COMPACT AND EFFICIENT ACCELERATORS FOR RADIOISOTOPE PRODUCTION

C. Oliver†, CIEMAT, Madrid, Spain

Abstract

The production in an efficient way of radioisotopes for medical use is crucial. With the closing in the next ten years of nuclear reactors the problem of the production of some of them is being critical. New approaches of producing these radioisotopes via accelerators are being developed. In the other hand a big effort is being made for making the accelerators for the production of radioisotopes more compact, efficient and with an optimized cost. This paper describes the recent advances in this kind of accelerator techniques.

RADIONUCLIDE NEEDS

Cancer, cardiovascular and Alzheimer diseases and other dementias are found among the top leading causes of death and their occurrence tends to increase given the population ageing as well the current unhealthy practices, among other risk factors. A strong effort should be made for the development and implementation of techniques ensuring a better understanding of the diseases causes and allowing an early diagnosis and treatment. Especially important is to guarantee their access in low-income countries whose availability, in the case of cancer, is less than 30%, compared to more than 90% of high-income countries [1].

Although radioisotopes are nowadays extensively used in many applications as industry, national security and material science among others, it is in medicine that radionuclides play an essential role. In nuclear medicine, the use of radionuclides entails the injection into the patient of a radionuclide combined with a biologically active molecule that can preferentially localize specific organs or tumors. In case of imaging purposes, the radionuclides will decay by emitting gamma radiation which will be detected from the outside. For therapeutic purposes the radionuclide should decay emitting highly ionization particles which will destroy the malignant cells.

Radioisotopes For Diagnosis

Unlike other competing modalities such as MIR, CT or ultrasounds, nuclear medicine imaging provides unique information on physiological function and metabolic activity and thereby is able to give specific information about rapidly growing tissues such as tumors, metastasis, or even infections [2]. This will be a useful tool for the diagnosis, treatment planning and follow-up of different diseases. The optimum isotope for nuclear imaging will suffer γ-decay with energies ranging from 100 to 300 keV to be not significantly attenuated in the body and efficiently detected by the cameras. The half-life should be short to reduce the dose to the patient, but some longer half-life radioisotopes could be required for the tracing of longer metabolism processes. The use of radionuclides for molecular imaging in nuclear medicine can be broken into two modalities: Single-photon emission computed tomography (SPECT) and positron emission tomography (PET).

SPECT radionuclides injected into the patient will decay with the emission of a single γ (by isomeric transition or electron capture) which will be detected by a scintillator camera rotating around the patient to reconstruct a 3D SPECT image. ^{99m}Tc radionuclide is the most widely used in medicine, being employed in 80% of all nuclear medicine procedures [3]. The low energy γ ray, minimizing the radiation dose to the patient, its versatile chemistry which allows the formation of different tracers and the half-life of six hours make ^{99m}Tc the workhorse of the nuclear imaging.

A more recent development is the PET modality in where a positron-emitting isotope introduced into the patient decays with a positron, which promptly annihilates with a nearby electron resulting in the simultaneous emission of two identifiable 511 keV γ rays in opposite directions. They are subsequently detected in coincidence by a PET camera, providing a very precise reconstruction of the organ or tumor. The main PET isotopes, ^{18}F-FDG (the most commonly used), as well those non-metals with very short half-life and low energy positron emitters (^{11}C, ^{13}N and ^{15}O) are used predominantly in oncology being their applications in neurology and cardiology steadily growing [4]. The advances in PET technology, with the hybrid functional and anatomical imaging (high definition HD PET/CT, PET/MRI) or recently the Time-of-flight PET (TOF/PET), have improved the image diagnostic accuracy and continue to expand the clinical diagnostic horizons of PET.

Therapeutic Radioisotopes

The radiopharmaceutical therapy relies on the use of radionuclides with high ionizing emitted radiation, delivering a large therapeutic dose to the targeted disease cells while minimizing damage to the surrounding healthy tissues [5].

