitors (BPMs). Three BPMs were used corresponding to three independent particle energy measurements with a resolution of 50 keV. TOF measurements resulted in a proton energy and amounted to 41.4 ± 0.2 MeV. The entrance energy on the pressed $^{186}\text{WO}_3$ target was 20.7 MeV and the exit energy was 13.3 MeV. Figure 2 shows the niobium-encapsulated $^{186}\text{WO}_3$ powder in the IPF target holder, which was cut thinner than a regular IPF production to accommodate for the target capsule.

[Figure 2]

2.2 Gamma-ray spectrometry

Gamma-ray spectrometry was conducted using an EG&G Ortec Model GMX-35200-S HPGe detector system in combination with a Canberra Model 35-Plus multichannel analyzer. Detector diameter was 50.0 mm, detector length was 53.5 mm, Be window thickness was 0.5 mm, and outer dead-layer thickness was 0.3 μm . Detector response function determination and evaluation were performed using standards of radionuclide mixtures containing ^{241}Am , ^{109}Cd , ^{57}Co , ^{139}Ce , ^{203}Hg , ^{113}Sn , ^{137}Cs , ^{88}Y , and ^{60}Co , traceable to the National Institute of Standards and Technology (NIST) and supplied by Eckert & Ziegler (Atlanta, GA, USA). The detector was a p-type Al-windowed HPGe detector with a measured FWHM at 1333 keV of approximately 2.2 keV and a relative efficiency of about 10%. Relative total source activity uncertainties ranged from 2.6% to 3.3%. Counting dead time was kept below 10%.

2.3 Inductively coupled plasma mass spectrometry (ICP-MS)

ICP-MS was performed at the University of Missouri Research Reactor. An aliquot (200 μ L) of high specific activity $^{186}\text{gReO}_4^-$ in 0.1 M HCl from Los Alamos National Laboratory was diluted to 10 mL with 0.45 N HNO_3 . The sample was analyzed on a PerkinElmer NexION 300X ICP-MS run in KED mode with a He flow rate of 2 mL/min. The NexION was equipped with a glass cyclonic spray chamber and glass concentric nebulizer. Masses 178 through 193 were scanned for the analysis of tungsten, tantalum, rhenium, and osmium. Calibration standards for W, Ta and Re were prepared from a multielement mixture; Os standards were diluted from a single-element standard. All standards were purchased from and certified by High-Purity Standards (Charleston, SC), Indium and thallium were used as internal standards.

2.4 Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)

Determination of rhenium, tantalum, tungsten, and osmium concentrations, in addition to concentrations of common transition metals, were carried out via ICP-AES using a Shimadzu ICPE-9000 instrument equipped with a 2 cm x 2 cm CCD detector calibrated on the day of use. Calibration solutions were prepared from certified stocks, purchased from Fisher Scientific (Pittsburgh, PA, USA). Analyses were performed in triplicate and based on a 30 s sample exposure time. Output data were managed and analyzed using the ICPE Solutions software version 1.01 (Shimadzu Corp. 2005).

2.5 Target dissolution and chemical separation

Rhenium-186g was recovered from the target material as reported previously [25, 26]. The niobium window was cut from the target canister, and the WO_3 mass (original target fabrication weight 9.68 ± 0.02 g) was removed from the shell, weighed and dissolved in 250 mL of 1 M NaOH by boiling for 1 h. The resulting solution was allowed to cool and was then filtered. The Na_2WO_4 filtrate was then loaded onto an anion exchange column (Bio-Rad AG 1 $\times$ 8, resin bed column of 1.2 cm diameter $\times$ 13.3 cm length, pre-equilibrated with 1 M NaOH. The isotope ^{187}W ($t_{1/2} = 23.9\text{h}$; produced via the $^{186}\text{W}(\text{n},\gamma)^{187}\text{W}$ pathway [25]) was used as a tracer for tungsten throughout the separation experiment. Rhenium isotopes were quantitatively retained, while the Na_2WO_4 matrix solution eluted. Rhenium isotopes were not observed in the Na_2WO_4 effluent. The column was washed with 150 mL of a 0.5 M NaOH/ 0.5 M NaCl solution followed by 75 mL of 1.5 M HCl to remove coproduced ^{183}Ta and ^{181}Hf isotopes. Rhenium isotopes were subsequently eluted from the column with two 50 mL fractions of 10 M HNO_3 . This solution was evaporated to dryness, and the residue was dissolved with 20 mL of 0.1 M HCl.

