# Production of No-Carrier-Added $^{105}$Rh from Neutron Irradiated Ruthenium Target

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*Nuclear medicine radiotherapy involves the administration of a radiolabelled drug whose purpose is tissue damage and/or destruction at the point of localisation. Radionuclides useful for this application are those which emit particles (that is alpha, beta or Auger electrons) because they deposit their decay energy over a relatively short range (for example, at the tumour site). Rhodium-105 is a radionuclide with desirable nuclear properties for therapeutic applications (its half-life is 35.4 hours, the maximum $\beta^-$ energy is 0.56 MeV and it produces a 319 keV $\gamma$-ray suitable for imaging). However, this radionuclide is not readily available to most of the interested investigators due to the difficulty in production scale-up. The work reported here was designed to develop a viable method to produce and purify multi-millicurie quantities of $^{105}$Rh for radiotherapy research. Rhodium-105 was produced at the University of Missouri Research Reactor by the nuclear reaction, $^{104}$Ru (n, $\gamma$) $\rightarrow$ $^{105}$Ru ($\beta^-$ decay) $\rightarrow$ $^{105}$Rh and a new procedure was developed to chemically separate the no-carrier-added $^{105}$Rh from the neutron irradiated ruthenium target. Rhodium-105 production yields, for 10 runs, averaged about 5 mCi per milligram of ruthenium from a 72-hour irradiation at a thermal neutron flux of $8 \times 10^{13}$ neutrons $cm^{-2}$ $s^{-1}$. Rhodium-105 was successfully isolated from the ruthenium radionuclides and the non-radioactive ruthenium. This new separation technique was fast (a total time of 3 hours) and highly efficient for removing the ruthenium. The decontamination factor of ruthenium averaged 16,600, indicating that only 0.006 per cent of the ruthenium remained after separation.*

A therapeutic radiopharmaceutical typically consists of a biomolecule (such as an antibody, hormone or polypeptide) to which is bound a radionuclide of appropriate half-life, high specific activity and high radionuclidic purity. The biomolecule is generally labelled with the radionuclide by the incorporation of a bifunctional chelate which covalently bonds to both.
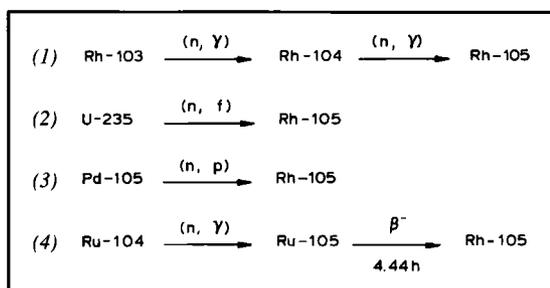
There has been much recent interest in the use of monoclonal antibody (MAb) and peptide conjugates of $^{105}$Rh for radioimmunotherapy (1–6). Bifunctional chelates of $^{105}$Rh conjugated to MAbs and peptides have been designed to target cancer cells through interactions with specific receptors on the tumour surface. The specificity of MAbs and peptides for their particular receptor makes them excellent candidates for delivering radio-

nuclides to cancer cells containing the receptor. The kinetic inertness of rhodium(III) complexes (low spin $d^6$ configuration) is expected to result in a much higher *in vivo* stability for $^{105}$Rh labelled monoclonal antibodies and peptides compared to those labelled with other radionuclides, such as $^{67}$Cu, $^{90}$Y, $^{186}$Re and $^{188}$Re. Various multidentate bifunctional ligands have been prepared and shown to form kinetically stable complexes *in vitro* with $^{105}$Rh. Examples of these ligands are 1,7-bis(2-hydroxybenzyl)-4-(p-aminobenzyl)-diethylenetriamine (2), hematoporphyrin (1), 3-[N-(4-aminobenzyl)]amino-3-methyl-2-butanoneoxime (7), N,N'-bis(2-hydroxybenzyl)-1,3-diaminopropane (3), cysteine (4), p-aminobenzylpropyleneamineoxime (6), and also 16-ane-S4-diol-macrocycle (8).

Rhodium-105 is a reactor-produced radio-

nuclide with moderate beta energy which is suitable for radiotherapy. It decays to stable $^{105}$Pd by two $\beta^-$ emissions, of 560 keV (70 per cent) and 250 keV (30 per cent). The 560 keV $\beta^-$ particles have a maximum range in body tissues of 2 mm. Rhodium-105 also emits imageable $\gamma$ rays of energy 319 keV (19 per cent) and 306 keV (6 per cent) that would allow initial diagnostic experiments prior to administering therapeutic doses of the same preparation.

$$^{105}\text{Rh} \rightarrow {}^{105}\text{Pd} + \beta^- + \gamma$$

In addition, the decay half-life (35.4 hours) of $^{105}$Rh is well matched to the *in vivo* pharmacokinetics of many peptides and antibody fragments.

