# RHENIUM RADIOISOTOPES FOR THERAPEUTIC RADIOPHARMACEUTICAL DEVELOPMENT*

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**Abstract.** Rhenium-186 and rhenium-188 represent two important radioisotopes which are of interest for a variety of therapeutic applications in oncology, nuclear medicine and interventional cardiology. Rhenium-186 is directly produced in a nuclear reactor and the 90 hour half-life allows distribution to distant sites. The relatively low specific activity of rhenium-186 produced in most reactors, however, permits use of phosphonates, but limits use for labelled peptides and antibodies. Rhenium-188 has a much shorter 16.9 hour half-life which makes distribution from direct reactor production difficult. However, rhenium-188 can be obtained carrier-free from a tungsten-188/rhenium-188 generator, which has a long useful shelf-life of several months which is cost-effective, especially for developing regions. In this paper we discuss the issues associated with the production of rhenium-186- and rhenium-188 and the development and use of various radiopharmaceuticals and devices labelled with these radioisotopes for bone pain palliation, endoradiotherapy of tumours by selective catheterization and tumour therapy using radiolabelled peptides and antibodies, radionuclide synovectomy and the new field of vascular radiation therapy.

## 1. INTRODUCTION

The availability of therapeutic radioisotopes at reasonable costs is important for applications in nuclear medicine, oncology and interventional cardiology. Rhenium-186 (Re-186) and rhenium-188 (Re-188) are two reactor-produced radioisotopes which are attractive for a variety of therapeutic applications. Rhenium-186 has a half-life of 90 hours and decays with emission of a β-particle with a maximum energy of 1.09 MeV and a 136 keV (9%) gamma emission which permits imaging. In contrast, Re-188 has a much shorter half-life of 16.9 hours and emits a β-particle with a much higher energy of 2.12 MeV ($E_{max}$) and a 155 keV gamma photon (15%) for imaging.

While Re-186 is unavailable from a generator system and must be directly produced in a nuclear reactor (Table 1), Re-188 can also be directly produced in a reactor with high specific activity, but is more conveniently and cost-effectively available as carrier-free sodium perrhenate by saline elution of the alumina-based tungsten-188 (W-188)/Re-188 generator system [1–2].

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TABLE I. PRODUCTION AND PROPERTIES OF RHENIUM-186 AND RHENIUM-188

| | **Rhenium-186** | **Rhenium-188** |
|---|---|---|
| Half-Life | 90 hours | 16.9 hours |
| Beta Particle, MeV | 1.09 | 2.12 |
| Gamma Photon, keV (%) | 136 (9%) | 155 (15%) |
| Direct Production Mode | $^{185}Re(n,\gamma)\ ^{186}Re$ | $^{187}Re(n,\gamma)\ ^{188}Re$ |
| Cross Section ($\sigma$) for Direct Production | 112 b | 76.4 b |
| Calculated Specific Activity — mCi/mg Target for 2-day Irradiation | | |
| $10^{14}$ neutrons/cm$^2$/sec | 500 | 600 |
| $10^{15}$ neutrons/cm$^2$/sec | 5000 | 6000 |
| Generator Production | None | $^{186}W(2n,\gamma)\ ^{188}W(\beta^-) \rightarrow\ ^{188}Re$ |
| Cross Section ($\sigma$) for Generator Parent Production | ..... | $^{186}W(n,\gamma)\ ^{187}W$ 37.9±0.6 b<br>$^{187}W(n,\gamma)\ ^{188}W$ 62±10 b |

## 2. PRODUCTION OF RHENIUM-186 AND RHENIUM-188

### *2.1. Rhenium-186*

One important advantage of using Re-186 is that it can be produced in many nuclear reactors throughout the world by direct neutron activation of enriched Re-185 (Figure 1), and the 90 hour half-life can often permit distribution to sites distant from the production facility. Which reactors can be used for routine production of Re-186 (Figure 2), and the shelf-life of Re-186 inventories, however, depend upon the specific activity requirements. While very high specific activity Re-186, for instance, is required for antibody and peptide radiolabelling [3], preparation of phosphonates for bone pain palliation [4] and use for intravascular radiotherapy for inhibition of coronary restenosis after angioplasty (*vide infra*) is possible with lower specific activity Re-186. The thermal neutron flux required for production of Re-186 will thus depend upon the particular application.

