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## Generator-produced Alpha-emitters

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This review briefly describes the nuclear characteristics and production parameters for 7.2-h  $^{211}\text{At}$ , 60.6-min  $^{212}\text{Bi}$ , 45.6-min  $^{213}\text{Bi}$ , 11-d  $^{233}\text{Ra}$ , and 20-h  $^{255}\text{Fm}$ . These  $\alpha$ -emitting radioisotopes are the subject of current interest for  $\alpha$ -particle-mediated radioimmunotherapy.

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### Introduction

Alpha particles are of considerable interest for radioimmunotherapy applications. Due to their short range in tissue (a few cell diameters), and high linear-energy-transfer (LET),  $\alpha$ - particles are especially suited for targeting micrometastases and single tumor cells such as leukemia and other blood-borne diseases (Bloomer *et al.*, 1984, Ruegg, *et al.*, 1990, Huneke, *et al.*, 1992, Junghans, *et al.*, 1993, Hartmann, *et al.*, 1994, Kennel and Mirzadeh, 1997, Scheinberg, 1997). The list of potential radionuclides for these applications includes only five  $\alpha$ -emitting radioisotopes, namely  $^{211}\text{At}$  ( $t_{1/2} = 7.2$  h),  $^{212}\text{Bi}$  ( $t_{1/2} = 60.6$  m),  $^{213}\text{Bi}$  ( $t_{1/2} = 45.6$  m),  $^{233}\text{Ra}$  ( $t_{1/2} = 11$  d), and  $^{255}\text{Fm}$  ( $t_{1/2} = 20$  h). A list of the generator-produced  $\alpha$ -emitters and the corresponding references are given in

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Table 1. The nuclear decay characteristics of  $^{211}\text{At}$ ,  $^{212}\text{Bi}$ ,  $^{213}\text{Bi}$ ,  $^{233}\text{Ra}$  and  $^{255}\text{Fm}$  are summarized in Table 2. The very short half lives of  $^{212}\text{Bi}$  and  $^{213}\text{Bi}$  limit the use of these radioisotopes to situations in which targeting is rapid, such as in leukemia (Scheinberg, D. A. *et al.*, 1997). Most recently, applications with vascular targeting antibodies for the treatment of lung cancer have also been reported (Kennel and Mirzadeh, 1997).

$^{211}\text{Rn}(14.6 \text{ h}) \rightarrow ^{211}\text{At}(7.2 \text{ h})$ . Astatine-211 can be produced through the decay of 14.6 h  $^{211}\text{Rn}$ . The  $^{211}\text{Rn}$ , in turn, is produced through a number of nuclear reactions which are summarized in Table 3. The corresponding references are also given in this table. These reactions include spallation of Th with high energy protons having a cross-section of 0.7 mb at 28 GeV protons or by photo-spallation of Th with a cross-section of 0.13 mb at a photon energy of 300 MeV. The production of  $^{211}\text{Rn}$  by the  $^{209}\text{Bi}[^6\text{Li},4n]^{211}\text{Rn}$  reaction, with a  $\sigma_{\text{max}} = 0.7 \text{ b}$  at  $E_{\text{Li}} = 54 \text{ MeV}$  and yield of  $\sim 2 \mu\text{Ci/nA}$  at  $\frac{1}{2}$  saturation, has also been reported. By far, the predominant nuclear reaction for the production of  $^{211}\text{At}$ , however, is not through a generator system but by direct activation of  $^{209}\text{Bi}$  with 28 MeV  $\alpha$  particles. The maximum of the excitation function for this reaction is  $\sim 1 \text{ b}$  at  $E_{\alpha} = 29 \text{ MeV}$ . In order to minimize the production of radiocontaminant  $^{210}\text{Po}$ , the  $\alpha$ -particle should exit the Bi target at  $E_{\alpha} = 20 \text{ MeV}$ , limiting the Bi thickness to only  $100 \mu\text{g}\cdot\text{cm}^{-2}$ . The typical yield is  $\sim 1.5 \text{ mCi}/\mu\text{A}$  at half saturation ( $\sim 3.5$  hours of irradiation). Since there are only a few cyclotrons in the U.S. capable of accelerating  $\alpha$ -particles to  $\sim 28 \text{ MeV}$ , the required energy for the production of  $^{211}\text{At}$  via the  $^{209}\text{Bi}[\alpha,2n]$  reaction, the availability of  $^{211}\text{At}$  is also very limited. There are a number of procedures reported for extracting  $^{211}\text{At}$  from an irradiated Bi target, and a recent review of the subject is available (Ruth et al, 1988). The dry distillation method is the most convenient approach and it has been described in detail elsewhere (Lambrecht and Mirzadeh, 1985).

