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REACTOR PRODUCTION AND PROCESSING OF RADIOISOTOPES FOR THERAPEUTIC APPLICATIONS IN NUCLEAR MEDICINE

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Nuclear reactors continue to play an important role in providing radioisotopes for nuclear medicine [1]. Many reactor-produced radioisotopes are "neutron rich" and decay by beta-emission and are thus of interest for therapeutic applications. This talk discusses the production and processing of a variety of reactor-produced radioisotopes of current interest, including those produced by the single neutron capture process, double neutron capture and those available from beta-decay of reactor-produced radioisotopes (Table I). Generators prepared from reactor-produced radioisotopes are of particular interest since repeated elution inexpensively provides many patient doses [2]. The development of the alumina-based W-188/Re-188 generator system is discussed in detail.

Examples Produced by Single Neutron Capture - Rhenium-186 is a key example of a radioisotope of current interest which can be produced by neutron capture of enriched Re-185. Although the cross section for neutron capture by Re-185 is relatively high, the very high specific activity of Re-186 required for antibody labeling may not be achieved using many low flux reactors. However, low specific activity Re-186 can be used for preparation of phosphonates for palliative treatment of bone pain from cancer [3]. Samarium-153 can be produced with high specific activity in low flux reactors. Tin-117m is produced with low specific activity by neutron irradiation of enriched Sn-116. Specific activity have been increased in the ORNL High Flux Isotope Reactor (HFIR) by a factor of about 3 by the Sn-117(n, n', γ)Sn-117m inelastic route [4].

Examples Available From Beta-Decay of Reactor-Produced Radioisotopes - Another useful approach which provides carrier-free radioisotopes for therapy is "batch" chemical separation of the product formed by β^--decay of the reactor-produced parent. Examples produced via this route include Ag-111, As-77 and Au-199. Silver-111 is readily obtained by anion exchange chromatographic separation of Pd-111, and the 7.47 day half-life readily permits shipment to other sites. Silver can probably be

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complexed with functionalized tetraazaheterocycles for attachment to antibodies or other therapeutic agents. Arsenic-77, which is separated from the Ge-77 reactor product, has chemistry similar to phosphorus, permitting preparation of arsonates and other potentially useful species. The last example, gold-199, has been of interest for many years and in carrier-free form can be attached to antibodies.

TABLE 1. EXAMPLES OF REACTOR-PRODUCED RADIOISOTOPES OF CURRENT INTEREST FOR THERAPY

Radioisotope	Half-Life	Target	Application/Comment
Examples Produced by Single Neutron Capture:			
Re-186	3.77 days	Re-185	Antibodies/Bone Pain
Sm-153	1.93 days	Sm-152	Bone Pain
Sn-117m	13.6 days	Sn-116 or Sn-117	Bone Pain
Examples Formed by Beta Decay of Reactor-Produced Parent:			
Ag-111 (From Pd-111)	7.47 days	Pd-110	Antibodies
As-77 (From Ge-77)	1.62 days	Ge-76	Phosphorus Analogue
Au-199 (From Pt-199)	3.14 days	Pt-198	Antibodies
Examples Produced by Double Neutron Capture (Generator Parents"):			
W-188 (Re-188 Daughter)	69 days	W-186	Bone Pain Antibodies/Arthritis
Dy-166 (Ho-166 Daughter)	3.4 days	Dy-164	Arthritis/Bone Pain

Examples Produced by Double Neutron Capture (Generator "Parents") - Since yields of radioisotopes produced by the double neutron capture process are proportional to the square of the flux (σ^2), the reactor neutron flux is an important factor. Two radioisotope parents produced by this process which are of current interest for generator systems are W-188 (parent of Re-188) and Dy-166 (parent of Ho-166). Rhenium-188 is readily separated from W-188 on alumina (*vide infra*) and is of interest for a variety of therapeutic applications.

Holmium-166 can be produced directly from neutron irradiation of Ho-165 (monoisotopic in nature) but long-lived Ho-166m [half-life 1,200 years; 810 keV (57 %) and 712 keV (54 %) gammas, etc.] is also produced [5]. As an alternative, Dy-166 produced from Dy-164 provides carrier-free Ho-166

with no Ho-166m. Holmium-166 is separated by HPLC methods and is currently used for radiation synovectomy and has been proposed for use as an "*in vivo*" generator system [6, 7].

The Tungsten-188/Rhenium-188 Generator System - Since some of the most attractive therapeutic radioisotopes are those which are inexpensively available from generators, we have focussed our efforts on the W-188/Re-188 generator. It is of interest because the parent has a long half-life and Re-188 is an attractive radioisotope for a variety of therapeutic applications. Rhenium-188 has a 16.9 hour half-life, decays via β^- emission with a maximum β^- energy of 2 MeV (average = 745 MeV) and emits a 155 keV (15%) gamma photon suitable for imaging. A major advantage is availability of carrier-free Re-188-perrhenate by saline elution of W-188/Re-188 alumina generators [8, 9, 10] or tungsten-zirconium "gel" type generators [11, 12]. These systems can provide Re-188 at any time in the clinical setting, and the costs of Re-188 are expected to be low. Since the chemistry of Re(VII) is in general "similar" to Tc-(VII), many of the general approaches available for labeling agents with Tc-99m can also be adapted for use with Re-188.

Optimization of Reactor Production and Processing of Tungsten-188 - Significant amounts (20-50 %) of an unidentified black material are often found in the irradiated target after long irradiations. This material can be solubilized in 5% sodium hypochlorite/0.1 N NaOH. Alternatively, irradiated W-186-enriched W-metal targets dissolve in < 30% hydrogen peroxide and 1 N NaOH. Using either method (Table 2), large amounts (> 5 Ci/batch) of very high specific activity W-188 (10-12 mCi/mg W-186) are produced in the ORNL High Flux Isotope Reactor (HFIR) (flux = approx. 2×10^{15} neutrons/cm^2/sec) [13].

TABLE 2. PROCESSING OF TUNGSTEN-186-ENRICHED TUNGSTEN OXIDE AND METAL TARGETS

Target Material	Processing Method	Irradiation Period (Days)	Specific Activity (mCi/mg W-186)
W-186 Oxide	0.1 N NaOH	38 Days	6.22
W-186 Oxide	5 % NaOCl + 0.1 N NaOH	37.1 Days	8.57
W-186 Metal	30 % H_2O_2 + 0.1 N NaOH	43.4 Days	9.73

Performance of Tungsten-188/Rhenium-188 Generators - Large "Clinical Scale" generators (> 500 mCi) are now routinely prepared [9, 13]. Elution of the bolus through alumina "SepPaks^{R}" effectively removes low levels of W-188 breakthrough [14]. A typical generator (1.038 Curies W-188; 7 gm alumina) provides over 700 mCi (> 70% yield) of Re-188-perrhenate at equilibrium (30-35 mCi/ml) or about 500 mCi (20-25 mCi/ml) for sequential daily elutions (24 h ingrowth). Good Re-188 yields (70-80%) and low W-188 breakthrough (< 0.0001 %/bolus) are maintained over at least 60 days ("dry storage" minimizes radiolysis). Specific volume (mCi/ml) can be increased further using "tandem" systems by subsequent elution of the Re-188 generator bolus through anion or cation exchange columns to provide perrhenic acid solutions, allowing use of low specific activity W-188 available from low flux reactors [14, 16].

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