

Future Prospects for Medical Radionuclide Production in The High Flux Isotope Reactor (HFIR) at The Oak Ridge National Laboratory (ORNL)

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Research reactors continue to play an important role for the production of "neutron-rich" therapeutic radioisotopes which have important applications in nuclear medicine, oncology and interventional cardiology. Important applications include the palliative treatment of metastatic bone pain, tumor therapy, treatment of arthritis and the inhibition of coronary restenosis following balloon angioplasty. A variety of β -emitting therapeutic radioisotopes of current interest, such as holmium-166, lutetium-177 and rhenium-186, can be readily produced with low or moderate neutron flux reactors (i.e. thermal neutron flux $10^{13}\sim 10^{14}$ neutrons/cm²/sec) via the simple radiative neutron capture route (n, γ). A high thermal neutron flux of $>5 \times 10^{14}\sim >1 \times 10^{15}$ neutrons/cm²/sec or a significant epithermal component is required, however, for effective production of several important radioisotopes such as tin-117m, tungsten-188 and copper-67. Tungsten-188 is produced by double neutron capture of tungsten-186 and used in a generator system as the parent of rhenium-188 (16.9 h, 2.12 MeV), which is of wide interest as an inexpensive therapeutic radioisotope available on demand from the generator with a long useful shelf-life of several months. Tin-117m (15 days, conversion electrons) is used for preparation of tin (IV)-DTPA for bone pain palliation and is most effectively produced by the inelastic tin-117 (n, n', γ)

tin-117m route, while scandium-47 (3.42-day half-life, β -emitter) for preparation of radiolabeled antibodies for tumor therapy is a key example which can be produced by the titanium-47 (n, p) scandium-47 route. A high neutron flux is also an important advantage when target volume is limited, and allows production of higher specific activity products and conserves expensive enriched target isotopes. The ORNL High Flux Isotope Reactor (HFIR) has a very high thermal neutron flux of about 2.5×10^{15} neutrons/cm²/sec (85 MW) and represents a unique resource for the production of a wide variety of medical radioisotopes. The versatile target irradiation and handling facilities provide the opportunity for production of a wide variety of therapeutic radioisotopes of current interest. Key examples include californium-252, dysprosium-166, holmium-166, lutetium-177, rhenium-186, tin-117m and tungsten-188. The nine hydraulic tube (HT) positions in the central high flux region permit the insertion and removal of targets at any time during the 22-24 day operating cycle. To increase the irradiation capabilities of the HFIR, special target holders have recently been installed in the six Peripheral Target Positions (PTP), which are also located in the high flux region. These positions are only accessible during reactor refueling and are used for full cycle irradiations, such as required for the production of tin-117m and tungsten-188. Each of the six PTP tubes houses a maximum of eight HT target holders, which has increased the maximum number of HT targets from 9 to 57, significantly expanding the high flux target vol-

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ume by over 600%. In this paper the current and projected medical radioisotope production capabilities of the ORNL HFIR are discussed, and examples of evolving medical applications of reactor-produced radioisotopes are described.

Key words: therapeutic radionuclide, HFIR, ORNL

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Applications of Radioisotopes in Nuclear Medicine

Radioisotopes or “twinkling atoms” have important diagnostic and therapeutic applications in medicine. In radiation oncology, “sealed” sources are used for cancer therapy and “unsealed” radioisotopes (i.e. tissue specific radiopharmaceuticals) are widely used for important diagnostic and therapeutic applications in nuclear medicine, oncology and interventional cardiology. The Society of Nuclear Medicine estimates that about 35,000 diagnostic nuclear medicine procedures are conducted daily in U.S. hospitals. These 12-13 million annual tests play an important role in providing diagnostic information to referring physicians. The therapeutic use of radioisotopes in nuclear medicine, oncology and cardiology is the most rapidly growing application of medical radioisotopes [1-4]. Since most therapeutic radioisotopes are “neutron rich” and decay by beta emission and are thus reactor-produced, nuclear reactors, such as the High Flux Isotope Reactor (HFIR) at the Oak Ridge National Laboratory (ORNL), will continue to play an important role in providing radioisotopes for nuclear medicine. Generators prepared from reactor-produced radioisotopes are of particular interest since repeated elution inexpensively provides many patient doses [4-6]. This is expected to be especially important for providing a source of radioisotopes to remote sites, especially in developing regions, which involve long distances and expensive distribution costs. Since therapy is the major growth area in nuclear medicine, the increasing use of these therapeutic β -emitting radioisotopes in nuclear medicine, oncology and interventional cardiology, illustrates that nuclear reactors and the HFIR will play an increasingly

important role in providing therapeutic radioisotopes and parent radioisotopes for radionuclide generator systems which provide therapeutic radioisotopes for these applications.