$^{224}\text{Ra}(3.7 \text{ d}) \rightarrow ^{212}\text{Pb}(10.6 \text{ h}) \rightarrow ^{212}\text{Bi}(60.6 \text{ min})$ . Bismuth-212 is available from the  $^{224}\text{Ra}/^{212}\text{Bi}$  generator system, where  $^{224}\text{Ra}$  is the daughter of 1.9-y  $^{228}\text{Th}$ . Th-228 is the second member of the  $^{232}\text{Th}$  decay chain and it is also the decay product of  $^{232}\text{U}$  (Fig. 1a). Ra-228 ( $t_{1/2} = 5.8 \text{ y}$ ) can be extracted from  $^{232}\text{Th}$ , purified, then allowed to decay to  $^{228}\text{Th}$ . Each ton of 30-year old  $^{232}\text{Th}$  yields  $\sim 100 \text{ mCi}$  of  $^{228}\text{Ra}$ . Th-228, however, can be produced from successive neutron capture and  $\beta^-$  decay of  $^{226}\text{Ra}$  (Fig.2). This irradiation has been demonstrated in the past to be feasible. However, additional process development is needed to determine production yields and cost. Figure 3 depicts the theoretical production yields of both  $^{228}\text{Th}$  and  $^{229}\text{Th}$  at the ORNL High Flux Isotope Reactor

(HFIR) as a function of irradiation time at a neutron flux of  $1 \times 10^{15} \text{ n.s}^{-1} \cdot \text{cm}^{-2}$ . For one cycle irradiation (~24 days), the yield of  $^{228}\text{Th}$  is ~45 mg (37 Ci) per gram of  $^{226}\text{Ra}$ . The major drawback for the use of  $^{212}\text{Bi}$  is the emission of relatively intense and very high energy  $\gamma$ -rays (2.6 MeV, 38%).

In the current generator system,  $^{224}\text{Ra}$  separated from  $^{228}\text{Th}$  is adsorbed on an organic cation exchange resin (highly cross-linked MP-50, ~300  $\mu\text{L}$  in volume), and the  $^{212}\text{Pb}$  and  $^{212}\text{Bi}$  mixture is eluted with a few mL of 2 M HCl or 0.5 M HI with ~70% yield and parent breakthrough of  $10^{-6}$ . It is also possible to elute  $^{212}\text{Bi}$  (free from  $^{212}\text{Pb}$ ) selectively with 0.5 M HCl or 0.15 M HI. The  $^{224}\text{Ra}/^{212}\text{Pb}/^{212}\text{Bi}$  generator has a shelf-life of about two weeks, and 10-mCi generators are routinely available from Argonne National Laboratory (ANL).

Unfortunately, radiolytic effects limit the scale of the current organic resin-based  $^{224}\text{Ra} \rightarrow ^{212}\text{Pb} \rightarrow ^{212}\text{Bi}$  generator to levels insufficient for clinical use. Evaporation (emanation)-based generator systems were developed to overcome this problem (Hursh and Lovaas, 1967, Norman *et al.*, 1991, and Hassfjell and Hoff 1994). At a 1-mCi activity level, the fraction of  $^{212}\text{Pb}$  recovered was decreased from 50% to 10% over a one-year period. No absolute values were given for the breakthrough of the Th, but it was stated that Th was not detected in the final solution (Hassfjell and Hoff 1994).

