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RESEARCH ARTICLE

Local Production of the Alpha-Emitting Radioisotope Actinium 225 with Low Impurities for Targeted Alpha Therapy by a Compact Neutron Generator System

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ABSTRACT

Alpha-particle emitting radioisotope Actinium225 (^{225}Ac) is of great interest for use in Targeted Alpha Therapy (TAT) treatments of e.g., brain tumors, bladder cancer, neuroendocrine tumors and leukemia. A suitable ^{225} Ac radioligand is also potentially resolutive for the treatment of advanced and metastatic Castration-Resistant Prostate Cancers (mCRPCs). The mCRPC has a mean survival rate of 9-36 months and encompasses a heterogeneous ample range of molecular cancer behavior with a high risk of progression.

Global demand for the ^{225} Ac has spurred several production efforts including extraction from ^{233}U, high energy protons or photon irradiation of ^{226}Ra or spallation of ^{232}Th by, at least, 100 MeV protons. Instead of using accelerators systems such as cyclotrons or LINACs, a Compact Neutron Generator (CNG) system has been developed. A 400kV-10 mA DC (D–^{7}Li) CNG potentially able to produce substantial amount of ^{225}Ac with low ^{227}Ac impurities is here presented. Exploiting the high flux of 10 and 13 MeV energy neutrons generated by the (D–^{7}Li) reactions to bombard a thin target layer of ^{226}Ra, ^{225}Ra/^{225}Ac is produced via the ^{226}Ra(n,2n)^{225}Ra nuclear reaction. By irradiating a 5 mm thick ^{226}Ra layer for 100 hours, about 11-13 mCi of ^{225}Ac can be produced – corresponding to the TAT treatment of about 65 oncological patients – with an estimated ^{227}Ac contamination of about one percent, which is below the acceptable limit for clinical use. This ^{225}Ac production scheme by a suitable CNG should allow to adopt a local/regional approach avoiding the shipment costs of ^{225}Ac.

The aim of this paper is to inform the production chain of radioisotopes to be used in medical field and the medical community involved in the application of radiopharmaceuticals for the cure of cancer, that a new technology based on Compact Neutron Generators (CNG) is in a R&D phase and will allow to produce the necessary quantity of radioisotopes for clinical and research purpose. This will be essential in treatment advanced metastatic cancer as for instance the metastatic Castration – Resistant Prostate Cancer.

Introduction

It is important, before introducing the technical parts of this paper, to underline that our CNG, as below described, being able to produce radioisotopes as Ac225 to be used in the formulation of neoadjuvant treatment of severe metastatic malignancies, will be a support to the actual used generators.

The cooperation between neutron physics and the design and construction of an apparatus able to fulfill the necessity of advanced R&D in radioisotopes production, have highlighted the actual and future demand of this integration using nuclear physics and advanced MCNP code method, both for medical therapies and imaging.

In this paper the authors have used the above integrated approach to design and built a prototype of a Compact Neutron Generator, an innovative and disruptive new technology, for the production of radioisotopes, to be used in the chain of production of radiopharmaceuticals. This generator has been conceived to be compact and suitable to be operated by few technicians. This will for sure have an impact on the costs of production and management.

The use of this new generator will allow the pharmaceutical companies to produce Ac225, but also other radioisotopes, for the formulation of new compounds, from the irradiation of Ra226 or other targets.
Among the currently available alpha-emitting radioisotope, Actinium255 (^{225}Ac) is considered the most promising one for the treatment of the metastatic Castration-Resistant Prostate Cancer (mCRPC), as well for the therapy of brain tumors, bladder cancer, neuroendocrine tumors and leukemia. [1,2,3,4,5,6,7].

In the case of the radiopharmaceutical therapy (RPT), the ionizing radiation - due in this case to alpha-particles delivered from the radioisotope ^{225}Ac [8,9,10], conjugated via a chelating agent to biological agents tied up to tumor cells or elements of the tumor microenvironment - induces the DNA Double Strand Breaks (DSBs) of the cancer cells. Some successful ^{225}Ac-labelled radiopharmaceuticals are:

- ^{225}Ac-PSMA-617, because the Prostate-Specific Membrane Antigen (PSMA) is highly expressed in mCRPC [11,12,13];
- or ^{225}Ac-DOTATOC and ^{225}A- DOTATE of the Peptide Receptor Radionuclide Therapy (PRRT) for the treatment of a heterogenous group of neuroendocrine tumors (NETs) which have improved the survival of patients with inoperable metastatic neuroendocrine tumors expressing somatostatin receptors [14].

