Production of the alpha particle emitting radionuclide ^{211}At for targeted radionuclide therapy

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Alpha particle radioimmunotherapy is considered to be a potentially powerful strategy to eradicate disseminated tumor cells and small clusters of metastases. Whereas solid tumors and large metastases can be treated with surgery and external beam radiation, radioimmunotherapy holds the promise to treat the infiltrating tumor and metastatic microclusters [1,2]. The promising results so far observed for the treatment of lymphoma tumors provide a reasonably expectation that radionuclide therapy, and specifically alpha particle emitting radioimmunotherapy, will be an effective strategy for the treatment of disseminated disease from solid tumors, including clinically indiscernible micro-metastases [3-6]. The beta particle emitting radionuclides ^{131}I and ^{90}Y have been used preferentially for their commercial availability and distribution and easy radiolabeling methods. However, beta particle emitting radionuclides generate low LET particles (~ 0.3 keV/μm for electrons) and their corresponding radiobiological effectiveness depends upon cumulated activity concentration, total absorbed dose and dose rate. On the other hand, alpha particle emitting radionuclides have significant radiobiological advantages. Alpha particles have a high LET (~ 100 keV/μm), the range of these alpha particles is less than 100 μm in tissue, which allows for a highly localized dose to tumors while sparing normal tissues [7,8]. Furthermore, the radiobiological effect of alpha particles is dose rate independent. Thus, the use of alpha particle emitting radionuclides carries a significant therapeutic potential for the treatment of minimal residual disease and metastatic micro-clusters.

The production of alpha particle emitting radionuclides remains difficult and dependent upon the availability of either generators or proximity to a cyclotron for direct production. Among all alpha particle emitting radionuclides, At-211 is one of the most promising for use in radionuclide therapy [9]. It has a high carrier free specific activity of 76 GBq/μg with a favorable decay scheme and a half-life of 7.214 h, which is sufficient for labeling, dispensing and administering the radiolabeled compound. The radionuclide ^{211}At has a α-branching of 41.80% decaying into ^{207}Bi and the remaining 58.20%, although decaying by EC, leads to the ultra-short-lived α-emitter Po-211g with a half-life of 516 ms and a α-branching of 100%. Therefore, the overall α-branching of ^{211}At/^{211g}Po is 100%. The range alpha particle energies produced by the decay of ^{211}At are less than 70 μm in water (see Table I) with a nominal LET between 100 and 130 keV/μm, which is about the maximum relative biological effectiveness (RBE) for heavy ions. In this report we present the production methods and results for the alpha particle emitting radionuclide ^{211}At via the ^{209}Bi(α,2n) reaction.

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TABLE I. Alpha particle energies and intensities emitted by the decay of At-211.

Alpha Particle Energy (MeV)	Intensity (%)	Range in Water (μm)	Approximate # of Cell Diameters
5.87	41.94	47.98	3.2
6.57	0.337	57.26	3.8
6.89	0.325	61.78	4.1
7.45	57.4	69.92	4.7

Experimental Design and Data Evaluation

The reaction ^{209}Bi(α,x) carries multiple open channels as a function of alpha particle energy (see Table II) and, therefore, the alpha particle beam energy produced by the K500 cyclotron required to be

TABLE II. Open channels of an alpha particle beam on a bismuth target (Bi-209, 99.995+ % purity).

Reaction product	Half-life, $T_{1/2}$	Open Channel	Q (MeV)
^{207}At	1.8 h	^{209}Bi(α,6n)	-51.02
^{208}At	1.63 h	^{209}Bi(α,5n)	-43.7
^{209}At	5.41 h	^{209}Bi(α,4n)	-35.29
^{210}At	8.1 h	^{209}Bi(α,3n)	-28.07
^{211}At	7.214 h	^{209}Bi(α,2n)	-20.33
^{212g}At	0.3124 s	^{209}Bi(α,n)	-15.29
^{212m}At	0.119 s	^{209}Bi(α,n)	-15.51
^{210}Po	138.37 d	^{209}Bi(α,p2n)	-23.31

degraded from its initial energy of 80 MeV to energies below 30 MeV using nine foils in order to avoid the production of unwanted radionuclides (see Fig. 1). The beam energy of 80 MeV was selected in order to obtain the maximum intensity of the beam. The order of the foils, their corresponding thicknesses, and energy degradation were estimated using the computer code Lise++ (see Table III). A final 500-μm thick metallic ^{209}Bi foil was used, and the particle currents used in both experiments were approximately 165 and 96 nA, respectively, which did not pose a problem in heat dissipation as higher currents can melt the ^{209}Bi target. Moreover, the cupper foils were used to monitor the beam intensity and energy.

