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The Development and Use of Radionuclide Generators in Nuclear Medicine - Recent Advances and Future Perspectives

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## ABSTRACT

Although the trend in radionuclide generator research has declined (FIG. 1), radionuclide generator systems continue to play an important role in nuclear medicine [1-3]. Technetium-99 $m$  obtained from the molybdenum-99/technetium-99 $m$  generator system is used in over 80 per cent of all diagnostic clinical studies and there is increasing interest and use of therapeutic radioisotopes obtained from generator systems. This paper focuses on a discussion of the major current areas of radionuclide generator research, and the expected areas of future research and applications.

### 1. The Molybdenum-99/Technetium-99 $m$ Generator

The easiest and preferred route for obtaining technetium-99 $m$  for radiopharmaceutical "kit" labeling is *via* elution of the chromatographic-type molybdenum-99/technetium-99 $m$  generator. Because technetium-99 $m$  is expected to continue to be the primary radioisotope used for imaging in diagnostic clinical nuclear medicine, the availability of molybdenum-99 is crucial to the radiopharmaceutical and clinical communities. In the more developed countries, fission-produced molybdenum-99 for is used for fabrication of the chromatographic-type molybdenum-99/technetium-99 $m$  generator [4]. Although until recently only one site provided most of the fission-produced molybdenum-99 for generator fabrication in North America, there are currently several new sites throughout the world producing this important radioisotope (Table 1). With these greatly increased availability of production and processing facilities, it is expected that the international demands for molybdenum-99 can be readily met.

Although the chromatographic-type generator using fission-produced molybdenum-99 would be the method of choice for obtaining technetium-99 $m$ , sublimation [5] and solvent extraction [6] techniques are still used in many parts of the world to obtain batches of technetium-99 $m$  where molybdenum-99 produced by neutron irradiation of enriched molybdenum-98 ( $n, \gamma$  route) is available as an alternative to fission-produced molybdenum-99. Solution methods using physiologically-compatible solutions are the safest and easiest methods for obtaining technetium-99 $m$ , since radiopharmaceutical "kit" labeling is solution-based. Although

solution-based generators are thus the method of choice, traditional chromatographic-type generators using alumina loaded with (n, $\gamma$ ) molybdenum-99 have been impractical for obtaining technetium-99m for "kit" labeling because of the low specific volume technetium-99m solutions. These dilute solutions result from the high volumes of eluant which are required to elute the bolus from the large generators required because of the low specific activity of the molybdenum-99. Although the use of (n, $\gamma$ ) molybdenum-99 has not been widely discussed in the recent literature, two approaches have been recently developed which may now make clinical use of such generators practical.

The use of the gel-type generator for low specific activity molybdenum-99 is based on the preparation of a zirconium gel by processing the irradiated molybdenum oxide target with zirconium oxide [7-9]. A similar strategy has been used successfully for the preparation of the gel-type tungsten-188/rhenium-188 generator. These generators are unique since the parent radioisotope is uniformly distributed throughout the gel matrix rather than being adsorbed on the top of the column bed as with the traditional chromatographic-type generators. Technetium-99m yields from this type of generator are reasonable.

Another alternative involves the post-column concentration of the low specific volume solutions of technetium-99m which are obtained from the chromatographic-type alumina generators loaded with low specific activity (n, $\gamma$ ) molybdenum-99. Two systems have been recently reported which use post-elution tandem cation/anion exchange system for technetium-99m concentration. Using these approaches, the high volumes required for generator elution do not represent a problem, since the solutions are subsequently easily and rapidly concentrated. The approaches are based on the selective anion trapping of the microscopic levels of the perrhenate anion following removal of the macroscopic levels of the anion of the generator salt eluant.

One method uses initial elution of the generator saline bolus through a strong cation resin cartridge which is impregnated with silver cations to trap all of the chloride anion as the insoluble silver chloride salt [10]. The cation column is attached in tandem with an amine-type anion column by connection with a three-way stopcock. (FIG. 2). As the silver is trapped on the silver-cation

column, the bolus solution then passes through the anion-exchange column. Since all of the chloride anion has been removed, the pertechnetate anion is specifically trapped on the anion column, with the bolus volume then passing through as waste. After adjusting the stopcock, the anion column can then be washed with water and the technetium-99m-pertechnetate subsequently eluted with a small volume of saline. Another advantage of this approach is that the useful shelf-life of the molybdenum-99/technetium-99m generator can be extended.