These radiopharmaceuticals are administered to the oncological patients systematically or locoregionally [15].

As alpha-particles traverse tissues, they deliver direct DNA DSBs which are two to three orders of magnitude greater than the ones achieved by photons and electrons. These DNA DSBs are the most cytotoxic cellular damages because they are randomly distributed and form clustered DNA damage to multiple base-pairs. Furthermore, alpha-particles induce an irrelevant Oxygen Enhancement Ratio (OER) and the associated high energy deposition density is carried out over a very short distance of about 100 micrometers.

Among the alpha-emitting radionuclides, ^{225}Ac is the most promising one, with a half-life of about 10 days and decaying to the stable isotope ^{209}Bi. It generates eight short-lived progenies, has a high-Linear Energy Transfer (LET, of about 100 KeV/micrometer), emits a total of four net high-energy alpha-particles (5-9 MeV) and two negative beta particles (50, 2300 KeV), for a total amount of about 28 MeV of energy administered to the surrounding media. Notice also that the Relative Biological Effectiveness (RBE) of alpha-particles can range from 3.5 to 4 for cell killing, while the RBE for photons and electrons is 1.

The main two problems for the global clinical use of ^{225}Ac are the small quantities that can be produced via the current production strategies [16,17,18,19,20,21,22,23,24,25,26], and the lacking of suitable chelating agents for the stable retention of ^{225}Ac and its progeny which will give rise to nonspecific radiotoxicity effects [27,28,29,30,31,32]. This stable retention issue is due to the not yet well understood coordination chemistry of ^{225}Ac and its progeny, as well as from the alpha recoil effect, because of the momentum conservation law that happens by the release of an alpha particle. ^{225}Ac can be obtained either from the decay of ^{233}U or from the neutron transmutation of ^{226}Ra by successive (n,γ) capture decay reactions (via ^{227}Ac, ^{228}Th to ^{229}Th) [33,34,35]. Presently, worldwide there are two production centers of ^{225}Ac:

1. US DOE, Oak Ridge National Laboratory (ORNL) in Oak Ridge, TN, USA;
2. Institute for Transuranium Elements in Karlsruhe, Germany, which is however not deputed to sell ^{225}Ac.

In both cases, the bulk of ^{225}Ac was derived from the US storage of Thorium229 (^{229}Th), produced over the course of Cold War at the Hanford and Savannah River sites, in reactors that were designed

to produce weapon usable plutonium. Another issue to be tackled today is the need to increase the chemical separation of ^{225}Ac at ORLN to meet the global demand by expanding the number of hot cells therein [36,37,38,39,40].

The successful treatment of patients with the Targeted Alpha Therapy (TAT) adopting ^{225}Ac requires that the radioisotope and its progeny must be delivered with high affinity and retained in tumor microenvironment over the course of their nuclear decays. These conditions demand that ^{225}Ac be covalently linked to a tumor-targeting vector by a bifunctional chelator agent that must be thermodynamically and kinetically stable with ^{225}Ac in the oxidation state +3 (Ac^{3+}). However, the development of effective bifunctional chelating agents for Ac^{3+} has been hampered by the insufficient knowledge of its coordination chemistry and in general of any other short-lived radioactive ions [41,42,43,44,45,46].

In this context, the 12-membered macrocycle - that provides octa dentate coordination via 4 tertiary amine nitrogen donors and 4 carboxylic acid pendent arms known as DOTA - is amply used for the stable chelation of many radiometals such as ^{225}Ac [47,48,49].