$^{225}\text{Ac}(10.0 \text{ d}) \rightarrow ^{213}\text{Bi}(45.6 \text{ min})$ . Among the potential candidates,  $^{213}\text{Bi}$  is well suited to clinical applications as  $^{213}\text{Bi}$  labeled monoclonal antibody (MAb) and has recently entered phase I of human trial against leukemia (Sheinberg, 1997). MAb targeting  $^{213}\text{Bi}$  to lung vasculature has also been successful in the therapy of lung tumors in mice (Kennel and Mirzadeh, 1997). Bismuth-213 decays with a  $t_{1/2}$  of 45.6 min and emits an 8.4 MeV  $\alpha$ -particle 97.8% of the time. The decay of  $^{213}\text{Bi}$  follows with the emission of rather low intensity  $\gamma$ -rays; 440 keV (26%) and 1566 keV (2%). Similar to the  $^{224}\text{Ra} \rightarrow ^{212}\text{Bi}$  pathway, carrier-free  $^{213}\text{Bi}$  is available from the  $^{225}\text{Ac}/^{213}\text{Bi}$  generator system with  $^{225}\text{Ac}$  ( $t_{1/2} = 10 \text{ d}$ ) being the  $\beta^-$ -decay daughter of 14.8-d  $^{225}\text{Ra}$ . Ra-225 is the daughter of 7340-y  $^{229}\text{Th}$  which, in turn, is the decay daughter of long-lived  $^{233}\text{U}$ , Fig. 1b. A unique aspect of  $^{233}\text{U}$  is its availability at the National Repository of  $^{233}\text{U}$  which is located at ORNL. U-233 was produced at ORNL in 1960's and 1970's as part of a molten salt breeder reactor program. Currently, the  $^{233}\text{U}$  is in long-term storage with no immediate or anticipated need. It is estimated that from  $^{233}\text{U}$  stockpile, ~12 g (~2.5 Ci) of  $^{229}\text{Th}$  can be extracted.

Th-228 can also be produced from neutron transmutation of a  $^{226}\text{Ra}$  target (Fig. 2). The yield of  $^{229}\text{Th}$  is on the order of 7 mg (~150 mCi) per g of  $^{226}\text{Ra}$  for 24 days irradiation at a neutron

flux of  $1 \times 10^{15}$  n.s<sup>-1</sup>.cm<sup>-2</sup>, with a thermal to epithermal ratio of 10 (Fig. 3). Note that under these conditions, the mass of the contaminant <sup>228</sup>Th produced is ~4 times larger than that of <sup>229</sup>Th (the activity ratio is 250). Nevertheless, high purity <sup>225</sup>Ac can be obtained from the mixture by initially extracting Ra from Th and allowing the 3.7-d <sup>224</sup>Ra to decay (10-15 days) then extracting <sup>225</sup>Ac from the Ra mixture. Note that the <sup>224</sup>Ra  $\alpha$ -decays to <sup>220</sup>Rn with no  $\beta^-$ -decay to <sup>224</sup>Ac.

It is also possible to produce <sup>225</sup>Ac from proton and deuteron irradiation of <sup>226</sup>Ra, [p,2n] and [d,n] reactions (see Fig. 2). The author is not aware of any reported excitation functions for these reactions.

Although <sup>233</sup>U is the only viable source for high purity <sup>229</sup>Th, the anticipated difficulty with <sup>233</sup>U safeguards led us to look at the possibility of extracting Th from pre-existing processing waste of <sup>233</sup>U. After extensive purification, ~65 mCi of low specific activity (~0.4%) <sup>229</sup>Th has been recovered and 20 mCi of <sup>225</sup>Ac is available for sale through the ORNL Isotope Distribution Office on a bi-weekly schedule.

The chemistry of the <sup>225</sup>Ac/<sup>213</sup>Bi generator is also similar to that described for the <sup>212</sup>Bi generator. However, the lower cross-linked resin was found to be more suitable for rapid elution of <sup>213</sup>Bi from the generator with <sup>225</sup>Ac breakthrough of <1%. A summary of the <sup>213</sup>Bi yield and <sup>225</sup>Ac and <sup>225</sup>Ra breakthrough values are given in Table 4 (Boll and Mirzadeh, 1997). As indicated in the last column, the breakthrough of Ra in AG 50WX4 resin was substantially higher than Ac breakthrough. Thus it follows that in order to reduce the potential contamination of <sup>213</sup>Bi with Ra, the Ac generator-load solution should contain a low fraction of Ra. At the 2-3 mCi level, the radiolytic degradation of organic resin limits the useful shelf-life of a generator to about one week.