## Production of Rhodium-105

Radiotherapeutic research which uses $^{105}$Rh requires a route for the production of high specific activity $^{105}$Rh. Unfortunately, this radionuclide is not readily available to researchers (primarily due to the relatively stringent conditions and requirements in the isotope production and separation).

Rhodium-105 can be produced in a reactor by several routes, see Figure 1; the simplest of which is via a (2n, $\gamma$) reaction from a $^{103}$Rh target. Unfortunately, this does not yield $^{105}$Rh of high specific activity. $^{105}$Rh is also a product (about 1 per cent) of the fission of $^{235}$U. However, the most commonly used method for the production of no-carrier-added $^{105}$Rh is the indirect (n, $\gamma$) reaction using ruthenium metal as the target to produce $^{105}$Ru, which then decays to $^{105}$Rh. Significant byproducts from the production are $^{97}$Ru ($T_{1/2}$ = 2.89 days), $^{103}$Ru ($T_{1/2}$ = 39.27 days), $^{105}$Pd (stable) and $^{106}$Pd (stable). The use of enriched ruthenium metal ($^{104}$Ru > 99 per cent) as the target material

minimises the radionuclidic impurities from ruthenium and increases the production yield of $^{105}$Rh by five-fold.

A procedure proposed by Troutner and colleague has previously been used for the preparation of 5 to 150 millicuries of no-carrier-added $^{105}$Rh at the University of Missouri Research Reactor (MURR) (9). The separation of $^{105}$Rh from its $^{105}$Ru parent was based on a combination of procedures previously described by Kobayashi and Morris (10, 11). An irradiated metal target of enriched $^{104}$Ru is dissolved in alkaline solution in a reaction vial and oxidised to $RuO_4$ using chlorine gas. The $RuO_4$ is then removed from the solution by distillation (b.p. 108°C) into a series of hydrochloric acid (HCl) and sodium hydroxide (NaOH) traps. The $^{105}$Rh remains in the reaction vial and is converted to a mixture of Cl$^-$ complexes by the addition of HCl solution and heating. However, the major disadvantage of this process is the use of chlorine gas, which is a corrosive material (in the presence of water) and a highly toxic gas which requires a very effective trapping system. These disadvantages have somewhat discouraged the scale-up of this procedure for the production of higher quantities of $^{105}$Rh. In addition, the subsequent distillation of the oxidised product $RuO_4$, which is a highly toxic volatile chemical, also requires extreme precautions and a cumbersome trapping system. Although the system can be designed to trap both distilled $RuO_4$ and excess chlorine gas by the use of a series of HCl and NaOH solutions, the amount of liquid used in the traps would increase the volume of the radioactive waste, which mainly contains $^{103}$Ru ($T_{1/2}$ = 39.27 days). This would be a major disadvantage when scaling-up production.

A new separation procedure is reported here using magnesium oxide, MgO, as the adsorbent to purify no-carrier-added $^{105}$Rh in quantities of 10 to 100 mCi. The method eliminates the use of chlorine gas and the distillation of ruthenium tetraoxide, and has thus significantly increased the feasibility for scale-up (12).

## Production of $^{105}$Ru and $^{105}$Rh

Rhodium-105 was produced in quantities of 5 to 100 mCi at MURR using isotopically enriched $^{104}$Ru (99.08 per cent, natural abundance: 28.2 per cent). The thermal and epithermal capture cross-sections of $^{105}$Ru are 0.47 barns and 6 barns, respectively, while the burn-up thermal cross-section of $^{105}$Ru toward the formation of $^{106}$Ru is 0.3 barns. Rhodium-105 is produced from the radioactive decay of the $^{105}$Ru intermediate ($T_{1/2}$ = 4.44 hours) both during and after the irradiation. The irradiation samples were prepared by accurately weighing the target material into clean quartz vials, which were then sealed under vacuum. The sealed quartz vials were encapsulated in high purity aluminum capsules and loaded into reflector positions within the MURR reactor for 72 hour irradiations at neutron fluxes of $8 \times 10^{13}$ n cm$^{-2}$ s$^{-1}$. The irradiated samples were allowed to decay for more than 12 hours and processed in a dedicated glove box. For shorter irradiations, natural ruthenium metal and potassium ruthenate were used as target materials for process development. Ruthenium metal samples were prepared in quantities of 1 to 10 mg and sealed in high purity polyethylene vials (of diameter 11 mm and length 23 mm). These vials were embedded in Styrofoam cylinders to cushion shock and placed in high density polyethylene containers known as "rabbits" for neutron irradiation for up to 1 hour in the pneumatic tube facility at MURR. The activities of the $^{105}$Rh produced from these irradiations were in μCi quantities (less than 0.5 mCi).