In general, the chemical approach pursued is trivalent: first step, it is to identify a stable chelating agent for delivering ^{225}Ac in vivo to a target cell; second step, it is to internalize the ^{225}Ac in the target cell; third step, retaining the ^{225}Ac progeny inside the target cell and harnessing their cytotoxic potentials; and lastly, minimizing the loss of the ^{225}Ac daughters to non-target cells in order to minimizing systemic radiotoxicity. This approach can be realized concretely by the compound ^{225}Ac-DOTA-Antibody, that turns out to be stable and without systemic toxicity to the host. In short, the complex ^{225}Ac-DOTA-Antibody is safety and effective in the TAT [50,51,52,53].

To target prostate cancer cells, another path is to use the PSMA, that is a transmembrane protein expressed at high concentrations on the surface of prostate cancer cells, for the treatment of patients affected by mCRPC. Historically, ^{177}Lu-DOTATATE (trade name Lutathera®) [12,54], was the first type of peptide receptor radionuclide therapy (PRRT) [55,56] that garnered FDA and EMA approval in 2018 and 2017, respectively, for the treatment of somatostatin receptors, which are receptors for the ligand somatostatin positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Further, the FDA and EMA have approved ^{177}Lu-PSMA-617 for the radioligand therapy that delivers negative beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment [57,58,59,60,61,62].

Because ^{225}Ac-PSMA-617 could be more effective for the treatment of mCRPC patients, Novartis has started a Phase-I study of ^{225}Ac-PSMA-617 [13,54], in men with PSMA-positive prostate cancer with or without prior ^{177}Lu-PSMA-617 radioligand therapy, started in April 2021 and to be concluded in July 2025 [63,64].

To the best of the knowledge of the authors the clinical results are based essentially on retrospective studies of real-world experiences and there are no complete clinical trials relating to the administration of ^{225}Ac-PSMA-617 to mCRPC patients. However, these topics are out of the purpose of this article, which is instead concentrate on the production systems of ^{225}Ac [65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85].

As it has noticed above, the US primary source of ^{225}Ac comes from ^{229}Th decay considered as a waste product of the nuclear programs in the 1940s and 1950 therein. Because the global demand for ^{225}Ac is growing daily, the USA has established in 2015 the Ac225 Tri-Lab Effort consisting of Brookhaven, Los Alamos and Oak Ridge National Laboratories [86,87,88,89,90,91,92]. In these facilities, the ^{225}Ac production is sustained by the DOE Isotope Program (IP) using accelerator systems at Brookhaven National Laboratories and Los Alamos via high-energy proton bombardment of natural thorium (mainly ^{232}Th) targets. After bombardment, the targets are removed and shipped to ORNL for chemical processing, and lastly the purified product is shipped to the final customers. The annual supply of ^{225}Ac from the US Tri-Lab-Effort is currently about the 60% of the worldwide demand of this radioisotope.

In order to respond more directly to the growing worldwide demand for ^{225}Ac of end-users (hospitals, clinics, pharmaceutical companies, research facilities, etc.), this article presents a new approach potentially able to satisfy the local/regional demands of ^{225}Ac by adopting as production technology a specifically designed Compact Neutron Generator (CNG). This new approach is scalable and flexible to the local/regional demands and will requires a network of similar production facilities with reduced functional complexity and costs to meet the global needs of ^{225}Ac.

The designed CNG is based on the (D-^{7}Li) reactions: operating with a negative deuterium (D-) ion source, 10 and 13 MeV energy neutrons are generated by the (D-^{7}Li) reactions and used to irradiate a ^{226}Ra

target, in which the ^{225}Ac is produced via the reaction $^{226}Ra(n,2n)^{225}Ra$ and successive decay of ^{225}Ra (15 days half-life) in ^{225}Ac [93,94,95].

It has been estimated that with a 400kV-10mA D-beam power and structuring properly the (D–^{7}Li) target, about 11-13 mCi of ^{225}Ac can be produced by (the 10 and 13 MeV neutrons) bombardment of a 0.5 cm thick ^{226}Ra sample (16.5 cm^3 volume) for 100 hours of irradiation: this ^{225}Ac quantity should be enough for the TAT treatment of about 65 local/regional mCRPC affected patients.