<sup>227</sup>Th(18.7 d)  $\rightarrow$  <sup>223</sup>Ra(11.4 d). The <sup>227</sup>Th/<sup>223</sup>Ra system is a part of the actinium series and <sup>227</sup>Th is produced from  $\beta^-$  of 21-y <sup>227</sup>Ac. The <sup>227</sup>Ac can be extracted from <sup>235</sup>U or it can be produced by irradiation of <sup>226</sup>Ra target in a reactor by the <sup>226</sup>Ra[n, $\gamma$ ]<sup>227</sup>Ra ( $\beta^-$ , 42 min)  $\rightarrow$  <sup>227</sup>Ac reaction (Fig. 2). The irradiation route has high yield and eliminates the problem associated with the <sup>235</sup>U safeguards (Fig. 3). There are, however, two major difficulties with <sup>223</sup>Ra. The first is the lack of suitable chelating molecule for attachment of <sup>223</sup>Ra to monoclonal antibodies. The second concern is with the decay characteristic of this isotope. As indicated in Table 2, the third decay product of <sup>223</sup>Ra is the <sup>211</sup>Pb which has a half-life of 36 minutes. The kinetic energy imparted to <sup>211</sup>Pb due to  $\alpha$ -emission ejects the <sup>211</sup>Pb atom from the original carrier molecule and leaves the <sup>211</sup>Pb atom highly charged and reactive (Mirzadeh, 1993). A portion of unbound <sup>211</sup>Pb, having

sufficient time to re-enter the blood stream, results in a substantial dose to the non-targeted tissues. Note that  $^{211}\text{Pb}$  is a highly potent  $\alpha$ -emitter as well (see Fig. 1c).

$^{255}\text{Es}(40\text{ d}) \rightarrow ^{255}\text{Fm}(20.1\text{ h})$ . Among the potential candidates,  $^{255}\text{Fm}$  (the daughter of 40-d  $^{255}\text{Es}$ , a transuranium radioisotope) has the most convenient half-life, but it is doubtful that useful quantities of this radioisotope will be made available within the foreseeable future.

In summary, methods have been demonstrated for large scale production of  $\alpha$ -emitters for medical applications with the exception of  $^{255}\text{Fm}$ . Over the next few years, it is expected that clinical generators for in-house production of the short-lived  $^{212}\text{Bi}$  and  $^{213}\text{Bi}$  will be made available.

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### Figure Captions

- Figure 1. (a) Decay chain of  $^{228}\text{Th}$  (Thorium Series) , (b) Decay chain of  $^{229}\text{Th}$  (Neptunium Series), and (c) Decay chain of  $^{227}\text{Th}$  (Actinium Series). Minor branches are not shown.
- Figure 2. Reactor production of  $^{227}\text{Ac}$ ,  $^{228}\text{Th}$  and  $^{229}\text{Th}$  from  $^{226}\text{Ra}$  target.
- Figure 3. Theoretical production yields of  $^{227}\text{Ac}$ ,  $^{228}\text{Th}$  and  $^{229}\text{Th}$  from 1 g of  $^{226}\text{Ra}$  as a function of irradiation time at a neutron flux of  $1 \times 10^{15} \text{ n.s}^{-1} \cdot \text{cm}^{-2}$ , ( $t/\text{epi}=10$ ).

