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Medical Radioisotopes Produced with Cyclotron Beams in Warsaw

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Abstract

The various production routes of the prospective medical radioisotopes ^{43}Sc, ^{44g}Sc, ^{44m}Sc, ^{47}Sc, ^{44}Ti/^{44g}Sc, ^{99m}Tc, ^{72}Se/^{72}As and ^{211}At were investigated by a team from the Heavy Ion Laboratory, University of Warsaw (HIL-UW), the University of Silesia (US) and the National Centre for Nuclear Research (NCNR). Three cyclotrons were employed: the K=160 heavy-ion cyclotron with an internal 32 MeV alpha particle beam and the p/d PETtrace medical cyclotron at HIL and the C30 proton cyclotron at NCNR in Świerk, near Warsaw. The Thick Target Yields, activity at the End of Bombardment (EOB) and the impurities produced in addition to the main isotope are reported. The possible medical applications of these radioisotopes are briefly discussed.

Introduction

In 2012 a new unit, the Radiopharmaceuticals Production and Research Centre (RPRC) [1-4], devoted to the production of and research into innovative radioisotopes for medical diagnostics and therapy, was inaugurated at the Heavy Ion Laboratory of the University of Warsaw (HIL-UW). The unit is equipped with a PETtrace medical cyclotron (produced by the General Electric Company) providing proton and deuteron beams of 16.5 MeV and 8.4 MeV respectively. A range of chemical equipment for the synthesis and quality control of radiopharmaceuticals is also installed. In addition to the regular production of FDG for commercial use in Positron Emission Tomography the new unit enabled the laboratory team to enter a new research field in the applications of radioisotopes in medical diagnosis and therapy.

In parallel the K=160 heavy ion cyclotron [5], already in operation for almost two decades for basic research in nuclear physics and heavy ion applications, is employed to produce research quantities of medically interesting radioisotopes. In this work samples are irradiated by the internal alpha particle beam.

Additionally, the home made C30 cyclotron [6,7] operating at the National Centre for Nuclear Research in Świerk, near Warsaw, although with relatively low beam current, enables us to extend the available proton energy range up to 28 MeV. A proton beam with similar energy but with higher intensity will be available soon from a new machine accelerating protons, deuterons and alpha particles, currently under construction at Świerk.

The Heavy Ion Laboratory of the University of Warsaw

The Heavy Ion Laboratory (Figure 1) is a "User Facility" with around 100 national and foreign users per year. The isochronous K_{max}=160 cyclotron (Figure 2) delivers around 3000 h of gaseous or metallic heavy ion beams per year with energies between 2 MeV/nucleon and 10 MeV/nucleon and masses up to 40. The current HIL research programme comprises nuclear physics, atomic physics, materials science, solid state physics, biology, particle detector development and testing, and recently production of research quantities of medical radioisotopes. The last mentioned subject is discussed in the present paper.

A second proton-deuteron cyclotron (Figure 3) is devoted to the commercial production of radiopharmaceuticals for Positron Emission Tomography (PET) and research into innovative medical radioisotopes.

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Figure 1: The Heavy Ion Laboratory building, North side.

Figure 2: The K=160 heavy ion cyclotron, accelerating gaseous and metallic ions with masses up to 40 and energies up to about 10 MeV/nucleon.

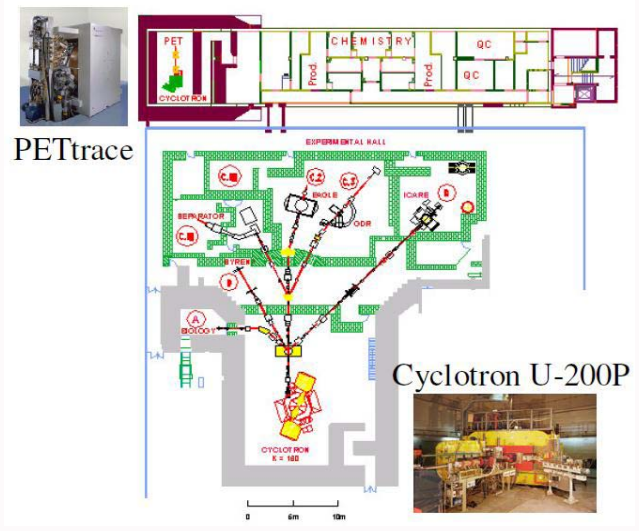

Figure 3: The layout of the University of Warsaw Heavy Ion Laboratory ground floor. The lower part of the figure shows the heavy ion cyclotron, its beam lines and six nuclear physics experimental stations. The Radiopharmaceuticals Production and Research Centre, (placed 6 m underground) is in the upper part of the figure.