The ^{227}Ac contamination of this ^{225}Ac-neutron generator produced radioisotope by the (D–^{7}Li) CNG system is estimated to be one percent in the 0.5 cm thick ^{226}Ra bombarded sample, which is below the acceptable limit for the clinical use [96,97,98]. Furthermore, by an opportune reduction of the ^{226}Ra target thickness, the 400kV-10mA (D–^{7}Li) CNG apparatus could also allow the local/regional supply of less micro quantities of ^{225}Ra to produce others neuroendocrine drugs.

Physical principles

There are two fusion reactions capable of producing high energy neutrons: the (Deuterium (D)–Tritium(T)) and the (D–^{7}Li) reactions. The latter produces both high energy neutrons and gamma photons:
$D + {}^{7}Li \rightarrow {}^{8}Be + n$ (10, 13 MeV) $\rightarrow {}^{9}Be + \gamma$ (12, 13, 14, 17 MeV)

To produce ^{225}Ra via the (n,2n) reaction in a ^{226}Ra sample, the energy of the incoming neutrons must exceed 6.5 MeV. While the (D - T) reaction produces 14 MeV neutrons which have a cross-section of ~700 mb for the (n, 2n) reaction, the $^{226}Ra(n,2n)^{225}Ra$ reaction cross-section for 10 and 13 MeV neutrons is ~ 2 barn.

Since the long-lived ^{227}Ac ($t^{1/2}$ = 21.8 y) isotope is not desirable for clinical TAT, it has been established that the acceptable clinical limit for this impurity is 2%. In comparison with the$^{226}Ra(n,2n)^{225}Ra$ reaction cross-section, the ^{226}Ra (n, γ)^{227}Ra neutron capture cross-section for 10 and 13 MeV neutrons is five orders of magnitude smaller. Therefore, the production probability of ^{227}Ra (and hence ^{227}Ac) induced by the 10 and 13 MeV neutrons is likely to be very low. Furthermore, even if some of these high energy neutrons can lose their energy by scattering crossing the ^{226}Ra layer and becoming epithermal or thermal, the ^{226}Ra capture cross-section (forming $^{227}Ra/^{227}Ac$) at these low energies is limited to ~ 0.1 barn.

The CNG system for ^{225}Ac Production

The (D-^{7}Li) CNG consists of three main components: a surface-production type negative ion source; an extraction and acceleration column; a Lithium beam target electrode for generating the high energy neutrons. Figs. 1 and 2 show the essential schematic blocks the (D-^{7}Li) CNG and with cross-sections views of the surface-conversion type D^- ion source (122). The deuterium plasma is first generated by 13.5 MHz RF induction discharge using an internal RF antenna coil. The D^- ions are formed on the surface of the converter electrode which is concave in shape with a radius of curvature of approximately 30 mm.

By biasing the converter at -250 V to -300 V relative to the plasma, D^- ions formed on the converter surface are accelerated across the plasma sheath and converge at the focal point located at the exit aperture of the ion source. The source exit electrode is biased +25 V to +35 V relative to the source chamber to eliminate the exit of D^+ ions generated within the source chamber. To enhance the D^- ion yield, cesium or barium is introduced into the plasma by using a SEAS getter dispenser. Indeed, a thin coating of cesium or barium can reduce the surface work function and thereby enhance the D^- ion yield by more than two orders of magnitude.

While in a positive D^+ ion-based neutron generator a large amount of secondary emission electrons (generated at the target electrode by the incoming ions and accelerated back, i.e., back-stream) can cause severe damages to the source chamber, in a negative D^- ion-based neutron generator all secondary emission electrons will return to the positively biased target electrode. The absence of back-streaming electrons greatly enhances the efficiency for neutron production and provides significantly better operational reliability. Further, since there are no stable negative molecular deuterium ions, a pure atomic D^- ion beam is extracted from the source and the fusion reactions at the target will occur at the full acceleration energy. It has also been demonstrated that the surface charging voltage, due to a negative ion beam impinging on a nonconducting target surface, is only several volts. This effect allows thick non-conducting Lithium targets for the (D–^{7}Li) reaction to be used and prevents the D^- ion beam from being deflected away from the target electrode.