The most effective isotopes for therapeutic purposes are β^-, α and Auger emitters. They have different radiobiological effectiveness and range of action, offering the possibility of choosing a nuclide whose physical and nuclear characteristics are better matched with a particular tumor type. The very short-range of Auger electrons (~10 μm) makes them very suited for therapy of small metastases and disseminated cancer cells [6]. Targeted Alpha Therapy (TAT), driven by the ^{223}Ra-Xofigo® radiopharmaceutical [7], is a growing field since the short range (up to 100 μm) of the α radiation can act in the DNA. Finally,

† concepcion.oliver@ciemat.es

β^--particles (ranges of ~1 mm) are better suited for treating bigger lesions or macro-metastatic [8].

Exciting advances are taking place in the targeted radiomunotherapy (RIT), the development of new nanoparticle platforms [9] and in the use of theranositcs, which involves labeling the same compound with an imaging and a therapy radionuclide offering a better-targeted diagnosis and treatments [10]. However, it must be underlined that extensive research is needed and successful application of radionuclide therapy is linked to the availability of radionuclides in high purity and adequate specific activity.

RADIOISOTOPE PRODUCTION

Radioisotopes for imaging and therapeutic purposes are produced in nuclear research reactors and particle accelerators.

Neutron-rich radioisotopes (^{99m}Tc, ^{131}I, ^{166}Ho, ^{177}Lu…) are generally produced in research reactors, with higher neutron flux and fuel enrichment than power reactor. Reactor-produced isotopes have generally high production yield but low specific activity.

On the other hand, neutron-deficient radioisotopes (^{18}F, ^{201}Tl, ^{123}I, ^{67}Ga …) are typically produced via charged-particle reactions in accelerators. Accelerators offer several advantages over nuclear reactors: smaller amount of radioactive waste, minimal nuclear weapon proliferation risk (except accelerator-driven system), less capital, operating and decommissioning costs and easier access than to reactors. Additionally they produce high specific activity products, with fewer radioisotopic impurities by selecting the energy window for irradiation, allowing suitable chemical or physical techniques for separation. However, as main drawback, sometimes enriched (and expensive) targets are required for the production of a sufficient amount of radionuclide, given the lower production yield compared to reactors.

The use of generator system, based on the production of a parent nuclide (e.g. ^{99}Mo) in reactors or accelerators, and the extraction of the daughter isotope (e.g. ^{99m}Tc) by efficient separation techniques, enables the on-demand availability of important radionuclides.

Present and Mid-Term Future of Isotope Production Market

Three main issues are leading the present and short to medium-term future radionuclide of the isotope production market: the crisis in reactor-based production, the demand for very short-lives radionuclides production and the need of therapeutic isotopes.

After the recent shutdown of two of the most reactor producers (OSIRIS in 2015 and NRU in 2016), the worldwide supply of reactor-produced medical isotopes relies, basically, on only six nuclear reactors. Main challenges on research reactors include reactors ageing (most constructed in the 1960s or earlier), the timeline of future proposals (MYRRHA, PALLAS) and the need of reducing reliance on HEU.

The current situation is a major concern for the most used radionuclide, ^{99}Mo/^{99m}Tc, where the shortages suffered in the last decade underscored the vulnerability in the supply chain [11]. Expected ^{99}M supply shortages after 2016 [12] and a demand increase of 0.5% and 5% per year for mature and emerging markets, respectively [13], urge the need to consolidate the isotope production with different accelerator-based approaches.

Furthermore, the expansion of the hallmark of nuclear medicine, PET, requires the availability of very short half-lives radioisotopes (^{11}C: 20.4 min, ^{13}N:10.0 min, ^{15}O: 2min). This is incompatible with the current remote distribution system that relies upon a few regional production centers to cater for the entire world's supply. As a consequence, the use of such short lived radionuclides is often restricted to places with local production or places that are well connected to production facilities. This is even more problematic in remote areas or in low-income countries. The development of compact, low cost accelerators would enable the on-site supply of very short-life isotopes, expanding the use of and contributing to democratize the use of radiopharmaceuticals in developing countries.