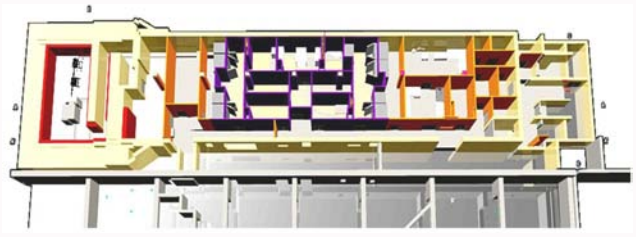

Figure 4: The layout of the Radiopharmaceuticals Production and Research Centre. The radioisotopes produced by the proton or deuteron beam from the PETtrace cyclotron (left of the figure) are transferred to one of the chemistry laboratories: L1 serving for the routine production of Fluoro-Deoxy-Glucose (FDG) or L2 devoted to research activity with ^{11}C, ^{15}O or ^{18}F radioisotopes. The quality control area (right of the figure) is also divided into two parts: for testing regularly produced FDG and for radiopharmaceuticals in the research stage.

Figure 5: The PETtrace p/d cyclotron installed in its cave.

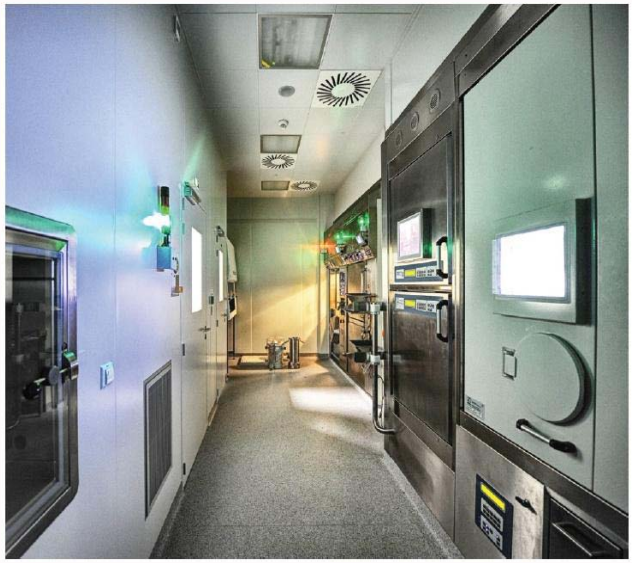

Figure 6: Hot cells in the research laboratory.

The convenient position of the HIL at the heart of the Scientific Campus Ochota where the scientific departments of the University of Warsaw, the Polish Academy of Sciences and Warsaw Medical University are located opens up possibilities for large interdisciplinary collaborations. The Institute of Nuclear Chemistry and Technology, located about 15 km from HIL, is also closely involved in the research

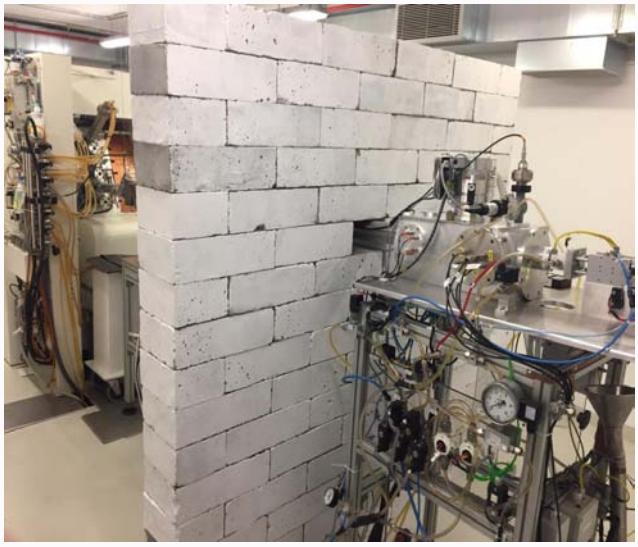

Figure 7: The external beam line installed on the PETtrace cyclotron for the irradiation of solid samples.

part of this project.

Radiopharmaceuticals Production and Research Centre

A 3D representation of the layout of the RPRC is given in Figure 4. The PETtrace cyclotron and one of the chemistry rooms are shown in Figure 5 and 6. An external beam line for the irradiation of solid samples was recently designed and constructed [8] in the laboratory and is presented in Figure 7. The specially developed cooling system allows rather high proton and deuteron beam intensities to be used for the irradiation of these samples.