2.6 $^{186\text{g}}\text{Re}$ SPECT phantom study

Using LANL produced $^{186\text{g}}\text{Re}$, a SPECT phantom study was conducted at the VA Puget Sound Medical Center, located in Seattle, WA, on a Mediso Nano SPECT/CT preclinical imaging camera (Mediso Medical Imaging Systems, Budapest, Hungary). A collimator consisting of nine pinholes per head with a pinhole size of 0.8 mm and a 1.6 cm field of view and a sensitivity >2200 cps/MBq (27 μCi) was used. A micro Derenzo phantom (rod sizes: 0.25 -0.6 mm) was filled with $^{99\text{m}}\text{Tc}$ in 70% EtOH (5 mL, 2.85mCi or 105 MBq total activity) and $^{186\text{g}}\text{Re}$ to the same specifications. The radioactivity present in each phantom was measured by dose-calibrator. Cir-

cular CT scans were acquired in 180 projections, at 45 kVp with 1000 ms exposure time and 3 minute scan duration. The scan range was 26 mm. Helical SPECT scans were acquired with acquisition times of 60 minutes.

2.7 ^{186}gRe radiolabeling studies

High specific activity $^{186}\text{gReO}_4^-$ from LANL was used at the University of Missouri to prepare $^{186}\text{gReOCl}_3(\text{PPh}_3)_2$ (Figure 3) using the method of Wagner et al. [31]. Briefly, 100 μL of $^{186}\text{gReO}_4^-$ (2.0-5.3 MBq; 53-143 μCi) were added to 3.39 mg of PPh_3 (12.9 mmol) dissolved in 388 μL of concentrated HCl (final HCl concentration was 9 M). To this solution, 388 μL of dichloromethane were added, and the resulting biphasic mixture was vortexed for 5 minutes before removal of the organic layer, which contained the $^{186}\text{gReOCl}_3(\text{PPh}_3)_2$ product. A similar rhenium labeling method was employed in an earlier Los Alamos study [32].

[Figure 3]

2.8 Recovery of $^{186}\text{WO}_3$ target material

The eluted $\text{Na}_2^{186}\text{WO}_4$ target material in 1 M NaOH was acidified with 20 mL of concentrated HCl resulting in the precipitation of the target material. The precipitate was filtered and washed with water. Following filtration, the precipitate was dried under vacuum and weighed to obtain a recovery yield. Additionally, a 43.3 mg fraction was dissolved in 1 M NaOH and assayed via gamma spectroscopy to determine the remaining radioactive contaminants.

3 Results

3.1 ^{186g}Re production and chemical recovery

The irradiation resulted in a production yield of 4.7 ± 0.3 GBq (126.9 ± 8.1 mCi) of ^{186g}Re (1.38 MBq/ μAh), as determined by HPGe analysis of the dissolved target material, which was 81% of total theoretical yield (TTY). Table 1 shows the ^{186}Re bulk production parameters obtained from the LANL-IPF irradiation. Rhenium-186g activity in the form of $^{186g}\text{Re}_2\text{O}_7$ had partially sublimed on the inside the target window during irradiation, however the window was washed and the material recovered. The activity of the recovered $^{186g}\text{Re}_2\text{O}_7$ was included in the TTY.

[Table 1]

The separation of ^{186g}Re resulted in a chemical recovery yield of 93 ± 3 % and a radiochemical purity of 99.9 ± 0.05 % as measured by HPGe analysis of characteristic gamma rays. A schematic of the processing scheme is shown in Figure 4. Radioactive impurities detected in the final product were ^{184}Re and ^{183}Re , representing 0.04% and 0.05% of the total activity at end of bombardment, respectively. Stable impurities were determined by ICP-AES/MS and are shown in Table 1. True specific activity, determined by ICP-AES analysis, was calculated to be 0.788 ± 0.089 GBq/ μg .