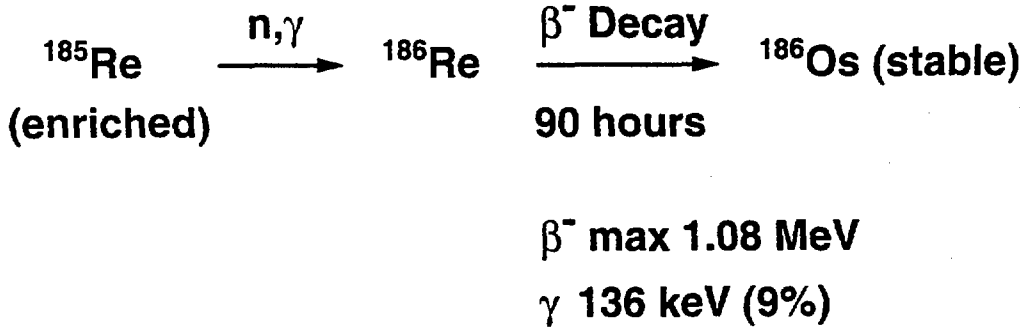


*FIG. 1. Reactor production of rhenium-186.*

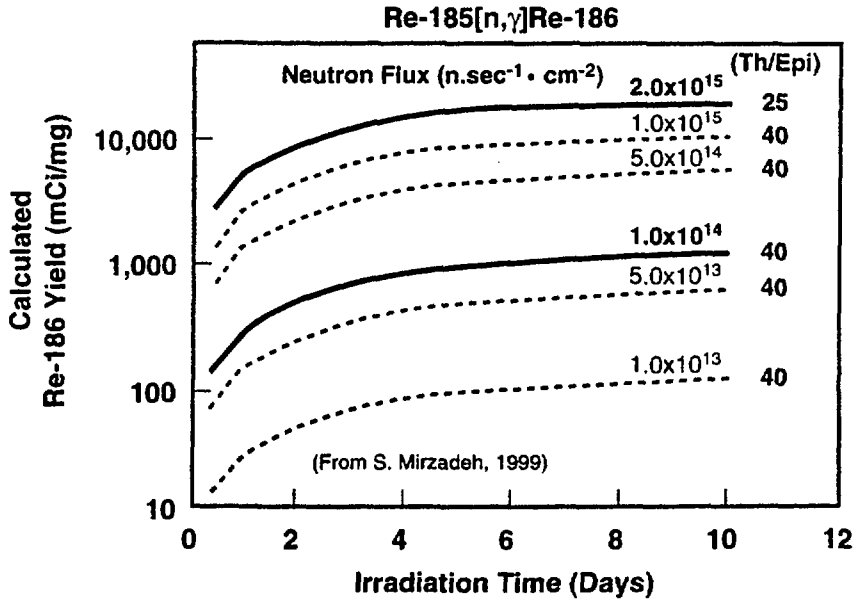


*FIG. 2. Calculated specific activity of reactor-produced rhenium-186 at various thermal neutron flux values.*

### *2.2. Rhenium-188*

Rhenium-188 can also be produced with relatively high specific activity by direct production in a nuclear reactor (Figure 3) by irradiation of enriched rhenium-187 (Figure 4). A major advantage for use of Re-188, however, is its carrier-free availability as Re-188-perrhenate from the W-188/Re-188 generator in the clinic at any time, since elution every 24 hours provides about 50% yields of Re-188. The availability of Re-188 on demand from this high performance generator provides great versatility for development of a range of Re-188-labelled therapeutic agents and the generators have a long useful shelf-life of > 6 months. Recent research and introduction of new agents labelled with rhenium radioisotopes has by far primarily focused on the use of Re-188 (Table 2).