Another more recent approach is the unique use of salts of weak acids rather than physiological saline for elution of molybdenum-99/technetium-99m generators [11-13]. This technique is described in detail in an accompanying paper [14] and is based on the use of ammonium acetate, for instance, rather than sodium chloride solution, during fabrication and elution of the generator prepared from low specific activity (n, $\gamma$ ) molybdenum-99. The post-elution tandem system in this case consists of a strong cation ion column connected *via* a three-way stopcock with an amine-type QMA SepPak<sup>TM</sup> anion exchange column [14]. Passage of the generator bolus eluant through the cation column converts the ammonium acetate to a solution of acetic acid, which is not ionized at this pH, allowing selective trapping of the pertechnetate anion on the amine-based anion column as described above. This approach also works very efficiently for concentration of rhenium-188 solutions obtained from the tungsten-188/rhenium-188 generator (*vide infra*).

These two simple methods will now allow use of chromatographic-type alumina generators fabricated with low specific activity molybdenum-99. In this manner, many research reactors throughout the world can be used to produce the molybdenum-99 by neutron irradiation of enriched molybdenum-98 targets. Major advantages for the use of (n, $\gamma$ ) molybdenum-99 compared to fission-produced molybdenum-99 include the use of enriched molybdenum-98 targets rather than the expense and complex regulations associated with the use of highly enriched uranium (HEU) targets. In addition, the complex issues associated with the handling and storage of highly radioactive waste produced from fission of HEU is precluded. Finally, multiple research reactors throughout the world can be used for the (n, $\gamma$ ) molybdenum-99 production route without expensive capital improvements. Factors which must still be evaluated to determine the usefulness of this approach for the broad use of low specific activity

molybdenum-99 include insuring that the large target volumes which are required for irradiation of large targets are available, and that the large amounts of enriched molybdenum-98 which will be required will be routinely available.

### 3. Radionuclide Generators As Convenient Source of Therapeutic Radioisotopes

The use of therapeutic radioisotopes is one of the greatest growth areas in nuclear medicine and oncology, and also more recently, in interventional cardiology for the inhibition of arterial restenosis. Two radionuclide generators (Table 2) which are of current major interest provide yttrium-90 (strontium-90/yttrium-90) [15] and rhenium-188 (tungsten-188/rhenium-188) [16-19]. In oncology, in addition to the treatment of primary tumors with radiolabeled antibodies and antibody fragments, the use of radiolabeled somatostatin analogues and other small "targeting" molecules is an important area of clinical research [20]. Palliative treatment of bone pain with a variety of agents targeted for cortical localization and radiolabeled with different therapeutic radioisotopes provides an important cost effective alternative for treatment of patients with advanced metastatic disease to the skeleton which can dramatically improve their quality of life [21].

An important new therapeutic strategy in the realm of interventional cardiology is the use of beta and gamma-emitting radioisotopes for vascular brachytherapy for the inhibition of coronary restenosis after balloon angioplasty (PTCA) [22-24]. Most of the radioisotopes for this application are reactor-produced and generator-derived beta-emitting radioisotopes such as rhenium-188 and yttrium-90, are expected to have important applications. In addition, the use of equilibrium mixtures of strontium-90 and yttrium-90 provide a convenient long-lived source for this application and in a sense represent a unique example of an "*in vivo*" generator as described below (*vide infra*). Since the very small volumes (140-200  $\mu\text{L}$ ) for angioplasty balloon inflation require very high specific volume solutions of rhenium-188 (80-100 mCi/mL), the availability of the simple, effective methods described earlier are very important for concentration of the rhenium-188 bolus obtained from the tungsten-188/rhenium-188 generator, similar to those methods described earlier for concentration of technetium-99m from the molybdenum-99/technetium-99m generator (*vide ante*).

### 3. The "*In Vivo*" Generator - A Unique Application of the Generator Concept

Although not a new concept, the use of the *in vivo* generator is gaining increased attention. In this unique approach, usually following removal of the daughter, the parent radioisotope is attached to a tissue-specific targeting molecule. After administration and localization at the target site, the decay of the parent continually produces the therapeutic daughter radioisotope. If the "recoil" during decay of the parent does not destroy the parent/daughter-carrier association and the daughter-carrier bond is not impaired, this is an interesting and potentially important approach for targeted therapy [25]. Although there are several candidates (Table 3), recent research has demonstrated the feasibility of this approach with the dysprosium-166/holmium-166 pair [24].

### 4. Generators Providing Alpha Emitters - Growing Interest for Cancer Therapy

Because of short range, independence from dose rate and oxygen tension, and in particular the high linear energy of transfer (LET), alpha-emitting radioisotopes (Table 4) are of continuing interest for therapeutic applications. Because of the extremely localized deposition of high energy from alpha particles, the possibility of using alpha-emitting radioisotopes for cancer therapy is of great interest [27]. In particular, those alpha-emitters which have the appropriate radionuclide properties and are available from generator systems are of prime interest because of availability and expected cost effectiveness. Intensive research at several centers is currently focused on the bismuth-213 alpha emitter ( $T_{1/2} = 45.6$  min.) which is obtained by decay of the actinium-225 parent ( $T_{1/2} = 10$  days) [28] available from thorium-229, which is produced through the decay chain from uranium-233.