Finally, despite the promising preliminary results obtained in the clinical studies, the costs and limited availability of a number of the best candidate therapeutic radioisotopes have limited their clinical use. The increase of production capability would foster the research of new nuclear medicine procedures.

ACCELERATORS

The investigation of new isotope production routes based on accelerator and the development of compact, reliable and low-cost machines can play a very important role in addressing the above problems, ensuring a reliable supply of medical isotopes in future.

Different reactions can be used for isotope production based on accelerators: direct production with hadron accelerators (cyclotron, linacs, FFAG, electrostatic machines), photo-induced reactions with electron machines, n-induced reactions (well based on Compact Accelerated Neutron Sources -CANS - or on high energy spallation-based reaction sources) or particle-induced fission reactions as in accelerator driven reactors.

The most suitable production route should provide the maximum yield of desired radionuclide combined with the minimum level of impurities. The choice of beam parameters (energy and current) plays a key role in the most demanding accelerator features: small footprint, low cost and efficiency. As the energy increases, more isotopes become accessible but it will increase the cost both in equipment and infrastructure as well the number of side channel reactions which can produce the unwanted radionuclides. Concerning intensity, high current would result in higher production yields but at the cost of additional target development, shielding and maintenance level. Therefore, a trade-off should be made between higher energy and/or current, resulting in a more versatile facility

ISBN 978-3-95450-182-3

and the compact, low cost facility achieved with beam parameters adapted to the real project needs.

It should be highlighted that the expansion and consolidation of isotope accelerator-based production relies not only in the development of compact, low-cost, reliable accelerator technologies but also in the targetry development, target processing and recycling to result in a cost-effective radiopharmaceutical fulfilling standard requirements.

This paper summarizes compact and efficient solutions for most important radioisotopes, limiting the description to low and medium energy machines, with special focus on PET and ^{99m}Tc radionuclide. The review of high energy, high power accelerators, mainly multi-purpose facilities, and uranium-based combined accelerator/reactor approaches are beyond the scope of this paper.

CYCLOTRONS

The very mature technology, compactness, relatively-low cost and commercially availability have led cyclotrons to be the most used accelerators for radioisotope production. The number of cyclotrons for that purpose has increased in the last decades and is expected to increase in conjunction with the expanding role of PET and SPECT in molecular imaging [14].

Almost all current available commercial cyclotrons are negative ion machines which particles, after acceleration, are effectively extracted by stripping mechanism to one or several targets. Internal/external ion sources are chosen as a trade-off between compactness and the demanded beam current. Typically internal H^- PIG ion sources are the preferred cost effective choice for currents <200 μA [15].

Current cyclotrons have been developed according to the main required features required for PET radioisotope production (<15 MeV, low current), SPECT and longer PET radioisotope (15-30 MeV, high current) and therapeutic applications (>30 MeV, high current). A wide range of cyclotrons for isotope production have been developed by companies and research centers, reported in Table 1.

PET Cyclotrons

With the PET expansion, there has been a surge in the production of low energy cyclotrons (9-19 MeV) exclusively for the production of short lived PET isotopes such as ^{18}F, ^{11}C, ^{13}N and ^{15}O. The short half-life demands moving from the centralized current production model to a localized, on-demand dose, production by cyclotrons in the (or very near) hospital-based facility. As consequence, the emphasis is made in the need of achieving compact, low cost solutions which allow the PET technology expansion at an affordable cost to the developing countries.

Although the beam requirements for the production of such isotopes are very modest (<15 MeV, a few tens of μA), the need of irradiation times lower than typically 3 half-life has motivated the beam current increase of several PET cyclotron in the last decade (~150 μA).