[Figure 4]

The original target material was recovered to demonstrate the ability to recycle the enriched target material. Precipitation of the target material resulted in a reclamation of 6.26 g of the original material corresponding to a recovery yield of ~65%. The radionuclidic contaminants present in the recovered material were ^{54}Mn (3.5 kBq), ^{56}Co (6.4 kBq), and ^{57}Co (74 Bq).

3.2 ^{186g}Re SPECT phantom and radiolabeling studies

A phantom study comparing $^{186\text{g}}\text{Re}$ SPECT resolution with that of $^{99\text{m}}\text{Tc}$ is shown in Figure 5. The image resolution of $^{186\text{g}}\text{Re}$ is shown to be comparable to that of $^{99\text{m}}\text{Tc}$. This validates the use of $^{186\text{g}}\text{Re}$ as a single isotope theranostic agent.

[Figure 5]

A Re(V) complex, $^{186\text{g}}\text{ReOCl}_3(\text{PPh}_3)_2$, was synthesized according to a literature-reported procedure [31] and obtained with similar radiolabeling yields (60-80%). This demonstrates the utility of our high specific activity $^{186\text{g}}\text{ReO}_4^-$ final product for use in radiolabeling studies. Additionally, $^{186\text{g}}\text{Re}$ from this production was used to successfully radiolabel $\text{N}_2\text{S}_2\text{-BBN}$ [30].

4 Discussion

The irradiation detailed in this manuscript yielded $^{186\text{g}}\text{Re}$ with a total theoretical yield (TTY) that validates the IAEA recommended cross section data [33]. Rhenium-186g was purified from the target material in high radiochemical yield and purity. The total time that elapsed from EOB through purification of the final product was 13 hrs. and resulted in a $^{186\text{g}}\text{Re}$ decay factor of 0.91. Additionally, the true specific activity of the final product exceeded that of a $^{185}\text{Re}(\text{n},\gamma)^{186\text{g}}\text{Re}$ reactor product by 6-7 times [14]. Higher true specific activity is important for therapeutic applications, as a much lower mass of material can be administered, thus lowering the overall chemical toxicity to the patient [34].

Furthermore, higher specific activities are needed to prevent blocking of the targeting agent at the intended receptor site specifically when targeted receptors have low expression levels. The true specific activity of the final product is still an order of magnitude lower than the theoretical maximum. This can be explained by the formation of isotopic byproducts, namely

(stable) ^{185}Re and (long-lived) $^{186\text{m}}\text{Re}$ as discussed previously [25]. The target material itself did not contain any ICP-AES detectable quantity of stable rhenium.

Due to the higher cost of enriched target material, a recycling method was investigated. Only 65% of the target material was recovered, primarily due to mechanically trapped $^{186}\text{WO}_3$ powder in the target capsule. The recovered target material contained minimal radioactive impurities and is suitable for the fabrication of a new target, which can be done in a hood due to low activity levels. For routine production of $^{186\text{g}}\text{Re}$, optimization of the capsule design would be necessary to maximize recovery of the target material for recycling purposes.

Phantom studies comparing the gold standard in SPECT imaging, $^{99\text{m}}\text{Tc}$, with $^{186\text{g}}\text{Re}$ were performed to demonstrate the imaging characteristics of $^{186\text{g}}\text{Re}$. The phantom images show that the resolution of $^{186\text{g}}\text{Re}$ is qualitatively very similar to that of $^{99\text{m}}\text{Tc}$. The potential to image therapeutic isotopes allows the monitoring of dose accumulated by the patient in the tumor along with non-target organs. The theranostic capability of $^{186\text{g}}\text{Re}$ is one of the advantages that makes this isotope of great interest to the nuclear medicine community.

Future work would include improving on the recovery process for the enriched target material. This would be done by adjusting the current target encapsulation to allow for maximum recovery of the enriched target material. Additionally, monitoring the change in true specific activity over repeated irradiation and recycling steps of the target material would help to evaluate the maximum attainable true specific activity.