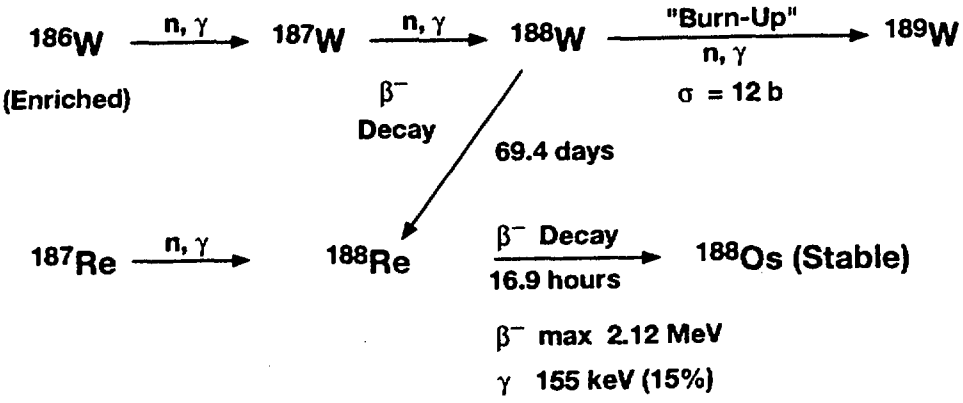


*FIG. 3. Reactor production and decay scheme for tungsten-188.*

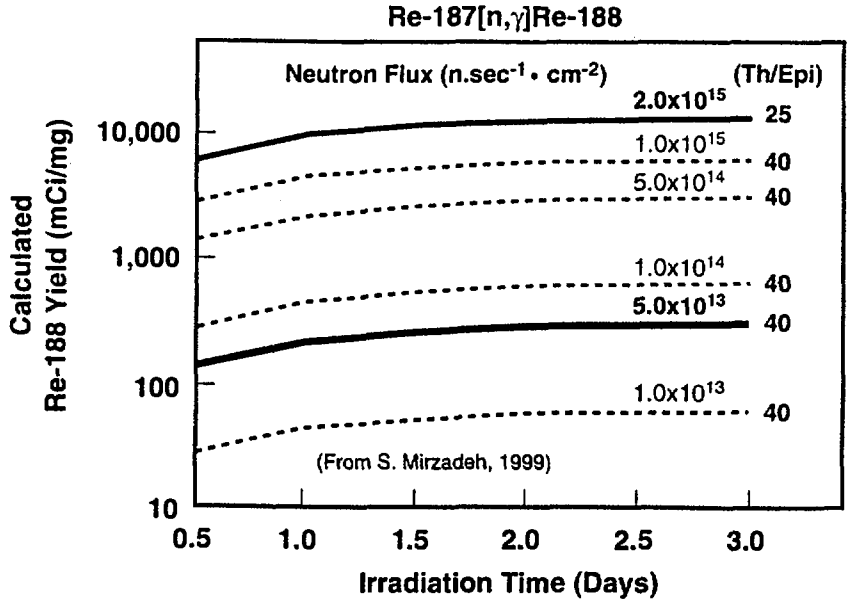


*FIG. 4. Calculated specific activity of "direct" reactor-production of rhenium-188 at various thermal neutron flux values.*

