

*International Seminar on Therapeutic Applications of Radiopharmaceuticals (IAEA-SR-209),
Hyderabad, India, January 18-22, 1999, Invited, in press.*

RHENIUM RADIOISOTOPES FOR THERAPEUTIC RADIOPHARMACEUTICAL
DEVELOPMENT

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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 radioisotope 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 1.08 MeV and a 135 keV (9%) gamma 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, 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]. Since a comprehensive overview of Re-186 and Re-188 therapeutic agents is beyond the scope of this *Extended Abstract*, the goal is to provide key examples of various agents currently in clinical use and those which are being developed for important clinical applications.

Rhenium-186 - One important advantage of using Re-186 is that it can be produced in many nuclear reactors throughout the world, 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, 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 radiolabeling [3], preparation of phosphonates for bone pain palliation [4] and use for introvascular radiotherapy for inhibition of coronary restenosis after angioplasty is possible with lower specific activity Re-186.

Rhenium-188 - A major advantage of the W-188/Re-188 generator is the availability in the clinic of carrier-free Re-188-perrhenate 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-labeled therapeutic agents and the generators have a long useful shelf-life of > 6 months. Although there are only a few high flux reactors available for production 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.

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 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.

Labeled Antibodies and Peptides for Tumor Therapy - Various tumor-specific antibodies have also been labeled with Re-186 and Re-188 [3,12]. More recently, somatostatin analogues radiolabeled with therapeutic radioisotopes are of interest for tumor treatment and the RC-160 somatostatin analogue has been directly labeled with Re-188 and evaluated in nude mice having human mammary gland, prostate and small lung cell carcinoma tumors resulting in significant reduction or elimination of the tumors [13]. The extremely short vascular stability of this agent, however, requires the direct tumor or cavity administration.

Radiation Synovectomy - An important treatment of inflammatory disease is the use of Re-186-labeled sulfur colloid particles for therapy of rheumatoid arthritis of the synovial joints [14]. Rhenium-186-labeled particles are commercially available in Europe, for example, for this clinical application, but are not yet available in the U.S. 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-labeled particles for this application [15-16]

Labeled Particles for Tumor Therapy - Rhenium-188-labeled particles are also being evaluated for direct tumor injection or administration *via* the tumor arterial supply. In one study, Re-188-labeled Aminex A27 microspheres (15-20 μm) [17] were directly injected into tumors 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 intratumoral 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-labeled microspheres has also been evaluated by incubation with human plasma and by biodistribution studies in rats [18]. The most favorable biodistribution properties were found for the Re-188-*B-20 HSA* microspheres (Mallinckrodt; 15-20 μm). The Re-188-labeled sulfur colloid is also simple to prepare [15], with a tight particle size range (86 % = 5 μm), with most activity retained in the liver *via* both intravenous and hepatic artery injection.

Treatment of Non-Malignant Disease - We have also proposed and evaluated Re-188-labeled 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 [19-20]. 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 2,500-3,000 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 demonstrated the inhibition of restenosis with the Re-188 liquid filled balloon approach after coronary overstretch injury [20] and patient studies are in progress. The use of Re-186-liquid-filled balloons for restenosis therapy is also being evaluated [21].

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