Characteristics of Proton, Deuteron and Alpha Particle Production Routes of the Investigated Radioisotopes

Tables 1-3 present the investigated radioisotopes and some characteristics of the production routes employed for the three projectiles. All our experimental data presented in these tables and obtained with carbonate, chloride or oxide targets (with the exception of metallic and natural ones) are recalculated to the highest commercially available target isotope enrichment. Short comments on a few of them are given below.

"^{43}Sc. This radioisotope [9,10], with prospective Positron Emission Tomography (PET) applications, has a substantially longer half-life ($T_{1/2}$=3.89 h) than the currently employed ^{18}F ($T_{1/2}$=1.8 h) or ^{68}Ga ($T_{1/2}$=68 min) and a strong β^+ branch. It can, therefore, be delivered to hospital PET scanners from much more distant production centers. ^{43}Sc is also an ideal theranostic partner for the therapeutic ^{47}Sc. We produced ^{43}Sc using four different nuclear reactions: (p,n), (d,n) and (α,p)+(α,n). The latter reactions produce very pure ^{43}Sc using a natural Ca target and are therefore preferred for centre's equipped with cyclotrons accelerating alpha particle beams to energies of 20 MeV or higher. The (d,n) route also gives a rather pure product, but with the currently employed medical accelerators the thick target efficiency for this reaction is rather low (it would be about a factor of two higher with 15 MeV deuterons). Finally, the (p,n) reaction has a good yield using medical accelerators but the resulting product is contaminated with ^{44}Sc.

^{44}Sc. A second Sc radioisotope [11,12] of a similar half-life ($T_{1/2}$=3.97 h) to ^{43}Sc with a strong positron branch. It decays almost completely to an excited state at 1157 keV. Also, an isomeric state of 271 keV above the ground state has a half-life of 2.4 d and decays to the ground state. These two properties of ^{44}Sc allow applications of this radioisotope to be extended to more sophisticated uses besides its classic use in PET techniques. Firstly, it was proposed a few years ago [13] to develop a new technique, the so called-three photon PET, in which the high energy gamma ray in coincidence with the two 511 keV annihilation quanta substantially improves the PET spatial resolution, caused by the non-negligible range of the annihilating positrons (the 1157 keV gamma line is emitted from the place where the radiopharmaceutical is absorbed). It was also shown [14] that this technique substantially decreases the PET patient dose. Secondly, the other particularity of ^{44}Sc, the existence of a much longer lived isomeric state, led to a proposal [15-17] for the synthesis of an *in vivo* ^{44m}Sc/^{44g}Sc generator for PET studies of long biological processes. In the present study two isomers of ^{44}Sc were produced by the (p,n) and (α,np+pn+d) reactions on $CaCO_3$ targets. The proton induced reaction gives a very high activity at EOB for the

Table 1: The prospective medical radioisotopes investigated using a proton beam. The column TTY/TY denotes the Thick Target Yield or Target Yield in MBq/μAh.

Isotope and $T_{1/2}$	Projectile energy (MeV)	Target	TTY / TY (MBq/μAh)	Activity after 4 h irradiation with 1 μA beam		Reference
				A_{EOB} (MBq)	Largest impurity (%)	
^{99m}Tc, 6 h	16-8, 26-8	^{100}Mo (99.815%)	404 (21), 910 (30)	1294 (67), 2914 (96)	1.26 (8) ^{100}Tc, 1.82 (7) ^{100}Tc	[30]
^{43}Sc, 3.89 h	17-4	$^{43}CaCO_3$ (90%)	320 (20)	930 (70)	11.0 (1.0) ^{44g}Sc	[18]
^{44g}Sc, 3.97 h	12-4	$^{44}CaCO_3$ (94.8%)	350 (50)	10.0 (1.4) E+2	0.42 (8) ^{44m}Sc	[18]
^{44m}Sc/^{44g}Sc, 2.4 d	12-4	$^{44}CaCO_3$ (94.8%)	1.08 (13)	4.2 (5)	2.7 (4) ^{48}Sc, apart from ^{44g}Sc	[18]
^{44g}Sc, 3.97 h	16-4	$^{44}CaCO_3$ (94.8%)	670 (80)	1.9 (2) E+3	0.66 (13) ^{44m}Sc	[18]
^{44m}Sc/^{44g}Sc, 2.4 d	16-4	$^{44}CaCO_3$ (94.8%)	3.2 (5)	13 (2)	1.3 (3) ^{48}Sc, apart from ^{44g}Sc	[18]
^{44g}Sc, 3.97 h	22-6	$^{44}CaCO_3$ (94.8%)	870 (80)	2.5 (2) E+3	11.5 (1.4) ^{43}Sc	[18]
^{44m}Sc/^{44g}Sc, 2.4 d	22-6	$^{44}CaCO_3$ (94.8%)	7.3 (6)	28 (2)	10.0 (1.2) E+2 ^{43}Sc, apart from ^{44g}Sc	[18]
^{47}Sc, 3.35 d	16-10	$^{48}CaCO_3$ (97.1%)	21 (2)	83 (8)	150 (20) ^{48}Sc	[18]
^{47}Sc, 3.35 d	22-17	$^{48}CaCO_3$ (97.1%)	49 (4)	193 (12)	35 (4) ^{48}Sc	[18]
^{47}Sc, 3.35 d	28-16	$^{48}CaCO_3$ (97.1%)	85 (5)	334 (16)	27 (2) ^{48}Sc	[18]
^{47}Sc, 3.35 d	28-18	$^{48}TiO_2$ (99.6%)	2.0 (1)	7.7 (3)	20.0 (1.1) E+2 ^{44g}Sc, 57 (3) ^{44m}Sc	[18]