Most cyclotrons are based on an internal H^- PIG ion source, high efficiency and variable energy extraction and superconducting magnets, which allow a reduction in the power consumption, size and weight. Some commercial solutions include fully automated radiochemistry systems, option of self-shielding and multiple targets. Important features driven by the desired location at hospitals are reliability, user-friendly, flexibility, minimum personnel dose, low-cost and minimum power and cooling requirements. A recent alternative to self-shielding of higher current PET cyclotrons is the use of an integrated compact beam-line to move the target (local-shielded) away from the cyclotron, reducing its radiation damage, activation and the dose exposure to the personnel as well optimizing the radioisotope production by providing active beam focusing and steering [16].

Table 1: Main Cyclotrons for Radioisotope Production

Cyclotron	E_p (MeV)	I_p (μA)	Peak B (T)	Weight (Tons)
LOW ENERGY				
GENtrace, GE [17]	7.8	-	2.2	6.7
MINItrace, GE [17]	9.6	>50	2.2	9.1
Eclipse, Siemens [18]	11	>120	1.9	11
Cyclone10, IBA [19]	10	>150	1.9	12
Cyclone11, IBA [20]	11	120	1.9	13
TR14, ACSI [21]	14	>100	2.1	23
BG-75, ABT [22]	7.5	5	1.8	3.2
AMIT, CIEMAT [23]	8.5	>10	4	-
ION12SC, Ionetix [24]	12	~10	4.5	2
LOTUS [25]	12	50	2.3	-
MEDIUM ENERGY				
BEST15, BEST[26]	15	400	-	14 (magnet)
PETrace ,GE [17]	16.5	>100	1.9	22
Cyclone18 IBA [27]	18	150	1.9	25
KIUBE, IBA [28]	18	<300	-	18
TR19, ACSI [21]	19	>300	2.1	22
TR24, ACSI [21]	24	>300	2.1	84
BEST25, BEST [26]	25	400	-	50 (magnet)
Cyclone30,IBA [29]	30	<1500	1.7	50
TR30, ACSI [30]	30	>1000	1.9	56
HIGH ENERGY				
BEST35, BEST [26]	35	1000	-	55 (magnet)
Cyclone70, IBA [31]	70	<750	1.6	145
BEST70, BEST [32]	70	700	1.6	195 (magnet)

As it can be seen in Table 1, there is a wide range of cyclotrons (some of them under development e.g. AMIT, LOTUS) providing energies lower than 15 MeV and limited current (25-100μA, although some products offer even higher) which allows a low-cost local PET production. The low energy (<10 MeV) choice in some machines provides a very compact design (with weight <10 tons), as in the case of MINItrace, BG-75 and AMIT cyclotrons.

It should be noted the use of a high magnetic field (4.5T), cold iron solution in the ION-12SC cyclotron, leading to a significant weight reduction (~2 tons). Additionally, some products (e.g. BG-75) offer fully integrated solutions, including microchemistry and Quality Control modules.

SPECT Cyclotrons

A range of cyclotron with medium energy (15-30 MeV) and relative high current (>300μA) are commercially available for a more versatile radionuclide production (^{67}Ga, ^{124}I, ^{123}I, ^{111}In, ^{201}Tl…). As a consequence of higher energies, these cyclotrons are bigger, heavier and more expensive than the devoted PET cyclotrons. The longer half-lives of SPECT isotopes allow cyclotrons to be located in dedicated larger throughput production centers connected to a good transport network. Although these facilities can be used for the combined production of ^{99m}Tc and PET radionuclides, attention should be paid to both practical scheduling.

Especially mention should be made with the cyclotron-based direct production of ^{99m}Tc, by using proton irradiation of an enriched ^{100}Mo solid target, ^{100}Mo(p,2n)^{99m}Tc, the most mature technology available, in a short-term, to develop a ^{99m}Tc local distribution. Firstly proposed by Beaver in 1971 [33], much progress has been made in the last several years in developing suitable targetry and chemistry for proton bombardment [34]. Although 16-18 MeV proton beam can be sufficient to support local ^{99m}Tc local demand, moving to 20-24 MeV energy range cyclotrons would double the production yield [35] making the manufacturing process shorter and more cost-effective per hour of manufacturing time. It has been found that the quality of the product (provided a good energy incident selection, proper ^{100}Mo preparation and purification and time after end of bombardment) as well the imaging efficacy are fully adequate for clinical use [36].