5 Conclusions

Results of this study demonstrated the ability to produce therapeutic quantities of $^{186\text{g}}\text{Re}$ using enriched $^{186}\text{WO}_3$ targets in a high current proton beam. For optimal production yields, the production of $^{186\text{g}}\text{Re}$ via the reaction $^{186}\text{W}(\text{p},\text{n})^{186\text{g}}\text{Re}$ requires a well-controlled incident energy of 40 MeV, which is not a routine operation mode for IPF. The $^{186\text{g}}\text{Re}$ product was isolated from the target material using a wet chemistry approach, and the ^{186}W target material was conveniently recovered and prepared for re-irradiation. The final $^{186\text{g}}\text{Re}$ product was obtained in high radiochemical purity and yield with a specific activity amenable to radiolabeling of biomolecules.

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Table 1.
Rhenium-186g bulk production parameters.

Target material	¹⁸⁶ WO ₃ : 9.68 ± .02 g: pressed at 111.21 kN for 1 min ¹⁸⁶ W enrichment : 99.90 ± 0.10 % Isotopic Impurities: ¹⁸⁴ W (0.10 ± 0.05 m-%) ^{180,182,183} W (<0.01 m-%)
Target cylinder dimensions	5.08 cm x 0.11 cm
Max. beam current, duration	230 µA, 16.5 h
Beam window entrance energy	41.38 ± 0.15 MeV (TOF)
Production energy interval (nominal)	20.7 → 13.3 MeV
^{186g}Re physical yield (EOB)	4.695 ± 0.33 GBq (1.38 MBq/µAh ; 81.4 % TTY)
^{186g}Re chemical recovery (EOB)	4.366 ± 0.15 GBq (93 %, ¹⁸⁶ ReO ₄ ⁻ in 0.1 M HCl)
^{186g}Re specific activity (ICP-AES, EOB)	0.788 ± 0.089 GBq/µg (0.146 ± 0.017 GBq/nmol)
^{186g}Re specific activity (ICP-MS, EOB)	0.751 ± 0.073 GBq/µg (0.140 ± 0.014 GBq/nmol)
Isotopic impurities (EOB)	Radioactive ¹⁸⁴ Re (0.04 %), ¹⁸³ Re (0.05 %) Stable ¹⁸⁵ Re (6.4 nmol)
Final ^{186g}ReO₄⁻ solution stable impurities (ppm)	ICP-AES Cr 0.7, Cu 3.8, Fe 0.2, Mo 0.3, Ni 1.0, W 0.27, Zn 4.4, Re 0.24 ICP-MS ¹⁸⁵ Re 0.26, ¹⁸⁷ Re 0.01

Figure Legend:

Figure 1. Simplified decay scheme for ^{186}Re [4].

Figure 2. Niobium-encapsulated $^{186}\text{WO}_3$ powder in an IPF target holder.

Figure 3: $^{186g}\text{ReOCl}_3(\text{PPh}_3)_2$ labeling step.

Figure 4. Flow chart for the processing of ^{186g}Re .

Figure 5: Comparison of SPECT phantom images acquired for ^{99m}Tc (left) and ^{186g}Re (right). SPECT images were obtained in a micro Derenzo phantom (rod sizes: 0.25 -0.6 mm) filled with (a) 0.57 mCi (21 MBq)/mL of ^{99m}Tc or (b) ^{186g}Re in 70% EtOH (2.85 mCi or 105 MBq total activity).

PPh_3, HCl

~10g of $^{186}\text{WO}_3$ enclosed
in a niobium capsule
irradiated with
~3800 μAh of protons

Niobium capsule opened
and $^{186}\text{WO}_3$ removed

Dissolution of $^{186}\text{WO}_3$
with 1 M NaOH

^{186}Re adsorbs on Ag 1 x 8
while $^{186}\text{WO}_4^{2-}$ elutes

Precipitation of $^{186}\text{WO}_3$
by acidification with HCl

Recovery of $^{186}\text{WO}_3$ via
filtration

Removal of residual $^{186}\text{WO}_3$ and
coproduced ^{183}Ta and ^{181}Hf
isotopes

Column washed with a 1:1 mixture
of 0.5 M NaCl/ 0.5 M NaOH
followed by a wash with 1.5 M
HCl

Eluted ^{186}Re
with 10 M
 HNO_3

Brought to
dryness and
reconstituted in
0.1 M HCl