## Separation and Purification of $^{105}$Rh

The irradiated ruthenium metal was placed into the $^{105}$Rh glovebox and transferred into a reaction vial which was connected to a trapping system containing HCl and NaOH solution. Sodium hypochlorite (NaOCl) (4 ml, 5 per cent) was added into the reaction vial and the mixture was stirred at room temperature for 30 minutes. About 2 ml of 2 M NaOH solution was added into the vial after the ruthenium target was dissolved. While stirring, 100 μl of 0.1 M magnesium chloride solution was carefully added into the ruthenium solution. The magnesium hydroxide suspension was then filtered through a 0.45 μm Teflon filter. After washing twice with water, the magnesium hydroxide precipitate and adsorbed $^{105}$Rh were dissolved with 0.5 M HCl in a new reaction vial. About 1 ml of NaOCl solution was added to the new vial and the $^{105}$Rh solution was stirred for 5 minutes. The $^{105}$Rh was re-precipitated on hydrous MgO on the addition of 1 ml of 5 M NaOH. The re-precipitated $^{105}$Rh and MgO were filtered, washed with water, and dissolved with 2 ml of 0.5 M HCl solution. This $^{105}$Rh solution was mixed with 1 ml of 4 M NaCl solution in a clean reaction vial and boiled for approximately 30 minutes. After cooling, the $^{105}$Rh solution was passed through a cation exchange column to remove Mg$^{2+}$. The final pH of $^{105}$Rh solution, as measured with pH paper, was ca. 1.

## Radioactivity Measurements

Aliquots of the sample were taken throughout the process and analysed to assess the recovery and radionuclidic purity of the $^{105}$Rh. Gamma spectra were obtained using an intrinsic hyperpure germanium (HPGe) spectrometer attached to a 4000 channel analyser. All fractions for spectral analysis were prepared as 10 ml solutions in glass scintillation vials.

Trace quantities of $^{103}$Ru in the $^{105}$Rh product processed from the enriched, irradiated ruthenium target were determined on the HPGe detector after the decay of $^{105}$Rh. Ruthenium decontamination factors were calculated by comparing the initial ratio of $^{103}$Ru:$^{105}$Rh prior to chemical separation to the ratio of $^{103}$Ru:$^{105}$Rh in the final $^{105}$Rh sample after the separation.

## Results

The radionuclide production resulting from the irradiation of an enriched ruthenium target in a reflector position in the MURR is shown in Figure 2.
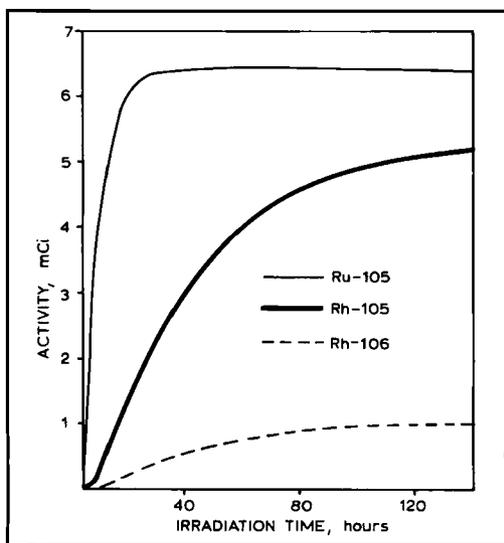
*Fig. 2* $^{105}Rh$ *production at MURR's Reflector Row-1 position (~ 6.5 × $10^{13}$ n $cm^{-2}$ $s^{-1}$) using 1 mg of enriched ruthenium metal ($^{104}Ru$ 99.05 per cent) as target material*

The average perturbed neutron flux at this position is about $6.5 × 10^{13}$ n $cm^{-2}$ $s^{-1}$. Ruthenium-105 reaches maximum activity after the first 20 hours of irradiation due to its short decay half-life ($T_{1/2}$ = 4.4 hours). Its decay product, $^{105}Rh$, gradually builds up and approaches saturation activity after 140 hours.