Nuclear Reactors and Medical Radioisotopes

Nuclear reactors continue to play an important role in providing radioisotopes for nuclear medicine. In this paper, key examples of radioisotopes of current interest and those which are expected to become important in the near future are discussed. In addition, the availability of complementary technologies required for a variety of clinical applications, such as tumor-specific peptides and antibodies, especially for tumor therapy and bone pain palliation, require the cost-effective availability of high purity radioisotopes. The issues associated with the production and processing of several key reactor-produced radioisotopes of current interest are also discussed, including those produced by various production pathways. Generators prepared from reactor-produced radioisotopes are of particular interest [6] since repeated elution inexpensively provides many patient doses. The development of the alumina-based tungsten-188/rhenium-188 generator system is discussed as a key example of a simple system which provides the rhenium-188 therapeutic radioisotope for a variety of important therapeutic applications.

There is no doubt that nuclear reactors will continue to play an increasingly important role in providing therapeutic radioisotopes for both physician-sponsored investigational applications and the higher levels which are required for commercialization for broad distribution, especially with the increasing use of β -emitting radioisotopes in nuclear medicine, oncology and interventional cardiology. A recent summary by the International Atomic Energy Agency [IAEA, 7] indicates that 297 research reactors were operating throughout the world in 1994, although only a limited number have been used for medical radioisotope production. Although a variety of research reactors are operating which have low to moderate thermal neutron flux in North America, Europe and the former Soviet Union, Africa and South America, the general trend is that most of these reactors are 20-30 years old, and no new reactors are currently planned, for example, for construction in the U.S. Fortunately, countries where new

reactors are planned for construction include Canada, Australia, Germany, and the TRR II reactor, Taiwan, which will represent important new resources for medical radioisotope production.

The ORNL High Flux Isotope Reactor (HFIR)

The ORNL HFIR in Oak Ridge, Tennessee, and has the highest steady-state thermal neutron flux and the highest power density available in the world. The HFIR is a major resource for production of many medical radioisotopes which can often be produced with higher specific activity and higher production yields than elsewhere, and began operation in 1965. The nine axial hydraulic tube (HT) positions in the high flux core position permit the insertion and removal of targets at any time during the operating cycle, allowing great flexibility in production schedules. The maximal thermal neutron flux is about 2.5×10^{15} neutrons/cm²/sec at the central # HT 5 position. In addition to serving as a key production site for californium-252 and other transuranium ("heavy") isotopes, key examples of therapeutic radioisotopes which are currently produced in the HFIR for distribution include dysprosium-166, rhenium-186, tin-117m and tungsten-188 (parent of rhenium-188). The nine hydraulic tube (HT) positions in the central high flux region permit the insertion and removal of targets at any time during the operating cycle (22-24 days) and have traditionally represented a major site for the production of medical radioisotopes.

Because of the importance of having the HT positions available for short term irradiations and the practical importance of increasing the target size (mass), the Peripheral Target Positions (PTP), which are located in the high flux region, have recently been modified to accept long target containers, each of which will house eight individual HT target tubes. Since there are six PTP positions, the maximum number of HT targets housed in the PTP positions now totals 48, which represents nearly a seven-fold increase in the number of earlier 9 HT positions which were available. Since the PTP targets can only be accessed during refueling when the top of the reactor vessel is removed, these positions are only suitable for longer term, multi-cycle irradiations, which is particularly well suited for production of tungsten-188 and

tin-117m. The use of HT targets in the PTP tubes is an important advantage of this design, since it permits removal of the targets from the PTP tubes in the HFIR pool area, with subsequent transportation to the hot cell processing area using the same carrier which is currently in use. The HFIR was temporarily out of service for a six-month period beginning in October 2000, for replacement of the beryllium reflector - which is required every ten years - and for other upgrades, which will insure that this important reactor will be available for production of medical radioisotopes for at least another 30 year period.