Table 2: The prospective medical radioisotopes investigated using a deuteron beam. The column TTY denotes the Thick Target Yield in MBq/μAh.

Isotope and $T_{1/2}$	Projectile energy (MeV)	Target	TTY (MBq/μAh)	Activity after 4 h irradiation with 1 μA beam		Reference
				A_{EOB} (MBq)	Largest impurity (%)	
^{43}Sc, 3.89 h	7-0	$^{42}CaCO_3$ (95.9%)	35 (2)	99 (7)	0.22 (3) ^{44g}Sc	[18]

Table 3: The prospective medical radioisotopes investigated using an alpha particle beam. The column TTY/TY denotes the Thick Target Yield or Target Yield in MBq/μAh.

Isotope and $T_{1/2}$	Projectile energy (MeV)	Target	TTY / TY (MBq/μAh)	Activity after 4 h irradiation with 1 μA beam		Reference
				A_{EOB} (MBq)	Largest impurity (%) at EOB	
^{211}At, 7.2 h	29-19	^{nat}Bi	37 (6)	123 (20)	0.025 (6) ^{210}At	[29]
^{72}As, 26 h	29-16	$^{70}GeO_2$ (95.3%)	11.7 (9)	44 (3)	220 (10) ^{73g}Sc	
^{72}Se/^{72}As, 8.5 d	29-16	$^{70}GeO_2$ (95.3%)	0.84 (0.14)	3.3 (6)	2950 (40) ^{73g}Se	
^{43}Sc, 3.89 h	20-0	$^{nat}CaCO_3$	84 (4)	240 (11)	0.034 (5) ^{47}Sc	[31]
^{43}Sc, 3.89 h	20-0	^{nat}Ca (metal)	210 (30)	600 (86)	0.035 (7) ^{47}Sc	[31]
^{43}Sc, 3.89 h	20-0	$^{40}CaCO_3$ (99.99%)	88 (13)	252 (37)	2.5 (1) E-4 ^{47}Sc	[31]
^{43}Sc, 3.89 h	31-0	^{nat}CaO	98 (10)	280 (28)	0.75 (9) ^{44g}Sc	[29]
^{43}Sc, 3.89 h	29-19	^{41}KCl (95.4%)	60 (9)	172 (26)	13 (1) ^{44g}Sc	[31]
^{44g}Sc, 3.97 h	29-12	$^{42}CaCO_3$ (95.9%)	44 (7)	127 (20)	13.7 (8) ^{44m}Sc	[31]
^{44m}Sc/^{44g}Sc, 2.4 d	29-12	$^{42}CaCO_3$ (95.9%)	4.7 (8)	18 (3)	40.6 (9) ^{43}Sc, apart from ^{44g}Sc	[31]
^{44g}Sc, 3.97 h	20-2	^{41}KCl (95.4%)	61 (10)	176 (29)	15.9 (7) ^{43}Sc	[31]
^{44m}Sc/^{44g}Sc, 2.4 d	20-2	^{41}KCl (95.4%)	3.0 (6)	12 (2)	233 (15) ^{43}Sc, apart from ^{44g}Sc	[31]
^{47}Sc, 3.35 d	20-0	$^{44}CaCO_3$ (99.2%)	1.0 (1)	3.7 (4)	51 (3) ^{43}Sc	[18]
^{44}Ti/^{44}Sc, 60 y	29-12	$^{42}CaCO_3$ (95.9%)	3.2 (8) E-5	1.3 (3) E-4	70 (20) ^{46}Sc *	