The accelerated deuterium ions will impinge on a thick Lithium target which takes the form of either a pure Lithium metal or a Lithium compound (such as Li_2O, LiF or LiH) for the 10 and 13 MeV neutrons production. For a D^+ ion beam, only the conducting lithium metal target will not create charging issue. Otherwise, with a D^- ion beam, the target can be either the conducting Lithium metal or the insulating Lithium compounds, which are preferable because

of the much higher melting temperature. To dissipate the high beam power (4 kW), the target electrode is actively cooled by circulating air.

The source chamber is surrounded with rows of ceramic magnets to form a multi-cusp magnetic field configuration for plasma confinement. After exiting the ion source chamber, the D^- ions are accelerated to 400 kV by means of a single gap accelerator column made of high-density polyethylene (HDPE). The hollow part of the HDPE column is connected to a pumping station to maintain an internal column pressure lower than 5×10^{-4} Torr. The high energy neutrons produced via (D-^{7}Li) reactions are emitted isotropically from the Lithium target. As shown in Fig. 3, by positioning the Lithium target in a narrow protuberance in the frontal part of the apparatus and surrounding it with a layer of ^{226}Ra samples, the ^{225}Ra isotope - decaying in ^{225} Ac in about 15 days - can be produced by the 10 and 13 MeV neutrons via the ^{226}Ra(n,2n)^{225}Ra nuclear reaction.

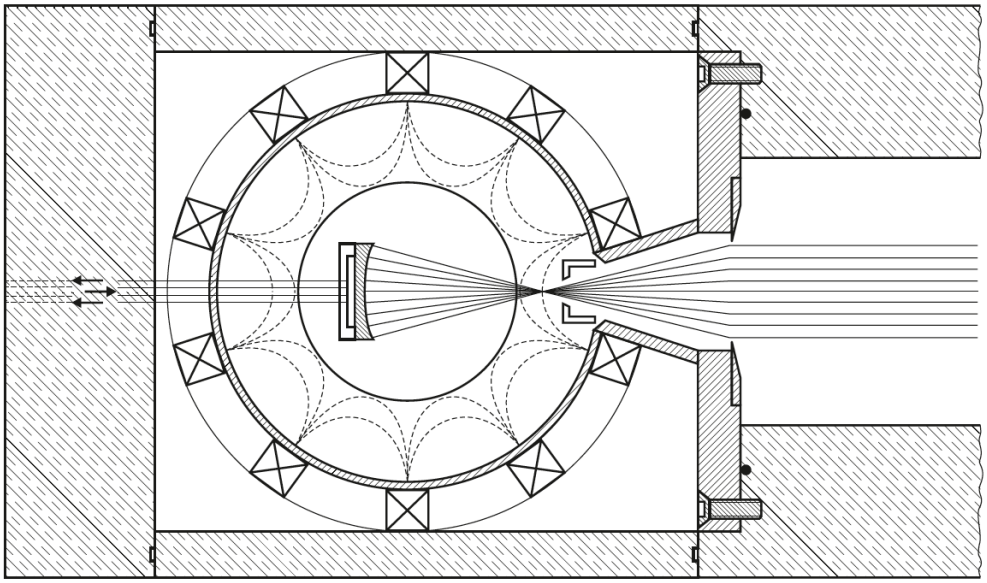

FIG. **1** Vertical cross-section view of the surface-conversion type D^- ion source.