Importance of Reactor-Produced Radioisotopes for Therapy

One of the most rapidly growing areas of clinical nuclear medicine is the therapeutic use of radioisotopes, and with the rapidly increasing development and evaluation of new agents and their introduction into clinical use and commercialization, the availability of high levels of the therapeutic reactor-produced neutron-rich radioisotopes is of increasing importance. A recent study by Frost & Sullivan (Journal of Nuclear Medicine, pp 14N-27N, July 1998) has projected that the 1996 revenue of \$ 48 million dollars from the U.S. therapy market is expected to increase to \$ 62 million dollars by the year 2000, and that therapy could represent as high as an incredible \$ 6 billion dollar market by the year 2020. Since this estimate does not include the expected widespread introduction of therapeutic radioisotopes for intravascular brachytherapy (IVB), the projected market figures could even be higher. Key examples of therapeutic radioisotopes of current interest and their specific clinical applications are summarized in Table 1.

Reactor-Production of Therapeutic Radioisotopes

Medical radioisotopes are produced in a nuclear reactor by a variety of mechanisms, based on different incident neutron particle reactions with the target nucleus. The production yields are dependent upon a variety of factors, primarily including the cross section, or probability of the neutron interacting with the target nucleus, and the neutron flux of the reactor. In this section, a few basic examples are used to

Table 1. Examples of reactor-produced radioisotopes of current interest for therapy

Radioisotope	Half-life	Target	Comment
Iodine-125	60 days	¹²⁴ Xe	Therapy of prostatic carcinoma
Lutetium-177	6.71 days	¹⁷⁶ Lu, ¹⁷⁶ Yb	High production yields - low energy beta for therapy
Scandium-47	3.42 days	⁴⁷ Ti	Substitute for ⁶⁷ Cu
Palladium-103	17 days	¹⁰² Pd	Therapy of prostatic carcinoma
Rhenium-188	16.9 hours	¹⁸⁷ Re (or from ¹⁸⁸ W generator)	Broad interest for palliation, tumor therapy, vascular radiation therapy, synovectomy, etc.
Rhenium-186	3.77 days	¹⁸⁵ Re	Antibodies/Bone pain palliation
Samarium-153	1.93 days	¹⁵² Sm	Bone pain palliation
Tin-117m	13.6 days	¹¹⁶ Sn or ¹¹⁷ Sn	Bone pain palliation
Gold-199 (From Platinum-199)	3.14 days	¹⁹⁸ Pt	Antibodies
Tungsten-188 (Rhenium-188 daughter)	69 days	¹⁸⁶ W	Bone pain/Antibodies/Synovectomy
Dysprosium-166 (Holmium-166 daughter)	3.4 days	¹⁶⁴ Dy	Synovectomy/Bone Pain

Table 2. Examples of medical radioisotopes of current interest produced by the (n, γ) radiative route

Target	Product	Comment
Palladium-102	Palladium-103	Encapsulated therapy - Prostate cancer/Cardiac stents
Rhenium-185	Rhenium-186	Cancer/Restenosis therapy
Rhenium-187	Rhenium-188	Cancer/Restenosis
Samarium-152	Samarium-153	Palliation of bone pain
Copper-63	Copper-64	High specific activity Example of positron emitter
Tin-116	Tin-117m	Palliation of bone pain

illustrate the production of various medical radioisotopes of current interest.

Examples Produced by Single Neutron Capture

The radiative capture of neutrons by target nuclei is by far the most common route for reactor production of medical radioisotopes. A large variety of radioisotopes produced by this route are of current interest, as shown in Tables 1 and 2. Rhenium-186 is a key example of a radioisotope of current interest which is produced by neutron capture of enriched rhenium-185. Although the neutron capture cross section is relatively high, very high specific activity rhenium-186 is often required for peptide/antibody labeling, which is not possible with low flux reactors. Although low specific activity rhenium-186 can be used for preparation of phosphonates