*for this very long-lived radioisotope the impurity at 1 y after EOB is indicated.

ground state formation and a more than 150 times lower one for the isomer after 4 h of the irradiation with 16 MeV protons. The isomer/ground state activity ratio at EOB substantially increases for the alpha particle route. However, due to the much larger range of protons than alpha particles in the $CaCO_3$ target, the isomer activity is only 1.5 lower than the ground state one for protons than for alpha particles of the same beam intensity and for the appropriate beam energies. Evidently, due to much larger ^{44g}Sc production a much longer cooling time is necessary for proton irradiation in order to obtain a pure ^{44m}Sc. All these aspects should be considered if an *in vivo* generator is to be synthesized [18].

^{47}Sc. This therapeutic radioisotope, with a low energy β-decay, is the theranostic partner of Sc positron emitters and was previously produced using slow or fast neutrons from nuclear reactors [19-21]. The alternative accelerator routes are currently being investigated in a number of research centre's under the Cooperative Research Programme of the IAEA [22]. The (p,2n) reaction for the formation of this isotope was recently proposed [10,22] and was investigated in detail by our group [18]. It was shown that only a rather limited proton energy range can be used to produce relatively pure ^{47}Sc and even then a long cooling time of the irradiated sample is necessary to avoid the presence of ^{48}Sc, a radioisotope emitting a few high energy gamma lines, strongly increasing the patient dose (for 10 hours irradiation time, 150 hours after EOB the ^{48}Sc activity is 10% of the ^{47}Sc one and 420 hours are necessary to reach 1% contamination). Assuming that an activity of 2 GBq of ^{47}Sc is necessary for one therapeutic application, that the irradiation time is 10 hours and that the proton beam current is 100 μA, one irradiation leads to one patient application containing 1% contamination of the injected sample with ^{48}Sc.

The (p,2p) reaction on the rather cheap ^{48}Ti oxide was also investigated [18]. The reaction yield obtained at 28 MeV to 18 MeV was, however, 12 times smaller than with the (p,2n) reaction and a substantial cooling time was also necessary.

^{44}Ti/^{44g}Sc. This 60 y half-life generator was previously produced by the Mainz team [23] using a 200 mA proton beam at 25 MeV on a thick ^{45}Sc target. As the half-life of the mother isotope is very long, the irradiation time was 200 days in order to obtain 185 MBq of ^{44}Ti activity. We have produced this isotope by the (α,2n) reaction on a thick ^{42}Ca target using a 29 MeV alpha particle beam. In Table 3, we present the TTY of ^{44}Ti production for an alpha particle beam within the investigated energy range. However, a substantial cross section for this reaction extends up to much higher energies. Therefore, using JANIS library, we also calculated the TTY value for the energy range 56 MeV to 12 MeV, the upper energy value corresponding to the expected alpha particle energy of the future high current SPIRAL2 linear accelerator [24]. The value obtained was 76 MBq/μAh. Assuming e.g. the future SPIRAL2 alpha particle beam intensity to be 3.6 pmA the production of ^{44}Ti/^{44g}Sc with equivalent strength to the Mainz generator would need about 20 days of irradiation time of maximum enriched, commercially available target material. Evidently, the question of whether the target can sustain such a high current should be resolved first.

^{211}At. This prospective therapeutic alpha emitter has been studied at a number of places around the world [25-27]. The main problem encountered is the stability of the injected radiopharmaceuticals. Within our programme this radioisotope was and is currently produced by irradiation of a natural, mono-isotopic Bi target with a He^+ internal cyclotron beam [28,29]. The various ways of forming radiopharmaceuticals with it are being studied by our collaborators from the Institute of Nuclear Chemistry and Technology in Warsaw. The production efficiency as a function of the He^+ bombarding energy and the level of contamination by the very dangerous ^{210}At

was determined [29].

Summary and Conclusions

Research into the production of prospective medical radioisotopes conducted at the Heavy Ion Laboratory of the University of Warsaw was begun a few years ago and is being actively pursued. In this paper a list of the targets and nuclear reactions investigated up to the present time was presented. Research on the synthesis of radiopharmaceuticals is performed at the Institute of Nuclear Chemistry and Technology in Warsaw and the POLATOM Department of the National Centre for Nuclear Research in Świerk, near Warsaw using the radioisotopes thus produced. The location of HIL in the Warsaw University scientific campus opens possibilities for large-scale interdisciplinary activity using the produced medical radioisotopes.

Acknowledgments

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