One important factor, which needs to be considered in the production, is that the product, $^{105}Rh$, has very high neutron cross-sections (thermal: $\sigma_{th}$ = 16,000 barns and epithermal: $\sigma_{epi}$ = 17,000 barns) and thus will tend to capture a neutron to form $^{106}Rh$, a short-lived radionuclide with $T_{1/2}$ = 30 seconds. Thus, $^{106}Rh$ is produced in fairly high quantity and the actual production yield of $^{105}Rh$ becomes significantly lower than the theoretical calculation which does not take into account such an "isotope burn-up" process.

The short-lived $^{105}Ru$ and $^{106}Rh$, produced during the production process of $^{105}Rh$, are allowed to decay before the irradiated samples are radiochemically processed. The maximum activity of $^{105}Rh$ is obtained about 14 hours after the end of irradiation (EOI), see Figure 3. This is, indeed, ideal "timing", since the short-lived and high dose rate radionuclides, such as $^{105}Ru$, $^{106}Rh$ and $^{31}Si$ (2.62 hours, from irradiation of the quartz vial) are decaying and

approaching their minimum quantities. The radiochemical separation of the samples can then usually begin 12 to 20 hours after the EOI.

Hydrous MgO adsorbed or co-precipitated rhodium(III) with very high efficiency. Rhodium-105 was collected and concentrated with a small quantity (typically ~500 µg) of solid MgO/ Mg(OH)$_2$ which was then readily separated from the alkaline solution containing radioactive ruthenate. Both natural and enriched $^{104}Ru$ metal targets were used to develop the MgO separation procedure, and the distillation procedure which uses chlorine gas was used as a control for comparison of method efficiency. A decontamination factor of 11,300 was obtained from this control procedure (distillation) using chlorine gas as the oxidant and a natural ruthenium target. The decontamination factor from the procedure employing hydrous MgO averaged 16,600 for both natural and enriched ruthenium targets, for over 3 trials each. Total $^{105}Rh$ recovery averaged above 85 per cent from either procedure.

## Discussion

The solution chemistry of ruthenium is complicated since, in most cases, ruthenium is present as more than one chemical species (13). Therefore it
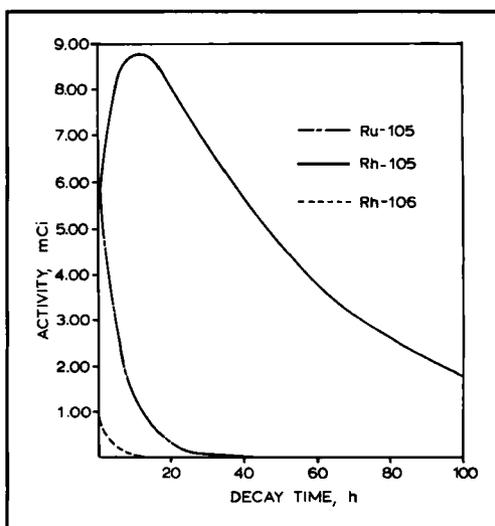


*Fig. 3 The decay of a ruthenium target after irradiation, showing that the maximum activity of $^{105}Rh$ is obtained ~ 14 hours after the end of the irradiation*

is necessary to use a multi-step separation procedure to remove these various ruthenium species. The use of MgO to separate the $^{105}$Rh from the Ru (ruthenate) solution followed by a re-precipitation and column separation step for purification of $^{105}$Rh seems to be a good choice. The decontamination factor obtained from this procedure was as good or better than that of the distillation procedure (control).

This new procedure is superior to the distillation procedure in terms of simplicity and the radionuclidic purity of the isolated $^{105}$Rh. In addition, this procedure can be readily scaled up to processing multi-curie quantities of $^{105}$Rh, because the use of hazardous materials, such as chlorine gas and volatile ruthenium tetraoxide, is avoided.

One important concept that this paper is intended to address is that there are always isotopic carriers and radiochemical contaminants present in a "pure" or "no-carrier-added" sample, which are produced during the currently available separation methodologies. Because of the trace quantity of the "no-carrier-added" radionuclide (the concentration for 10 mCi of $^{105}$Rh in 5 ml solution is about $2 \times 10^{-11}$ M), the major components or elements present in the product may not be the specific radionuclides of interest. The ratio of ruthenium:rhodium at the end of a 72-hour irradiation is calculated to be around 200,000, from a comparison of the number of atoms of $^{105}$Rh produced during the irradiation and the total number of ruthenium atoms available. The theoretical ratio of ruthenium:rhodium in the $^{105}$Rh sample separated from a ruthenium target using the MgO adsorption method is in the region of $\sim$ 12, assuming a decontamination factor of 16,600 is achieved.