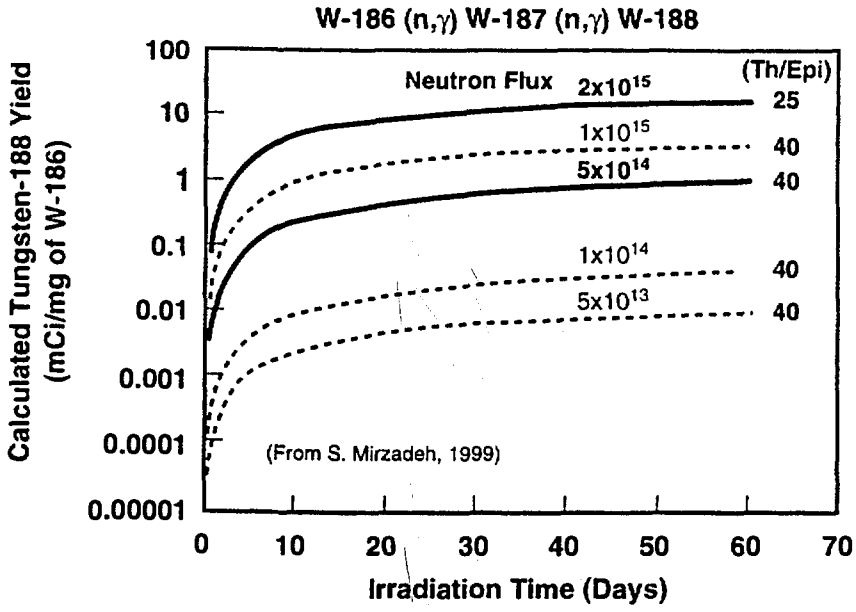


*FIG. 5. Calculated specific activity of reactor-produced tungsten-188 at various thermal neutron flux values*

Although there are only a few high flux reactors available for production (Figure 5) of the W-188 parent [5], the logistics for production and processing of W-188 and the distribution of the W-188/Re-188 can be easily coordinated. Use of inexpensive disposable tandem concentration units [6] is simple and provides very high specific volume solutions of Re-188 (i.e. > 700 mCi/mL from 1 Ci generator). The W-188/Re-188 generator is especially important for providing a reliable source of this versatile therapeutic radioisotope to remote sites, especially in developing regions, which involve long distances and expensive distribution costs.

## 3. THERAPEUTIC AGENTS FOR TREATMENT OF MALIGNANT DISEASE LABELLED WITH RHENIUM-186 AND RHENIUM-188

### *3.1. Agents for bone pain palliation*

Rhenium-186-*HEDP* is widely used in Europe for the palliative treatment of bone pain from skeletal metastases [4,7]. As alternatives, both Re-188-*HEDP* [8–10] and Re-188(V)-*DMSA* [11] have been developed for bone pain palliation. Patient studies with Re-188-*HEDP* are in progress in Bonn [8] and Dresden [9], Germany, in Montevideo, Uruguay [10], and several other sites, and the Re-188(V)-*DMSA* is being evaluated in patients at the Canterbury and Kent Hospital in Great Britain [11]. Imaging of the 155 keV gamma photon is an advantage which provides an opportunity for estimation of radiation dose to metastatic sites.

TABLE II. EXAMPLES OF CURRENT PRECLINICAL AND CLINICAL TRIALS WITH RHENIUM-188-LABELLED AGENTS

| Re-188 Agent | Application | Institution |
|---|---|---|
| Re-188-HEDP | Bone pain palliation | Bonn and Dresden Germany; Montevideo, Uruguay; Szeged, Hungary; Athens, Greece |
| Re-188-(V)-DMSA | Bone pain palliation | Kent and Canterbury Hospital, Great Britain |
| Re-188-Perrhenate | Endovascular radiation therapy | Cedars Sinai Medical Center, Los Angeles; Perth, Australia |
| Re-188-MAG3 | Endovascular radiation therapy | Columbia University, New York |
| Re-188-Peptides | Tumour therapy | Preclinical — Bonn, Germany |
| Re-188-Particles | Endoradiotherapy of Tumours — catheter administration | Preclinical — Dresden, Germany; Seoul, Republic of Korea; Kaichung, Taiwan (China) |
| Re-188-Labelled Antigranulocyte Antibodies | Marrow ablation prior to stem cell rescue | Ulm, Germany |

### *3.2. Labelled antibodies and peptides for tumour therapy*

Various tumour-specific antibodies have also been labelled with Re-186 and Re-188 [3,12]. More recently, somatostatin analogues radiolabelled with therapeutic radioisotopes are of interest for tumour treatment and the RC-160 somatostatin analogue has been directly labelled with Re-188 and evaluated in nude mice having human mammary gland, prostate and small lung cell carcinoma tumours resulting in significant reduction or elimination of the tumours [13]. The extremely short vascular stability of this agent, however, requires the direct tumour or cavity administration. More recently, the P829 and P773 peptides have been directly labelled with rhenium-188 and are being evaluated for therapy of non small cell lung tumours in a CD1 nu/nu nude mice tumour model [14].