for palliative treatment of bone pain from cancer, for distribution to distant sites, high specific activity rhenium-186 is important. Samarium-153 is another reactor-produced radioisotope for bone pain palliation. Tin-117m is produced with low specific activity by neutron irradiation of enriched tin-116 in most reactors. Specific activity can be increased in the HFIR by a factor of about 3 by the inelastic tin-117 (n, n', γ) tin-117m inelastic route, as described later. Palladium-103 has been reactor-produced by irradiation of enriched palladium-102 and represents a major radioactive implantation device for the treatment of prostatic carcinoma. Theragenics, Inc., recently announced that they will invest > \$ 20 million in the Oak Ridge area to build a palladium-102 enrichment and palladium-103 processing facility and will use the ORNL HFIR for production of the palladium-103, which

will be used for development of radiolabeled therapeutic devices in addition to prostate therapy. More recently, lutetium-177m has become of interest for therapy, although it is a low beta energy emission, it can be produced in high specific activity, even in low to moderate flux reactors.

Examples Available from Beta-Decay of Reactor-Produced Radioisotopes

Another very useful approach which provides carrier-free radioisotopes for therapy even when high thermal neutron flux is not available, is the “batch” chemical separation of the no carrier added product which is formed by β -decay of the reactor-produced parent. Examples produced via this route are shown in Table 3, and include lutetium-177, which is of recent interest for radiolabeling octreotide peptide analogues which are internalized into the cell after receptor imaging. Relatively high lutetium-177 can be produced even in moderate flux reactors, but production of no-carrier-added lutetium-177 by decay of reactor-produced ytterbium-177 is an attractive alternative route when very high specific activity is required. In the some context, promethium-149 and ruthenium-105 are other attractive candidates for therapy which can be produced by similar beta decay routes from reactor-produced parent radioisotopes. Other examples include silver-111, arsenic-77 and gold-199. Silver-111 is readily obtained by anion exchange chromatographic separation of palladium-111, and the 7.47-day half-life readily permits shipment to other sites. Silver can be complexed with functionalized tetraazaheterocycles for attachment to anti-

bodies or other therapeutic agents. Arsenic-77 is readily separated from the germanium-77 reactor product and has chemistry similar to phosphorus, permitting preparation of arsonates and other potentially useful species.

Examples Produced by Double Neutron Capture and the Inelastic Neutron Reaction and (n, p) Routes

Since yields of radioisotopes produced by the double neutron capture process are proportional to the square of the flux, the reactor neutron flux is an important factor, and the HFIR has a key role in producing several important parent radioisotopes which are used for fabrication of radionuclide generators systems. Two radioisotope parents produced by this process which are of current interest for generator systems are tungsten-188 (parent of rhenium-188), discussed later, and dysprosium-166 (parent of holmium-166). Holmium-166 can also be produced directly from neutron irradiation of holmium-165 (monoisotopic in nature) but long-lived holmium-166m [half-life 1,200 years; 810 keV (57 %) and 712 keV (54 %) gammas, etc.] is also produced. As an alternative, dysprosium-166 produced from dysprosium-164 provides carrier-free holmium-166 with no holmium-166m. Although holmium-166 can be separated from dysprosium-166 by high performance liquid chromatography, this is not currently a practical approach since the parent is also eluted and must be reapplied to the system. Holmium is currently of interest for radiation synovectomy and tumor therapy. Rhenium-188 is readily separated from tungsten-188 on alumina (vide infra) and is of interest for a variety of ther-

Table 3. Examples of medical radioisotopes produced by beta decay of short-lived reactor products via the $[n, \gamma](\beta \rightarrow)$ route

Target	Intermediate Product	Carrier-Free Product	Half-Life (Days)
Ytterbium-176	Ytterbium-177	Lutetium-177	6.7
Neodymium-148	Neodymium-149	Promethium-149	2.21
Platinum-198	Platinum-199	Gold-199	3.14
Ruthenium-104	Ruthenium-105	Rhodium-105	1.47

Table 4. Examples of medical radioisotopes produced by the (n, p) reaction

Target	Product	Comment
Sulfur-32	Phosphorus-32	Therapy - Cancer/Restenosis
Titanium-47	Scandium-47	Interest for therapy (+3) Surrogate for copper-67
Zinc-67	Copper-67	Expensive target material Low production yields even at high flux

Table 5. Key examples of reactor-produced radioisotopes for bone pain palliation

Radioisotope	Half-Life (Days)	Beta Energy, MeV	Gamma Energy, keV (%)	Chemical Form For Clinical Use
Strontium-89	50.5	1.46	None	Ionic - Chloride
Phosphorus-32	14.3	1.71	None	Phosphate
Tin-117m	13.6	None, CE	159 (86 %)	Sn(IV)-DTPA
Samarium-153	1.93	0.81	103 (28 %)	EDTMP
Rhenium-186	3.71	1.08	137 (9.2 %)	HEDP
Rhenium-188	0.70	2.1	155 (15 %)	HEDP, Re(V)-DMSA

apeutic applications.