**Table 1. Generator-Produced Alpha-emitters**

Parent/daughter pair	Reference
$^{211}\text{Rn}(14.6 \text{ h}) \rightarrow ^{211}\text{At}(7.2 \text{ h})$	Mirzadeh and Lambrecht (1987), Meyer and Lambrecht (1980), Visser <i>et al.</i> (1979).
$^{224}\text{Ra}(3.7 \text{ d}) \rightarrow ^{212}\text{Pb}(10 \text{ h}) \rightarrow ^{212}\text{Bi}(60 \text{ m})$	Atcher <i>et al.</i> (1987), Hassfjell and Hoff (1994) Zucchini and Friedman (1982),
$^{225}\text{Ra}(14.8) \rightarrow ^{225}\text{Ac}(10.0 \text{ d}) \rightarrow ^{213}\text{Bi}(45.6 \text{ m})$	Boll and Mirzadeh (1997), Sitnikov <i>et al.</i> (1996)
$^{227}\text{Th}(18.7 \text{ d}) \rightarrow ^{223}\text{Ra}(11.4 \text{ h})$	Mani, 1987
$^{255}\text{Es}(40 \text{ d}) \rightarrow ^{255}\text{Fm}(20.1 \text{ h})$	Mirzadeh <i>et al.</i> , 1992

**Table 2. Decay properties of radionuclides with potential use in alpha-particle-mediated radioimmunotherapy**

Radio-nuclide	Half-life	Decay mode (%) <sup>a</sup>	Decay product	Av. $E_\alpha$ or $E_\beta$ <sup>b</sup> (keV)	$E_\gamma$ ( $I_\gamma$ ) (keV)(%) <sup>c</sup>
<sup>211</sup> At	7.2 h	EC (58.3)	516-ms <sup>211</sup> Po	-	76.9 (13)
		$\alpha$ (41.7)	30.7-y <sup>207</sup> Bi	2447	79.3 (22)
<sup>211</sup> Po	516 ms	$\alpha$	stable <sup>207</sup> Pb	7443	
<sup>212</sup> Bi	60.6 m	$\beta$ (64.1)	298-ns <sup>212</sup> Po	492	727 (6.3)
		$\alpha$ (35.9)	3.05-m <sup>208</sup> Tl	2174	-
<sup>212</sup> Po	298 ns	$\alpha$	stable <sup>208</sup> Pb	8784	583 (86)
<sup>208</sup> Tl	3.05 m	$\beta$	stable <sup>208</sup> Pb	560	2615 (100)
<sup>213</sup> Bi	45.6 m	$\beta$ (97.8)	4.2- $\mu$ s <sup>213</sup> Po	444	440 (26)
		$\alpha$ (2.16)	2.2-m <sup>209</sup> Tl	5869	-
<sup>213</sup> Po	4.2 $\mu$ s	$\alpha$	3.3-h <sup>209</sup> Pb	8375	-
<sup>209</sup> Tl	2.2 m	$\beta$	3.3-h <sup>209</sup> Pb	659	117 (81)
					467 (81)
					566( 98)
<sup>209</sup> Pb	3.3 h	$\beta$	stable <sup>209</sup> Pb	198	-
<sup>223</sup> Ra	11.4 d	$\alpha$	4-s <sup>219</sup> Rn	5697	269 (14)
<sup>219</sup> Rn	3.96 s	$\alpha$	1.8-ms <sup>215</sup> Po	6812	271 (10)
					402 (6.6)
<sup>215</sup> Po	1.78 ms	$\alpha$	36-m <sup>211</sup> Pb	7386	-
<sup>211</sup> Pb	36.1 m	$\beta$	2.1-m <sup>211</sup> Bi	447	405 (3.5)
					832 (3.1)
<sup>211</sup> Bi	2.14 m	$\beta$ (0.27)	516-ms <sup>211</sup> Po	0.5	-
		$\alpha$ (99.7)	4.8-m <sup>207</sup> Tl	6550	351 (13)
<sup>211</sup> Po	516 ms	$\alpha$	stable <sup>207</sup> Pb	7443	-
<sup>207</sup> Tl	4.8 m	$\beta$	stable <sup>207</sup> Pb	493	-
<sup>255</sup> Fm	20.1 h	$\alpha$	898-d <sup>251</sup> Cf	7091	81.5 (0.01)

<sup>a</sup> When not indicated, branching is 100%.