### 5. Molecular Nuclear Medicine - Targeting the Nucleus with Therapeutic Radioisotopes Available from Radionuclide Generator Systems - A New Challenge

An important new challenge for nuclear medicine is the possibility of targeting radioisotopes to the cell nucleus. As with all radiopharmaceutical agents, effective targeting is the major challenge. While techniques for stable attachment of most radioisotopes for both diagnosis and therapy are well established, the identification of the labeled carrier molecules which effectively target is still the major challenge, especially for therapeutic agents, to deliver the maximal dose to the target tissue while minimizing adsorbed dose to non-target tissues. This

strategy involves the attachment of specific radioisotopes with "tailored" radionuclidic properties to carrier molecules which effectively localize in the nuclei of targeted cells. In this manner, instead of using high energy beta emitters, low energy Auger emitters could be used for therapeutic applications, such as rhodium-103m ( $T_{1/2}$  65.1 m), which is available from the ruthenium-103/rhodium-103m generator fabricated from reactor-produced ruthenium-103 ( $T_{1/2}$  39 d).

### SUMMARY AND CONCLUSIONS

Although research and development with radionuclide generators is not currently as intense compared to 2-3 decades earlier, the need for high levels of generator-derived radionuclides is reflected in the resurgence of interest in the use of therapeutic radioisotopes from generator systems. The increasing applications and use of therapeutic radioisotopes in clinical nuclear medicine practice requires increasing access to generator-derived beta- and alpha-emitting radioisotopes, including yttrium-90, rhenium-188 and bismuth-213. As applications and use of these and other generator-produced radioisotopes increase, it would be expected that more efficient and automated generators will become available for routine widespread use.

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## FIGURE LEGENDS

- FIG. 1. Comparison of radionuclide generator publications from 1970 to 1998 (*Data from the U.S. Energy Science and Technology Database*).
- FIG. 2. Illustration of the tandem silver-cation/anion tandem system used for the concentration of low specific volume solutions of rhenium-188 and technetium-99m.

Table 1. Availability of Fission-produced Molybdenum-99 - 1998 <sup>§</sup>

Country for Production	Institution/Reactor	Approximate Curies Produced Per Week - 1998	Approximate Maximal Production Capacity Per Week
Canada	MDS-Nordion - NRU Reactor	60,000	> 120,000
The Netherlands	Mallinckrodt - Petten HFR Reactor	11,000	18,000
Belgium	IRE, Fleureus - Various European Reactors	3,500	....
South Africa	AEC , Ltd. - Pelindaba	400	2,400

<sup>§</sup> Data obtained from manufacturers, February 1998, which represent actual production Curies and not calibrated Curies.

Table 2. Examples of Key Radionuclide Generators of Current Interest Which Provide Therapeutic Daughter Radioisotopes

Parent	Daughter	Examples of Clinical Applications	Comment
Strontium-90	Yttrium-90	Tumor Therapy, Bone Pain Palliation, Intravascular Brachytherapy	Advantage - long-lived and readily available parent; disadvantage - bone seekers
Tungsten-188	Rhenium-188	Tumor Therapy, Bone Pain Palliation, Introvascular Brachytherapy	Advantage - efficient generator with long shelf-life; disadvantage - limited high-flux reactors for W-188 production
Dysprosium-166	Holmium-166	Tumor Therapy, Bone Pain Palliation, "In Vivo" Concept	Advantage - useful high energy beta; disadvantage - routine separation difficult
Actinium-225	Bismuth-213	Alpha Particle-Mediated Therapy - Myelogenous Leukemia	Advantage - alpha therapy very effective; disadvantage - limited range, specific applications

**Table 3. Examples of Parent-Daughter Pairs for Use with the *In Vivo* Generator Concept [23]**

Parent	Half-Life	Daughter	Half-Life
Dysprosium-166	81.6 hours	Holmium-166	26.4 hours
Lead-212	10.6 hours	Bismuth-212	60.6 minutes
Nickel-66	2.52 hours	Copper-66	5.1 minutes
Palladium-112	21.64 hours	Silver-112	3.13 hours

**Table 4. Examples of Radionuclide Generators Providing Alpha-Emitting Daughters**

Parent	Half-Life	Daughter	Half-Life	Daughter	Half-Life
Thorium-228 → Radium-224	3.7 days	Lead-212	10.6 hours	Bismuth-212	60.6 Minutes
Uranium-223 → Thorium-229	7,340 years	Actinium-225	10.0 days	Bismuth-213	45.6 minutes

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