Production of medical radioisotopes by the (n, p) route is another method which provides no carrier added products, as shown in Table 4. The disadvantage is that the production yields can be low, as in the case of production of copper-67 using enriched zinc-67 targets, but often the yields are quite acceptable, as for the production of phosphorus-32 from sulfur-32 targets and the production of scandium-67 from the irradiation of enriched titanium-67 targets. Scandium-47 is also of interest as a surrogate for copper-67, which is not widely available, and is produced by the titanium-47 (n, p) scandium-47 route [3,8].

In contrast to the other radioisotopes of current interest for palliation [3,9], tin-117m decays by conversion electron emission (Table 1). The low energy conversion electrons travel only a very limited distance in tissue, and potential bone marrow depression, which can be a limiting factor with high energy β -emitting radioisotopes, is precluded. Potential advantages of tin-117m are the absence of high energy beta particles, the emission of a gamma photon of nearly optimal energy for imaging, and high metastatic uptake.

Production of tin-117m in nuclear reactor involves radiative capture by the (n, γ) route by irradiation of enriched tin-116, or via the inelastic (n, n', γ) route by irradiation of enriched tin-117. We have evaluated both these routes in detail using the ORNL HFIR [10]. Although specific activity values by either route are not high, the tin-117 target is now routinely used since the specific activity of tin-117m produced by this route is significantly higher than produced by irradiation of tin-116. Disadvantages for widespread use of tin-117m for bone pain palliation may thus be the expected high costs associated with the relatively low specific activity values, and the availability of only limited reactor sites

(HFIR) with sufficiently high neutron flux for production of this radioisotope. In the ORNL HFIR the production specific activity values of 8-10 mCi/mg from enriched tin-117 and long irradiation time (1 cycle = 24 days) are routinely obtained. The metallic powder target is shipped directly to customers for processing and preparation of the tin-117m (IV)-DTPA complex.

The Tungsten-188/Rhenium-188 Generator System

Since some of the most attractive therapeutic radioisotopes are those which are inexpensively available from generators, nuclear reactors will continue to play an important role in providing radioisotopes for both diagnostic and therapeutic applications in nuclear medicine. Radionuclide generator systems [11] prepared from reactor-produced parent radioisotopes are thus attractive to obtain the daughter products at facilities remote from the production site. For therapeutic applications, the rhenium-188 radioisotope (half-life 16.9 h; β_{max} 2.12 MeV; 15% gamma 155 keV suitable for imaging) has many attractive properties, since it is obtained carrier-free from the reactor-produced tungsten-188 parent (half-life 69 days). The tungsten-188/rhenium-188 generator is of interest because the parent has a long half-life and rhenium-188 is an attractive radioisotope for a variety of therapeutic applications. A major advantage is availability of carrier-free rhenium-188-perrhenate by saline elution of tungsten-188/rhenium-188 alumina generators [4-5], providing rhenium-188 at any time in the clinic and the costs of rhenium-188 are expected to be low. The chemistry of rhenium (VII) is similar to technetium(VII). The generator which we have developed and optimized at ORNL is a chromatographic system which uses alumina as the adsorbent [4-6]. A major important advantage for use of rhenium-188 is the

inexpensive, ready availability from the generator which has a very long useful shelf-life.