<sup>b</sup>  $\langle E_\beta \rangle = (\text{Av. } E_\beta \cdot I_\beta) / \Sigma I_\beta$ ,  $\langle E_\alpha \rangle = (E_\alpha \cdot I_\alpha) / \Sigma I_\alpha$

<sup>c</sup> Number of emission per 100 decay.

Table 3. Nuclear Reaction for Production of  $^{211}\text{At}$

Nuclear Reaction	Incident particle energy	References
$^{209}\text{Bi}[\alpha, 2n]^{211}\text{At}$	$20 \leq E_\alpha \leq 28$ $\sigma_{\text{max}} = 1 \text{ b @ } E_\alpha = 29 \text{ MeV}$ Yield = $\sim 1.5 \text{ mCi}/\mu\text{A @ } \frac{1}{2} \text{ sat.}$	Lambrech and Mirzadeh (1985) Mirzadeh and Lambrecht (1987)
$^{209}\text{Bi}[^6\text{Li}, 4n]^{211}\text{Rn} \rightarrow ^{211}\text{At}$	$38 \text{ MeV} \leq E_{\text{Li}} \leq 60 \text{ MeV}$ $\sigma_{\text{max}} = 0.7 \text{ b @ } E_{\text{Li}} = 54 \text{ MeV}$ Yield = $\sim 2 \mu\text{Ci}/\text{nA @ } \frac{1}{2} \text{ sat.}$	Meyer and Lambrecht (1980)
$^{232}\text{Th}[\text{p}, \text{spall}]^{211}\text{Rn} \rightarrow ^{211}\text{At}$	$E_p \geq 200 \text{ MeV}$ $\sigma = 0.7 \text{ mb @ } E_p = 28 \text{ GeV}$	Mirzadeh and Lambrecht (1987)
$^{232}\text{Th}[\gamma, \text{spall}]^{211}\text{Rn} \rightarrow ^{211}\text{At}$	$\sigma = 0.13 \text{ mb @ } E_\gamma = 300 \text{ MeV}$	Visser <i>et al.</i> (1979)

**Table 4.  $^{225}\text{Ac}/^{213}\text{Bi}$  Generator --  $^{213}\text{Bi}$  Yield,  $^{225}\text{Ac}$  and  $^{225}\text{Ra}$  Breakthrough**

Elution		$^{213}\text{Bi}$ Yield		Breakthrough				Ra/Ac
				$^{225}\text{Ac}$		$^{225}\text{Ra}$		
No.	Days	( $\mu\text{Ci}$ )	(%)	( $\mu\text{Ci}$ )	(%)	( $\mu\text{Ci}$ )	(%)	
1	3	650	96	$4.3 \times 10^{-3}$	$6.4 \times 10^{-4}$	$2.8 \times 10^{-3}$	$2.9 \times 10^{-1}$	453
6	4	615	98	$6.7 \times 10^{-3}$	$1.1 \times 10^{-3}$	$1.2 \times 10^{-3}$	$1.3 \times 10^{-1}$	118
15	10	400	97	$2.9 \times 10^{-2}$	$7.5 \times 10^{-3}$	$1.5 \times 10^{-3}$	$2.3 \times 10^{-1}$	31
19	12	351	97	$2.9 \times 10^{-1}$	$8.6 \times 10^{-2}$	$1.4 \times 10^{-3}$	$2.4 \times 10^{-1}$	2.8
23	13	325	96	$6.0 \times 10^{-2}$	$1.9 \times 10^{-2}$	$1.3 \times 10^{-3}$	$2.3 \times 10^{-1}$	12
28	18	218	91	$1.3 \times 10^{-2}$	$5.6 \times 10^{-3}$	$1.3 \times 10^{-3}$	$2.7 \times 10^{-1}$	52

Column: ~2x15 mm, ~ 200 mg of AG50W-X4 resin  
 Load: 830  $\mu\text{Ci}$   $^{225}\text{Ac}$  and 1.1  $\mu\text{Ci}$   $^{225}\text{Ra}$  in 100  $\mu\text{L}$  of 0.03 M  $\text{HNO}_3$   
 Eluent: 200  $\mu\text{L}$  of 0.15 M  $\text{HI}$ , Flow rate: ~0.5 mL/min