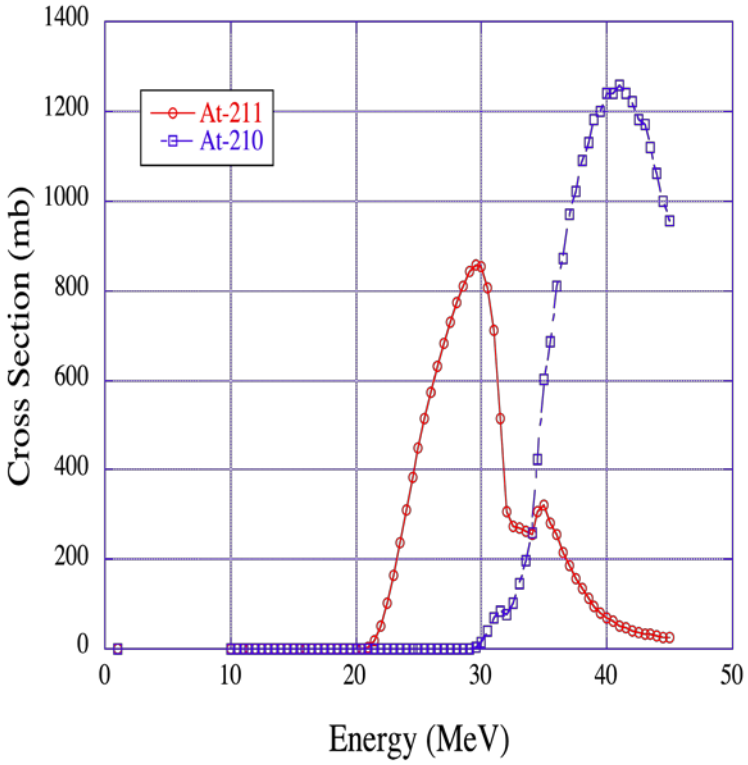

FIG. 1. Evaluated cross section for the reactions ^{209}Bi(α,3n)^{210}At and ^{209}Bi(α,2n)^{211}At as a function of alpha particle energy. The cross sections were evaluated using the program Talys.

TABLE III. Implemented stack foil order used for energy degradation and monitoring. The initial energy of the alpha particle beam was 80 MeV and it was degraded to a final energy of approximately 28.1 and 25.7 MeV for the two experiments, respectively. The residual energy of the alpha particle beam was estimated using the computer code Lise++.

Number	Foil	Thickness (μm)	E_{in} (MeV)	E_{out} (MeV)	E_{loss} (MeV)	Thickness (μm)	E_{in} (MeV)	E_{out} (MeV)	E_{loss} (MeV)
1	Cu	100.0	80.0	74.1	5.9	100.0	80.0	74.1	5.9
2	Cu	100.0	74.1	67.7	6.3	100.0	74.1	67.7	6.3
3	Cu	100.0	67.7	61.0	6.8	100.0	67.7	61.0	6.8
4	Cu	100.0	61.0	53.6	7.4	100.0	61.0	53.6	7.4
5	Cu	100.0	53.6	45.3	8.2	100.0	53.6	45.3	8.2
6	Cu	100.0	45.3	35.8	9.5	100.0	45.3	35.8	9.5
7	Al	127.0	35.8	30.4	5.3	127.0	35.8	30.4	5.3
8	Al	50.0	30.4	28.1	2.3	127.0	30.4	25.7	4.8
9	Bi	500.0	28.1	0.0	28.1	500.0	25.7	0.0	25.7

Results

The initial experimental run using a degraded nominal energy of 28 MeV resulted in the substantial production of the contaminant ^{210}At, even though our calculations predicted that the production of ^{210}At should be minimal or negligible. The average yield of ^{210}At was 0.83 MBq/μA-h. This can be attributed to the broad energy spectrum of the alpha particle beam, with an initial energy of 80 MeV, which could spread about ± 4 MeV after degradation. This effect was corroborated when our second experiment was carried out using a lower nominal energy of 25 MeV. In this experiment, the production of ^{210}At was not observed. The estimated ^{211}At production yields from both experiments were 34.5 and 12.9 MBq/μA-h, which are in accordance to those results published in the open literature of around 30 MBq/μA-h.

Conclusions

Based on these initial experiments we successfully produced ^{211}At with no major impurities using a high purity Bismuth target (99.995%). There were neither physical deformation nor melting of the bismuth foil at the beam currents used in these experiments, which will allow us to proceed to activate bismuth nanoparticles for further studies in radioimmunotherapy.

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