For production of the tungsten-188 parent, we have had extensive experience over the last several years in HFIR production of tungsten-188, from both enriched tungsten-186 tungsten metal and tungsten oxide targets [12,13]. The metallic powder targets are usually processed by oxidation with hydrogen peroxide and/or hypochlorite in the presence of base and oxide targets are dissolved in base with concomitant oxidation. The reactor production yields of tungsten-188 are about one order of magnitude lower than the calculated values using the published cross section values for the tungsten-186 (n, γ) tungsten-187 ($\sigma = 37.9 \pm 0.6$ barn) and for the tungsten-187 (n, γ) tungsten-188 ($\sigma = 64 \pm 10$ barn) reactions. The neutron burn-up cross section for the tungsten-188 (n, γ) tungsten-189 nuclear reaction is one factor which has been recently shown to contribute to the reduced production yields observed for tungsten-188. By irradiation of tungsten-188, a value of 12.0 ± 2.5 barns has been calculated for this neutron burn-up cross section [13]. Because of the relatively low density of powder targets and the limited space in the HT target holders, we have recently developed a pressed enriched tungsten-186 metal target configuration, where the density is increased by a factor of 8-10 [14]. Pressing and sintering ($> 1000^\circ\text{C}$) provides cylindrical targets that do not dissolve by the usual peroxide/hypochlorite oxidation methods but which are readily converted to tungsten oxide by heating under an air stream in a split-tube furnace. Subsequent dissolution in base then provides solutions of sodium tungstate. We estimate that greater than 1 kilo Curie of tungsten-188 per cycle can be produced in the HFIR using this new technology.

Clinical Applications of Reactor-Produced Therapeutic Radioisotopes

Examples of several representative important clinical applications of reactor-produced therapeutic radioisotopes include cancer treatment, palliative treatment of bone pain from metastases of cancer to the skeleton, treatment of arthritis of the synovial joints and the inhibition of arterial restenosis after high pressure balloon angioplasty. Ongoing research at ORNL and other research centers provides new

and improved methods for production and processing of radioisotopes which are required for both research and clinical use.

Bone Pain Palliation

One very important application of current interest which requires reactor-produced radioisotopes is focused on the palliative treatment of bone pain resulting from skeletal metastases [9,15,16], which is often encountered in patients with primary tumors of the breast, prostate and lung. Although many of these patients are often "end-stage", the quality of life can be significantly improved with the cessation of intractable pain. It is important to note that all of these radioisotopes used for bone pain palliation are reactor-produced and that HFIR-produced tin-117m, rhenium-186 and strontium-89 are currently provided to commercial customers from ORNL. The treatment of painful skeletal metastases is a common clinical problem and the use of therapeutic radioisotopes which localize at metastatic sites has been found to be an inexpensive and effective method for treatment of pain, especially for multiple sites for which the use of external beam irradiation is impractical. There are currently several metastatic-targeted agents radiolabeled with various therapeutic radioisotopes which are in various stages of clinical investigation (Table 5). Since neutron-rich radioisotopes are produced in research reactors and often decay by emission of β^- particles, most radioisotopes used for bone pain palliation are reactor-produced. Key examples produced by single neutron capture of enriched targets include rhenium-186 and samarium-153. In addition, generator systems which provide therapeutic daughter radioisotopes from the decay of reactor-produced parent radioisotopes are also of interest.

One important example is rhenium-188, available from generators via decay of reactor-produced tungsten-188 [17]. Tin-117m is an example of a reactor-produced radioisotope which decays with the emission of low energy conversion electrons rather than by β^- decay. Each of these agents and/or radioisotopes has specific advantages and disadvantages, however, the ideal agent for bone pain palliation has not yet been identified.

Vascular Brachytherapy

An emerging application which we have originally proposed and which is expected to have very important applications is the use of solutions of rhenium-188 agents for the inhibition of coronary artery restenosis following percutaneous transluminal coronary angioplasty (PTCA) [18,19]. This new and unique approach involves the low pressure intracoronary balloon expansion using solutions of rhenium-188, since solutions offer the most uniform vessel wall radiation dose delivery system. Production of tungsten-188 and yttrium-90 wires is also of interest for vascular therapy to inhibit restenosis after percutaneous transluminal angioplasty (PTCA). In addition, the new method (*vide infra*) involving angioplasty balloons filled with rhenium-188 available from our alumina-based generator from decay of tungsten-188 or rhenium-186 requires the dependable availability of these reactor-produced radioisotopes. The chemical species which are being evaluated for this application include rhenium-188-perrhenat, the rhenium-188-MAG₃ agent (MAG₃ = mercaptoacetyltriglycine) and rhenium-188-DTPA complex [20]. The use of these rhenium-188-labeled agents may be unique for balloon inflation, since the species are rapidly excreted via the urinary bladder in the unlikely event of balloon rupture [21].