In other words, in the separated $^{105}$Rh sample, the major metal element is ruthenium, rather than rhodium, even though nearly 100 per cent of the ruthenium has been chemically removed.

Additionally, it is probably worth mentioning that the $^{105}$Rh is recovered as a mixture of chloroaquorhodium (III) complexes. In dilute HCl solution where chloride [Cl$^-$] is less than 1 M, there is a mixture of $RhCl_4(H_2O)_2^-$, $RhCl_5(H_2O)^{2-}$, and $RhCl_6^{3-}$. $RhCl_3(H_2O)_3$ may also exist in the solution (14).

$$RhCl_3(H_2O)_3 \Leftrightarrow RhCl_4(H_2O)_2^- \Leftrightarrow$$
$$RhCl_5(H_2O)^{2-} \Leftrightarrow RhCl_6^{3-}$$
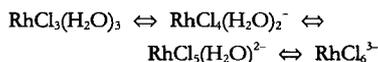
It has been reported that at high temperature ($> 50°C$) and at a high concentration of chloride ([Cl$^-$] = 1.5–3 M), the above reaction is effectively unidirectional toward the formation of $RhCl_5(H_2O)^{2-}$ and $RhCl_6^{3-}$ which may undergo aquation by the release of chloride to form neutral or cationic species when reaction conditions are changed (14). It is difficult, in most cases, to directly use the processed $^{105}$Rh for radiolabelling due to its unknown speciation. The problem of converting all rhodium chloroaquo complexes to one chemical form for the subsequent radiosynthesis with bifunctional ligands or proteins – in order to obtain a uniform product with high efficiency – remains.

## Conclusion

Rhodium-105 can be produced in quantities and purities suitable for radiotherapy research using a novel separation method based on MgO adsorption. The contamination from residual ruthenium does not apparently cause a problem for the practical use of $^{105}$Rh. Ruthenium removal is less an issue than making sure all the rhodium is in the same chemical form.

This adsorption method eliminates the use of chlorine gas and the production of ruthenium tetraoxide, and thus is desirable for use in large-scale isotope production. This will lead to the potential availability of $^{105}$Rh in multicurie quantities. However, at present no clinical trials are underway or are planned.

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# Pressure Tuning of a Platinum Kondo Insulator

The application of high pressures to a material can alter its internal interaction parameters, such as the magnetic and electronic effects, structures and densities, so that new solid state materials with useful properties may result. The high pressures affect the properties of a material, often giving it a completely new set of characteristics and behaviours. Pressure can be varied rapidly and be applied in particular directions, and thus be used to 'tune' the interaction parameters, and hence the properties. Thermoelectric materials are especially sensitive to pressure, so the use of pressure tuning techniques to study their thermoelectric properties and to search for new, improved semiconductor materials, is of interest.

One class of compounds known as Kondo insulators, which are semiconducting insulators with a narrow band gap energy, exhibiting intermediate valence properties, have some of the highest thermoelectric properties known. Scientists at Pennsylvania State University, Cornell University and the Carnegie Institution of Washington have now managed to pressure tune a neodymium-doped Kondo insulator, $Nd_xCe_{3-x}Pt_3Sb_4$, where $x = 0.27$ or $0.45$, so as to increase its thermoelectric properties significantly (J. F. Meng, D. A. Polvani, C. D. W. Jones, F. J. DiSalvo, Y. Fei and J. V. Badding, *Chem. Mater.*, 2000, **12**, (1), 197–201).

On placing $Nd_{0.45}Ce_{2.55}Pt_3Sb_4$ in an octahedral multi-anvil pressure cell, its thermopower was increased from 80 $\mu V\ K^{-1}$ near ambient pressure at 298 K to 100 $\mu V\ K^{-1}$ at 2 GPa. However, when it was compressed inside a nonhydrostatic diamond anvil cell, its electrical conductivity increased by a factor of 1.5–2 and its thermopower increased from 82 $\mu V\ K^{-1}$ at ambient pressure to a maximum of 263 $\mu V\ K^{-1}$ at 1.9 GPa. Upon further increase in pressure, the thermopower dropped and when the pressure was reduced hysteresis was seen, probably due to irreversible structural changes. No hysteresis occurs if pressure is only increased to produce the maximum thermoelectric power.

Pressure tuning can therefore act as an indicator of which materials, in this case thermoelectric materials, are worthy of chemical synthesis for further study at ambient pressures.

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