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The production of radionuclides for nuclear medicine from a compact, low-energy accelerator system

William D. Webster [a,*], Geoffrey T. Parks [a], Dmitry Titov [b], Paul Beasley [c]

[a] Department of Engineering, University of Cambridge, Cambridge, CB2 1PZ, United Kingdom
[b] Siemens Ltd, Corporate Technology, Moscow
[c] Siemens CT TIP Technology and Concepts, Oxford

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ABSTRACT

Introduction: The field of nuclear medicine is reliant on radionuclides for medical imaging procedures and radioimmunotherapy (RIT). The recent shut-downs of key radionuclide producers have highlighted the fragility of the current radionuclide supply network, however. To ensure that nuclear medicine can continue to grow, adding new diagnostic and therapy options to healthcare, novel and reliable production methods are required. Siemens are developing a low-energy, high-current – up to 10 MeV and 1 mA respectively – accelerator. The capability of this low-cost, compact system for radionuclide production, for use in nuclear medicine procedures, has been considered.
Methodology: The production of three medically important radionuclides – ^{89}Zr, ^{64}Cu, and ^{103}Pd – has been considered, via the ^{89}Y(p,n), ^{64}Ni(p,n) and ^{103}Rh(p,n) reactions, respectively. Theoretical cross-sections were generated using TALYS and compared to experimental data available from EXFOR. Stopping power values generated by SRIM have been used, with the TALYS-generated excitation functions, to calculate potential yields and isotopic purity in different irradiation regimes.
Results: The TALYS excitation functions were found to have a good agreement with the experimental data available from the EXFOR database. It was found that both ^{89}Zr and ^{64}Cu could be produced with high isotopic purity (over 99%), with activity yields suitable for medical diagnostics and therapy, at a proton energy of 10 MeV. At 10 MeV, the irradiation of ^{103}Rh produced appreciable quantities of ^{102}Pd, reducing the isotopic purity. A reduction in beam energy to 9.5 MeV increased the radioisotopic purity to 99% with only a small reduction in activity yield.
Conclusion: This work demonstrates that the low-energy, compact accelerator system under development by Siemens would be capable of providing sufficient quantities of ^{89}Zr, ^{64}Cu, and ^{103}Pd for use in medical diagnostics and therapy. It is suggested that the system could be used to produce many other isotopes currently useful to nuclear medicine.

1. Introduction

Radionuclides – such as ^{99m}Tc, ^{18}F and ^{131}I – are a key part of the field of nuclear medicine [1]. Since the development of the radiotracer principle and its first application in the early 1920s, to the development of the SPECT and PET imaging modalities in the 1970s and the progression of radiotherapy for cancer treatment, radioactive isotopes have made an increasingly important contribution to medicine [2]. They have advanced our understanding of disease pathways and progression, allowing the development of more advanced methods for their diagnosis. The recent entry to the market of Xofigo [3], a compound containing the alpha-emitter ^{223}Ra targeted at bone cancer, has opened up a new spectrum of possibilities for targeted radioimmunotherapy (RIT). Theranostics, which involves labelling the same compound with either an imaging or a therapy radionuclide, will allow for better targeting and dose profiling of radiotherapy agents, ultimately improving end treatment for the patient [4]. The range of medically useful radionuclides, and their applications, is continually expanding and the demand for key isotopes such as ^{99m}Tc and ^{18}F is rising [5]. Consistency and security in their supply is paramount to the future development and expansion of nuclear medicine. In recent years, shortages of ^{99m}Tc, a key isotope in a series of nuclear medicine routines and the dominant isotope in the industry as a whole, led to approximately 30 million patients worldwide having their treatments either delayed or cancelled. Initiated by the shut-down of two major isotope producing reactors, the National Research Universal reactor at Chalk River, Canada, and the High Flux Reactor at Petten, the Netherlands, the shortage highlighted the fragility of this key area of the nuclear medicine

* Corresponding author. Tel.: +44 1223748569.
E-mail address: wdw24@cam.ac.uk (W.D. Webster).

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supply chain [6]. With the capabilities and interests of nuclear medicine constantly growing and diversifying, there is the urgent need for the radionuclide production methods to grow and diversify in-kind.

Siemens, in association with engineers at the Rutherford Appleton Laboratory in Oxford, are developing a compact DC electrostatic accelerator for the production of medical radionuclides [7]. Intended to deliver high currents of protons, up to 10 MeV in energy, the system aims to be a low-cost, compact alternative to radionuclide production. Unlike reactor facilities or larger accelerators with yields high enough to supply a large area, this accelerator system aims to deliver isotopes to a local area of a few nuclear medicine facilities. A localised production method will significantly reduce the impact of unexpected facility shut-downs and allow nuclear medicine centres to produce only the quantity of radionuclides they need, reducing unnecessary waste from decay. It could also increase access to new radionuclides for fundamental research and clinical trials. Irradiating at energies of 10 MeV and below additionally has the potential to produce very pure radionuclides, with a minimum amount of isotopic impurities and fewer elemental impurities. The range of isotopes that can be produced at these energies is extensive but it is for the moment uncertain how many current and developing medical radionuclides could be produced in sufficient quantities from such an accelerator system.