Tumor Therapy

For use in one major type of cancer treatment, therapeutic radioisotopes are attached to antibodies or peptides which are specifically targeted to tumor cells after intravenous administration. This targeting approach delivers the radioisotope to the tumor cells where the radiation is localized and can destroy the tumor. A large variety of reactor-produced radioisotopes are being evaluated for this important application which are chemically converted to pharmaceutical species which are targeted to deliver the therapeutic radioisotope at the tumor site. High neutron flux is not required for the production of large amounts of many radioisotopes of current interest for these applications, such as lutetium-177, rhenium-186 and samarium-153. Broad interest has developed for the use of rhenium-188 for tumor therapy, because of the advantages of its availability from the tungsten-188/rhenium-188 generator, described later, and a

variety of targeting approaches are being evaluated [22-24].

Summary and Conclusions

There is no question that the use of unsealed radioisotopes for therapy is one of the major growth areas in nuclear medicine and that nuclear reactors are thus expected to play an increasingly important role in providing a variety of therapeutic radioisotopes and parent radioisotopes for radionuclide generator systems. The very high flux of the ORNL HFIR is a unique capability and represents an important resource for the production of radioisotopes which require a very thermal neutron flux, such as tungsten-188 and tin-117m. However, a variety of other research reactors with low or moderate neutron flux which are now operating or planned for construction nonetheless play a very important role in the production of a variety of medical radioisotopes which have important roles for therapeutic applications. Since the reduction of health care costs is a major issue throughout the world, the potential use of radionuclide generators which have a long shelf-life which would provide sufficient doses of a therapeutic radioisotope on a daily basis is an attractive capability. For this reason, interest in the use of rhenium-188 from the tungsten-188/rhenium-188 generator is rapidly growing and its commercialization as a radiopharmaceutical system and the possibility of its routine use in a hospital or centralized radiopharmacy are exciting possibilities.

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美國橡樹嶺國家實驗室 (ORNL) 高中子通率同位素反應器 (HFIR) 醫用同位素生產現況與展望

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研究用反應器生產治療用同位素扮演十分重要的角色，同時這些治療用同位素可廣泛應用於轉移性骨痛舒緩治療，腫瘤治療，滑膜液放射切除術及心臟血管狹窄放射治療等。鈦-166、鎳-177及銻-186等貝他同位素可以利用低中子通量反應器 (10^{13} - 10^{14} n/cm²/sec) 經由 (n, r) 核反應獲得，另外鎢-188、錫-117m及銅-67等同位素則需藉由高中子通量 (大於 5×10^{14} n/cm²/sec) 核反應獲得，其中鎢-188同位素之生產必須以鎢-186照射靶經二次中子核反應，然後以鎢-188鹼性溶液研製發生器，再滋生銻-188子核種 (半衰期16.9小時最高貝他2.12 MeV)，此方式所生產之銻-188放射液因生產過程簡易，價格便宜，比放射活度高，發生器可長久使用，甚具經濟價值。錫-117m (半衰期15天，放射內轉換電子)，可經由 (n, n', r) 核反應產生，再製備成錫 (IV)-DTPA標幟物後，應用於骨痛治療，於骨髓之吸收量小，副作用低。另外銦-47 (半衰期3.42天) 則可以銦-47為射靶，經 (n, p) 核反應生產，銦-47與單株抗體結合後可應用腫瘤治療。美國橡樹嶺國家實驗室高中子通率同位素反應器是一多功能研究用反應器，其最重要任務之一即是生產醫用同位素，包括銻-252、鎢-166、鎳-166、銻-186、錫-117m、鎢-188等。HFIR爐心照射設施包括有專為同位素生產之水送管照射設施乙支 (可放置9只照射靶)，其特點是可於反應器運轉期 (HFIR運轉週期為22~24天) 放置或取出照射靶。最近HFIR因應同位素擴量生產需求，於爐心周邊設計6套垂直照射設施 (每套可放置8只照射靶)，因此總計可提供57個照射靶位置，是目前可照射量的6倍，惟爐邊照射設施需要於停爐期間放置或取出照射物。本篇報告將討論HFIR生產核醫治療用同位素現況及其應用與展望。

關鍵詞：治療用放射性同位素，HFIR，ORNL

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