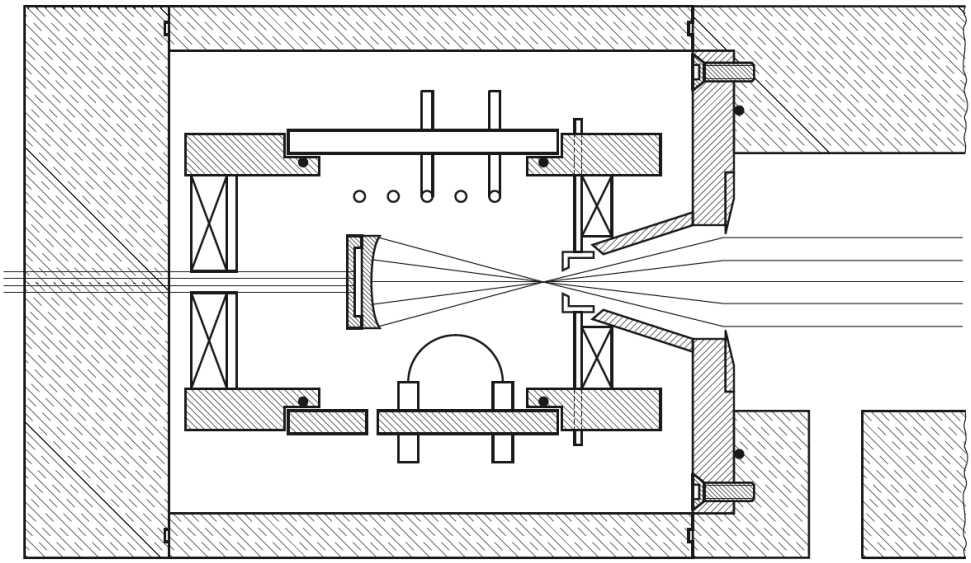

FIG. **2** Top plan view of the surface-conversion type D^- ion source.

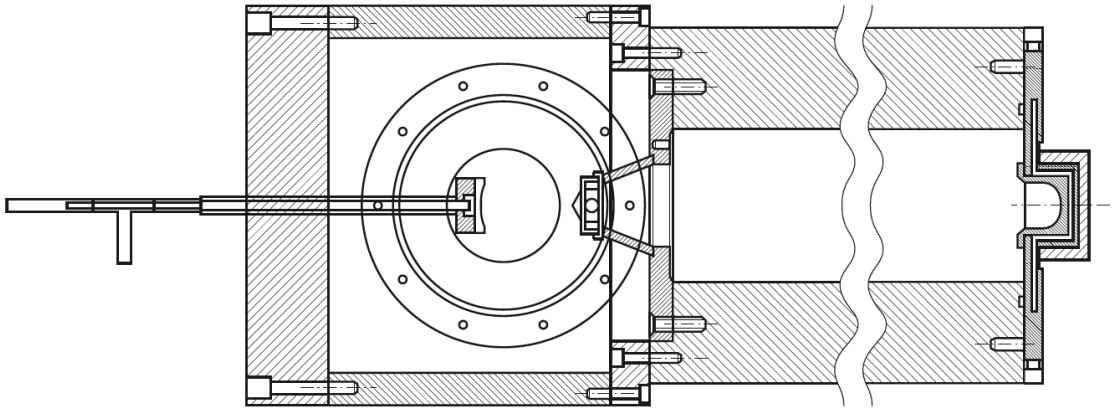

FIG. **3** Cross-sectional view of the whole CNG apparatus for the ^{225}Ac production.

Estimated ^{225}Ac production

Fig. 4 (not in scale) reports a cross-section view of the narrow protuberance in the frontal part of the apparatus. The Li target is placed on a cylindrical Al flange, surrounded by:

- a 2 mm air gap (with forced circulation) for the target cooling;
- the ^{226}Ra samples - for a total thickness of 5 mm - contained in a 0.5 mm thick Al can, positioned at the base and laterally respect to the cylindrical Al flange.

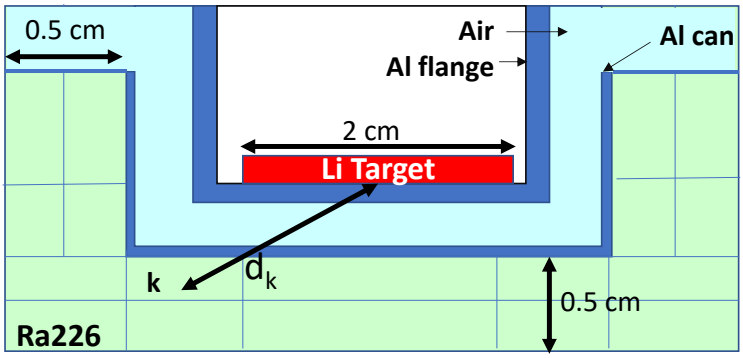

FIG. **4** Cross-section view of the frontal part of the apparatus and surrounding ^{226}Ra samples (light green).
The Li target (red), Al can and flange-holder (blue) and cooling air (light blue) are sketched.