Different cyclotrons are commercially available for SPECT (see Table 1). There is a high number of solutions in the 15-20 MeV range which offer 100-400μA relatively compact cyclotrons (with weights ~22 tons), being a good option for PET and SPECT isotope production. Higher energy (up to 30 MeV) cyclotrons with much higher current (>300μA) can provide higher production yield but at the cost of much heavier, bigger and costly machines. Additionally, it should be mentioned the development of some medical isotope production cyclotrons with an ironless or nearly ironless magnetic system, energy range of 20-25 MeV, and weight less than a few tons [37,38].

High Energy Cyclotrons

Cyclotrons with higher energies (~70 MeV) are involved in the production of additional radioisotopes as ^{82}Sr, ^{68}Ge, ^{67}Cu, ^{211}At, ^{47}Sc, ^{52}Fe, ^{55}Co and ^{76}Br. The primary need is for higher current cyclotrons in the 1mA range. These accelerators can provide beams of different energy and accelerate also α or deuterons. Two companies offer 70 MeV commercial solutions: CYCLONE70 (IBA) [31] and BEST70 (BCSI) [32].

LINACS

Although cyclotrons are the standard low-energy accelerator for medical applications, linear accelerators have been proven to be a feasible alternative. The advantage of linacs is the possibility of using multiple simultaneous target stations at several beam energies, the limited radiation levels and the associated reduced shielding as well the qualities of ease of operation and limited maintenance.

A compact p linac-based radioisotope production, already commercially available, since 2005, is the PULSAR®7 system, by AccSys Technology Inc., an RFQ-DTL machine producing a 7 MeV, 9 mA, 1% duty cycle proton beam for ^{18}F-FDG production [39]. Such low energy has been chosen to reduce the footprint, weight and cost of the accelerator, allowing, in the Mobile PULSAR™ variation, the installation of the accelerator in medical trailers, the only truly mobile PET lab available.

New developments in hadron linear accelerators technologies aimed to minimization of construction costs by reducing the linac length. An example is the novel based-linac solution for radioisotope production, developed by CERN, consisting in a high frequency 750 MHz compact RFQ linear proton accelerator [40]. Its modular design allows the combination of 2 RFQ modules to produce a 10 MeV, 20 μA average current, 4% duty cycle in only 4 meter. Solid-state amplifiers will be used for reduced cost and increased reliability, demanded by the radioisotope production application. The main advantage respect cyclotron is the reduced shielding (limited to the target). The RFQ beam tests will start soon.

Concerning electron linacs, several feasibility studies have demonstrated their viability [41]. A 25-50 MeV, kW electron beam (mainly already developed for the radiation processing industry) is required, which will impact on a high-Z converter target (typically W, Ta) to produce Bremsstrahlung radiation (10-25 MeV). Radionuclides can be produced typically either via photo-nuclear (photo-neutron and photo-proton) or photo-fission reactions.

Electron driven isotope production has several advantages. Electron accelerators, including the recent advances in superconducting radiofrequency (SRF) accelerating structures, are generally reliable, high current machines with a more compact, simpler and more cost-effective design than corresponding hadron linacs. The main advantage compared to cyclotron-based production is the use of a simpler, cheaper and thicker target, as no enriched materials are need and as not be subjected to the direct beam heating. In addition, fewer gamma-reaction channels are available resulting in a reduction of the undesired isotopes and the consequent radioactive waste.

Despite the numerous advantages this route is not widely used yet. The photo-induced yield production is typically one to two orders smaller than nuclear reactions obtained with cyclotron. This demands a high power electron linac, which in combination with a thicker target, could produce a total isotope yield sufficiently high. On the other hand, a carefully design of electron-photon converter is required, where only a fraction of electrons are

converted to photons, with the consequent energy inefficiency and activation. A proposal is the use of a superconducting RF Energy Recovery Linac ERL technology for radioisotope production, which would allow recycling more than 90% of the beam power [42]. As a consequence there is a considerable reduction of activation of the facility, with the additional benefit of energy cost to produce a given amount of isotope.