This work will consider current, accelerator based production methods for several medically important radionuclides and the potential of the Siemens accelerator system for their production. Theoretical calculations will be used to estimate the activities of radionuclides that could be produced, and their isotopic and elemental purity. These will be compared to available experimental data with a view to quantifying the potential for their low-energy production.

2. A low-energy accelerator for medical radionuclides

Siemens are currently developing a low-energy DC electrostatic accelerator at the Rutherford Appleton Laboratory in Oxford, UK. Based on the design by Cockroft and Walton, using the Greinacher cascade rectifier, this modern interpretation aims to overcome some of the original design's practical limits, which prevented it from achieving high output currents [7]. The accelerator uses a novel system of concentric shells around a central high voltage electrode, placed in a high vacuum. Through this design, the DC voltage generator is integrated with the insulator and accelerator structure, significantly reducing the size of the accelerator system while increasing the currents and voltages it can achieve. The accelerator is intended to have a maximum energy of 10 MeV, a spatial footprint of less than 2 m^2 and achieve currents of up to 1 mA. A simple 'proof-of-principle' system was designed using four air-insulated shells [8]. Beam testing was then carried out using a 7-shell demonstrator in a full-size vacuum vessel that accelerated protons at a low voltage and a reasonably high current. Commissioning of the ion source has also been successful, achieving stable currents of over 300 μA [9]. Other key components such as the power-supplies, transformers and control system have also been tested at full power. Development work now focuses on the shells and insulator design with the aim of achieving much higher voltages, up to the intended 10 MeV. A compact, low-energy, high-current accelerator has many potential industrial applications [7]. Its low energy-consumption and intended low cost would make this accelerator ideal for medical radionuclide production on a smaller, more localised scale. A wide range of radionuclides could be delivered 'on-demand' to nearby nuclear medicine facilities, in large enough quantities for medical diagnostics, therapy or fundamental research. To test this hypothesis, information on the production requirements of several radionuclides – with current or potential application in nuclear medicine – has been collated.

2.1. ^{89}Zr

^{89}Zr has a half-life of 78.41 hours and decays by electron capture (76.6%) and β^+ (22.3%). It is being developed as a new PET isotope, primarily for immunoPET and the imaging of cancerous tumours [10]. It is also ideal for the labelling of monoclonal antibodies (mAbs) [11]. Despite ^{89}Zr's many promising applications, it has had a slow uptake within nuclear medicine. This has been partly blamed on inefficient methods for separating the produced zirconium from its favoured target material, yttrium [12].

There are four potential routes for ^{89}Zr production: $^{89}Y(p,n)$, $^{89}Y(d,2n)$, $^{nat}Sr(\alpha,X)$ and $^{90}Zr(n,2n)$. The yttrium-based irradiation routes are favoured as yttrium is mono-isotopic; it has only one stable isotope, ^{89}Y, so the production of other zirconium isotopes is limited. No expensive target enrichment is required and there is the potential to produce no carrier added, high specific activity ^{89}Zr [10]. In contrast, the alpha irradiation of natural strontium, which has four stable isotopes – ^{84}Sr, ^{86}Sr, ^{87}Sr and ^{88}Sr – leads to the production of more contaminant zirconium isotopes.

2.2. ^{64}Cu

^{64}Cu has a half-life of 12.7 hours and is both a β^- (38.5%) and β^+ emitter (17.6%). This produces ^{64}Zn and ^{64}Ni respectively. The remainder of the decay is electron capture, which also produces ^{64}Ni. As a result of this, ^{64}Cu has been identified as a bi-functional radionuclide and has applications in both PET imaging and RIT [13]. Copper itself is the third most abundant trace metal in the human body and has many roles in human biochemistry and metabolism [14]. ^{64}Cu is ideal for examining those roles, via PET, that are too slow for analysis by shorter lived isotopes [15]. It also has roles in imaging of peptides and antibodies, exploring cardiovascular disease, inflammation and cancer [16]. The most common mechanism for its production is the $^{64}Ni(p,n)$ reaction [13,15,16].

2.3. ^{103}Pd

^{103}Pd has a half-life of 16.991 days and decays primarily by electron capture to ^{103m}Rh, which subsequently decays through internal transition. The combination of Auger-electrons and X-rays emitted by these decay processes has made ^{103}Pd a favoured isotope for brachytherapy [17]. The radionuclide is prepared into small seeds which are then implanted into sites of rapid cancer growth and proliferation. This is known as interstitial implantation. ^{125}I was the dominant isotope in this field of medicine but ^{103}Pd was found to have more suitable properties for treating rapidly growing tumours [18]. It was first proposed for interstitial implants in 1958 but it wasn't until 1987 that it became commercially available [19]. Since then, ^{103}Pd has been used successfully to treat a wide range of cancers including eye, brain, neck, uterus and colon [20]. It is predominantly produced via the $^{103}Rh(p,n)$ reaction [17,21]. It can also be produced via neutron capture on ^{102}Pd in nuclear reactors. This was the preferred production mechanism in its early years but the cost of enriching a ^{102}Pd target and the poor yields of the reaction proved prohibitive and cyclotrons became the dominant source [22].

2.4. Production requirements

There are strict regulations on the use of radionuclides in radiopharmaceuticals and nuclear medicine. Radionuclides are required to have a very high standard of radionuclidic and radiochemical purity [23]. This can be achieved through a combination of using enriched target materials (in this work it has been assumed that all

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