To estimate the ^{225}Ac production, the neutron flux in different portions of the ^{226}Ra samples was evaluated by ^{225}Ac considering its attenuation in depth. For this purpose, as indicated in Fig. 4, the 5 mm sample thickness was divided in 2 x 2.5 mm thick cells (numbered by k, having different shapes in base and lateral positions). By a 400 kV–10 mA D- ion beam, the neutron yield generated by the (D-^{7}Li) reaction results to be:

Y (400 kV-10 mA) = 4 10^{11} n s^{-1} [1]

where neutrons are emitted with 10 and 13 MeV (50% / 50%) energy and a spatial isotropic distribution.

Neutrons are emitted isotropically from the volume of the Li target (1 cm radius, 2 mm thickness) impinged by the D- ion beam. With a good approximation, they can be assumed as emitted from the center of the Li target and the distance "d_k" between (the centre of) every base and lateral cell "k" and (the centre of) the Li target can be calculated:

$$d_k = t_{Al\ flange} + t_{air} + t_{Al\ can} + \Sigma_{Ra} t_{Ra} \qquad [2]$$

Starting from the yield (1) - and the corresponding flux Φ_0 at the Li target outer surface - the neutron flux Φ_k in the centre of every sample portion k can be calculated:

$$\Phi_k = \Phi_0 exp\{-[\Sigma_{Al} t_{Al\ flange} + \Sigma_{air} t_{air} + \Sigma_{Al} t_{Al\ can} + \Sigma_{Ra} t_{Ra}]\} \qquad [3]$$

where "Σ_i" and "t_i" are the total macroscopic cross sections and thicknesses of the material "i" crossed by the neutron flux (i.e., Al flange and can, cooling air and ^{226}Ra sample portions). Using the flux values

"Φ_k", the "production density" of ^{225}Ra atoms per unit time in each sample portion k ($PD_{k,Ra225}$; cm^{-3} s^{-1}) was estimated:

$$PD_{k,Ra225} = N_{Ra226}\,\Phi_k\,\sigma_{n,2n} \qquad [4]$$

where N_{Ra226} is the atomic density of ^{226}Ra (cm^{-3}) and $\sigma_{n,2n}$ is its (n,2n) microscopic cross section. Multiplying the production density [4] in every sample portion k by its volume and adding all the contributes of the (base and lateral) cells, the ^{225}Ra production rate (s^{-1}) of the whole sample can be retrieved. Finally, by taking into account:

- a 15% partial moderation of the neutron flux below ≈7.5 MeV (threshold of the $\sigma_{n,2n}$ reaction, assumed 2 barn for neutrons energy above 7.5 MeV);
- the 44.6% of ^{225}Ra atoms contributing to the ^{225}Ac production, with the activity (A) peak after 13-17 days ($A_{Ac225} = \lambda\, N_{Ra225}$, $\lambda = 5.38\ 10^{-7}$ s^{-1});

with 100 hours of irradiation the ^{225}Ac produced by the 0.5 cm thick ^{226}Ra sample (16.5 cm^3 volume) is estimated to be 11÷13 mCi.

Short market analysis of this route for the local/regional production of ^{225}Ac

Based on data from 2022 the global Radiopharmaceuticals Market is expected to grow with a CAGR of 9.4% for the forecast years 2023-2030.

The actual larger region for this market is USA and the fastest growing is Asia Pacific. Europe is following with increasing numbers.

The market segmentation includes also the radiopharmaceuticals used in diagnostic nuclear medicine. The therapeutic nuclear medicine is supporting the growing of this sector due to new technological advancements, R&D activities, introduction of new medicines, improving legislation steps for the regulations in the usage of radiopharmaceuticals worldwide [99,100,101,102].

A promising input to the market of radioisotopes is given by the recent clinical and commercial successes of drugs used for therapies containing radiopharmaceuticals compounds.

New products are expected to enter the market in the next 5-10 years. This belief is strengthened by R&D activities [103,104,105,106] and good clinical results in the past decades and ongoing clinical trials using radionuclides [107,108,109,110,111,112].

The fast-growing incidence of cancer in the world, as stated by "WHO-Cancer for tomorrow", is expected to be 30.2M in 2040, but it is also growing the number of hospitals and clinics with nuclear medicine practices and the number of companies investing in the research of new radiopharmaceuticals.