### *3.3. Labelled particles for tumour therapy*

Rhenium-188-labelled particles (Table 3) are also being evaluated for direct tumour injection or for endoradiotherapy by administration to the tumour arterial supply *via* a catheter. In one study, Re-188-labelled Aminex A27 microspheres (15–20 μm) [15] were directly injected into tumours from N1-S1 hepatoma cells in the lobes of the livers of Sprague-Dawley rats. About 80 per cent of the treated rats survived over 60 days after intratumoural injection, while only about 26 per cent of the non-treated rats survived during the same time period. The stability of several other Re-188-labelled

microspheres has also been evaluated by incubation with human plasma and by biodistribution studies in rats [16]. The most favorable biodistribution properties were found for the Re-188-*B-20 HSA* microspheres (Mallinckrodt; 15–20 μm). The Re-188-labelled sulfur colloid is also simple to prepare [17], with a tight particle size range (86% = 5 μm) , with most activity retained in the liver *via* both intravenous and hepatic artery injection.

TABLE III. EXAMPLES OF RHENIUM-188-LABELLED PARTICLES BEING EVALUATED FOR TUMOUR THERAPY

| Particle | Size | Application | Refs. | Status | Comment |
|---|---|---|---|---|---|
| B20 HSA Particles | 15–20 microns | Endoradiotherapy of tumours | 15–16 | Preclinical | Dresden, Germany — Planning of Clinical Trials in Progress |
| Aminex A27 | 15 microns | Endoradiotherapy, Synovectomy | 19 | Preclinical | Taichung, Taiwan (China) |
| Sulfur Colloid | 1–5 microns | Endoradiotherapy, Synovectomy | 20 | Preclinical | Seoul, Republic of Korea; Taichung, Taiwan (China) |

## 4. THERAPEUTIC AGENTS FOR TREATMENT OF NON-MALIGNANT DISEASE LABELLED WITH RHENIUM-186 AND RHENIUM-188

### *4.1. Radiation synovectomy*

An important treatment of inflammatory disease is the use of Re-186-labelled sulfur colloid particles for therapy of rheumatoid arthritis of the synovial joints [18–19]. Rhenium-186-labelled particles are commercially available in Europe, for example, for this clinical application, but are not yet available in the USA. Because of expected cost effective on-site preparation in the nuclear pharmacy when required, several groups are also exploring the use of the Re-188-labelled particles for this application [20-22].

### *4.2. Intravascular radiation therapy*

We have also proposed and evaluated Re-188-labelled agents for the use of Re-188 liquid-filled angioplasty balloons inflated at low pressure following coronary angioplasty for the inhibition of coronary restenosis by high dose delivery [23–25]. Angioplasty balloons are filled at low pressure (2–3 atmospheres of inflation pressure) with a solution of Re-188-perrhenate or Re-188-*MAG3* following high pressure angioplasty to deliver a dose of 2500–3000 rad at 0.5 mm of depth. This application is expected to be important for the inhibition of the hyperplastic component of coronary restenosis. Swine studies have also demonstrated the inhibition of restenosis with the Re-188 liquid filled balloon approach after coronary overstretch injury [25] and patient studies are in progress at several Institutions in the USA, Europe and Australia (Table 2). The use of Re-186-liquid-filled balloons for restenosis therapy is also being evaluated [26].

## 5. SUMMARY AND CONCLUSIONS

Because of their attractive radionuclidic and chemical properties and relatively ready availability, rhenium-186 and rhenium-188 continue to be of interest for the radiolabelling of a variety of therapeutic agents for applications in nuclear medicine, oncology and interventional cardiology. The use of rhenium-188 is of particular interest, since the availability of the tungsten-188/rhenium-188 alumina-based generator system represents a convenient system to provide the rhenium-188 for a variety of therapeutic applications.

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