High-energy electrons accelerators can be used to produced short-life PET radionuclides (^{11}C, ^{13}N, ^{15}O, ^{18}F) via γ-n reaction on their respectively natural abundant isotope target nuclei (^{12}C, ^{14}N, ^{16}O,^{19}F respectively), avoiding the use of enriched, and therefore expensive, targets [47]. Other medical radionuclides such as ^{48}Sc, ^{148}P, ^{67}Cu, ^{225}Ac can also be produced on electron accelerators [43]. In addition to the most favored ^{99m}Tc direct production with cyclotrons,^{100}Mo(γ,n)^{99}Mo is a promising ^{99m}Tc route, requiring the production of a 14 MeV photon by an electron beam [44]. The lower specific activity compared with the ^{99}Mo produced by fission has required the development of an automated separation process for low specific ^{99}Mo [45].

ELECTROSTATIC ACCELERATORS

Electrostatic accelerators arise also as an alternative to the reactor-based radioisotope production. A good example is the ONIAC system, developed by Siemens in collaboration with STFC [46]. The accelerator uses a novel system of concentric shells around a central high voltage electrode, placed in a high vacuum. The key innovation for the proposed concept is to integrate the DC voltage generator with the insulator and accelerator structure. It provides 10 MeV p (5 MeV d) with very high current to a few mA, with a reduced spatial footprint (2 m^2). Irradiating at energies lower than 10 MeV has the potential to produce very pure radionuclides, with a minimum amount of isotopic impurities and fewer elemental impurities. The low machine activation, low consumption and cost, and the simple, compact and modular design makes ONIAC ideal for medical radionuclide production on a localized production system.

OTHER ACCELERATOR-BASED ALTERNATIVES FOR ISOTOPE PRODUCTION

Beyond the most common accelerators (cyclotrons, linacs, electrostatic machines), some other promising technologies emerge with possible effective applications for radionuclide production.

The strong focusing present in a Fixed-Field Alternating Gradient (FFAG) accelerator results in higher beam currents that can be used for isotope production. An example is the proposal of a compact non-scaling FFAG [47] providing 28 MeV for ^{99m}Tc and other new isotopes. Separator sector magnets with non-scaling, non-linear field gradients are optimized to achieve isochronism at the level of 0.3%, enabling CW operation. A thin internal target could improve the production efficiency [48]. The maximum magnet radius (1.7 m) is small enough to allow on-site isotope production at hospitals.

Some other proposals, not yet available in a short-term, are those based on plasma and laser techniques. The high-peak powers lasers developed in many laboratories worldwide [49] could provide the production of isotopes of medical interest through as (γ, n) and (γ, p) reactions [50]. The simulation of the high specific activity production of ^{99}Mo/^{99m}Tc,^{225}Ra/^{225}Ac and ^{186}Re using the high-brilliance γ-beam of the Extreme Light Infrastructure – Nuclear Physics (ELI–NP) conclude that it provides an unprecedented possibility for the production of new radioisotopes in sufficient quantities for nuclear medicine research [51]. In addition to photon-nuclear reactions, the MeV protons, produced by an intense (PetaWatt) laser beam interacting with solid targets, can also be used for PET isotope production [52]. The table-top TW laser proposals [53], with the easy to shield the compact laser technology, make laser-systems a future option for on-site isotope production. On the other hand, studies are ongoing to analyze the potential of plasma facilities for the production of short-lived radioisotopes [54]. However, the cost and timeline of these new accelerating technologies for isotope production remain to be studied.

CONCLUSION

Accelerators play an important role in the achievement of a stable global supply chain for radioisotopes with medical applications. Different accelerating technologies have been reviewed. The compact, low-cost and efficient solutions presented here can contribute to expand medical nuclear procedures worldwide.

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