One of the main barriers of this market is represented by the shortage of radionuclides that impact on the use on clinical bases and for the developing of further products in this field.

The current supply of ^{225}Ac, with its short half-life, is insufficient for the widespread use and the routine applications in many fields. The production capacity cannot sustain the necessary growth based on essential clinical trials and medicines with this isotope.

The supply is also hindered by the transportation, as ^{225}Ac needs short transit time: the 10 days half-life is forcing a fast delivery with appropriate packing.

The solution should be a scalable commercial production allowing the product to be available on the spot in about once a week (i.e., 100 h irradiation) and the CNG system here presented could potentially satisfy this market request. The apparatus could be useful for hospitals and clinics - but also for diagnostic centres, companies investing in the development of new radiopharmaceuticals, academic and research centres - and could represent a sustainable and secure local/regional supply of ^{225}Ac (as a system complementary to the current supply chain).

Furthermore, the CNG technology could be a feasible solution in a reasonable time-window, without significant impacts on the structures where it will be allocated, thus allowing the positioning, use, commissioning, and maintenance of the ^{225}Ac-production system with a practical management. Indeed, the CNG system has the necessity to be operated in an appropriate concrete structure for the radioprotection of the nearby operators, medical staff, and environment. But, at same time, the bunker required will have relatively small dimensions and could be set by the end-users (hospitals, clinics, pharmaceutical companies, etc.) for the local ^{225}Ac production.
Mapping the actual radioisotopes production infrastructure, we see that, in less than 20 years, 5 European research reactors will stop operations and of course, new building plans are on course, but now with limited potential to increase production capacity in a short time.

Our intent is to give to the market a practical solution, that can be implemented, starting from the current status of our research, with a timeline of maximum 1-2 years. The output is a limited quantity of ^{225}Ac supply, ready to be used on the spot, avoiding the delivery and time problems, and making it possible to plan recurring therapy practices and laboratory studies on a regular basis.

Conclusions

The technology here proposed for the production of Ra225/Ac225 by a 400kV - 10mA (D-Li7) CNG could provide with 100 hours of irradiation the amount of Ac225 for about 65 oncological patients.

The main limitation is represented by the very small quantities of Ra226 produced globally and by its extremely high cost even for few miligrams. For this reason nowadays Ra226 is not a radioisotope of global interest for the treatment of some cancers, for instance as seeds of brachytherapy, and therefore it has an interest confined to the research arena.

Nevertheless:

- from the technological point of view, the program of production of Ra225/Ac225 by the CNGs here described will be feasable in limited times (e.g., one year) in consideration of the compact dimension of the device,
- the technological readiness level of this device is at a stage 2/3 with the first prototype ready to be tested in an suitable environment by a partner company with the necessary skills to test and perform it to the maximum level,
- but, economically, the production of Ac225 through the here described device, could be pursued only by State Agencies or entities which are looking to all means to produce this rarous radioisotope.

Indeed, in the framework of an increasing global demand of radiosotopes, a new revival of the Radium based medical radiotherapy could be realised by State Funds, Governmental Agencies or entities with a dedicated program for the Ra226 production (e.g., collecting it from nuclear facilities for reaseach and energy production).

Finally, it is worth to notice that the technology of CNG systems can be also used for the high-LET and high-RBE radiotherapy aimed to the treatment of severe solid cancers employing a 2.45 MeV neutron beam (produced by the D-D fusion reaction) as shown in the reference of Martellini, Sarotto, Leung, Gherardi, "A Compact Neutron Generator for the nIORT® Treatment of Severe Solid Cancers", Medical Research Archives, ESMED, March 2023, https://doi.org/10.18103/mra.v11i3.3799

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Ethical Statement

The authors are accountable for all aspects of the work and contributed equally to this work.

Author contributions

Maurizio Martellini, Ka-Ngo Leung, Giuseppe Gherardi, and Lidia Falzone contributed equally to this work.

Conflict of Interests

Authors Maurizio Martellini, Ka-Ngo Leung, Giuseppe Gherardi and Lidia Falzone declare that they have no conflict of interest.

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