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REVIEW ARTICLE

ARRONAX, a high-energy and high-intensity cyclotron for nuclear medicine

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Abstract
Purpose This study was aimed at establishing a list of radionuclides of interest for nuclear medicine that can be produced in a high-intensity and high-energy cyclotron.
Methods We have considered both therapeutic and positron emission tomography radionuclides that can be produced using a high-energy and a high-intensity cyclotron such as ARRONAX, which will be operating in Nantes (France) by the end of 2008. Novel radionuclides or radionuclides of current limited availability have been selected according to the following criteria: emission of positrons, low-energy beta or alpha particles, stable or short half-life daughters, half-life between 3 h and 10 days or generator-produced, favourable dosimetry, production from stable isotopes with reasonable cross sections.
Results Three radionuclides appear well suited to targeted radionuclide therapy using beta (^{67}Cu, ^{47}Sc) or alpha (^{211}At) particles. Positron emitters allowing dosimetry studies prior to radionuclide therapy (^{64}Cu, ^{124}I, ^{44}Sc), or that can be generator-produced (^{82}Rb, ^{68}Ga) or providing the opportunity of a new imaging modality (^{44}Sc) are considered to have a great interest at short term whereas ^{86}Y, ^{52}Fe, ^{55}Co, ^{76}Br or ^{89}Zr are considered to have a potential interest at middle term.
Conclusions Several radionuclides not currently used in routine nuclear medicine or not available in sufficient amount for clinical research have been selected for future production. High-energy, high-intensity cyclotrons are necessary to produce some of the selected radionuclides and make possible future clinical developments in nuclear medicine. Associated with appropriate carriers, these radionuclides will respond to a maximum of unmet clinical needs.

Keywords Cyclotron · Radionuclides · Positron emission tomography (PET) · Targeted radionuclide therapy · Dosimetry

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Introduction

A limited number of radionuclides is available for systemic diagnostic and therapeutic applications. Several other innovative radionuclides have been proposed to develop new diagnostic or therapeutic radiopharmaceuticals, but their availability is quite limited. For example, ^{124}I or ^{68}Ga for positron emission tomography (PET) [1] or ^{67}Cu for therapy [2] are considered as potentially very useful but not readily available. Pairs of beta+/beta− radionuclides, such as ^{124}I/^{131}I [3] or ^{64}Cu/^{67}Cu, would permit coordinated dosimetric PET imaging and therapy. Finally, the current development of radiopharmaceuticals using alpha emitters in therapy is limited to a few radionuclides, the most commonly used being ^{223}Ra (for bone pain palliation), ^{213}Bi and ^{211}At [4]. Paradoxically, the production of radionuclides (extraction from nuclear waste, reactors or

cyclotrons) tends to become more limited with the dismantling of research nuclear reactors and cyclotrons, which is not balanced by new equipments that are almost always dedicated to ^{18}F production.

This is the reason why a new high-energy and high-intensity cyclotron, named ARRONAX and devoted to radionuclide production for nuclear medicine, will be operating in Nantes, France, at the end of 2008. The rationale for such an important financial investment and the choice of the cyclotron characteristics were based on the potential usefulness of the radionuclides that could be produced. Thus, a list of radionuclides considered for production at ARRONAX was established that is presented along with a short review for each isotope of interest.

Materials and methods

ARRONAX characteristics

ARRONAX (http://www.cyclotron-nantes.fr/) will turn into operation in the last quarter of 2008. This cyclotron will accelerate both positive ions (HH+, He++) and negative ions (H−, D−) up to 70 MeV. It has been designed to deliver up to 750 μA of protons and 35 μA of alpha particles. The capabilities of ARRONAX are summarised in Table 1.

Negative ions will be extracted using the stripper foil technique. This technique allows beam extraction within a large range of incident energy by changing the radial position of the foil. Here, the proton beam can be extracted from 30 MeV up to 70 MeV. ARRONAX will be equipped with two of such devices diametrically opposed. This will give it the ability to deliver two beams with different energies and intensities (up to 350 μA each for protons) at the same time.

Positive ions will be extracted using an electromagnetic septum. In this case, only one beam output will be available at a fixed energy (70 MeV for alpha particles and 17.5 MeV for protons)

Table 1 Characteristics of the available beams at ARRONAX

Beam	Accelerated particles	Energy range (MeV)	Intensity (μA)
Protons	H−	30–70	<350 (×2)
	HH+	17.5	<50
Deuterons	D−	15–35	50[a]
α-particles	He++	70	<35

[a] The deuteron intensity limit is set for radioprotection reasons by the authorities

The surrounding facility

ARRONAX will deliver a particle beam in six experimental vaults named AX, A1, A2, P1, P2 and P3 (Fig. 1). Due to the extraction method, which is different for negative and positive ions, protons and deuterons will be available in every experimental vaults whereas alpha particles will be available only in vaults A1, A2 and AX.

Vaults A1, A2, P1, P2 and P3 will be devoted to radionuclide production and will be equipped with appropriate target systems and with a pneumatic transfer system (rabbit system) connected to the hot cells. These five dedicated vaults will allow flexibility and, together with the high intensity, will ensure availability of radionuclides on a regular schedule. Vault P1 will also be used to perform Research and Development on high-intensity current beams.

The largest vault, AX, will be devoted to experiments on radiolysis, radiobiology and physics and for high-grade student training. This vault will possess two specific characteristics:

- The beam line in vault AX will deliver a vertical beam. This will be very useful to irradiate solutions for radiolysis and radiobiology experiments.
- The alpha beam can be pulsed. Each pulse can contain up to 7×10^6 alpha particles within a pulse width equal to 3.3 ns. A variable delay (from 1 ms up to a few seconds) can be set between consecutive pulses.

Finally, several laboratories (radiochemistry, biochemistry, hot cells, radiolabelling, chemical analysis, nuclear metrology...) will be available allowing the production of radionuclides according to good manufacturing practices.

Selection criteria for PET radionuclides

Half-life

^{18}F-FDG is considered as a real breakthrough in diagnostic nuclear medicine [5]. However, if the physical half-life of ^{18}F fits well with the fast kinetics of small molecules such as FDG, it does not fit with the relatively long kinetics of antibodies or of many other biological molecules. Short half-lives also complicate the logistics. As a result, all the positron emitters considered here have a half-life between 3 and 150 h or may be produced via generators.

Decay scheme A beta+ branching ratio greater than 10% was arbitrarily considered as a minimum. Radionuclides decaying to either a stable or rapidly decaying daughter nuclei into a stable element have been favoured.

Beam energy We have selected radionuclides that require high-energy beam for their production to benefit from ARRONAX's capabilities

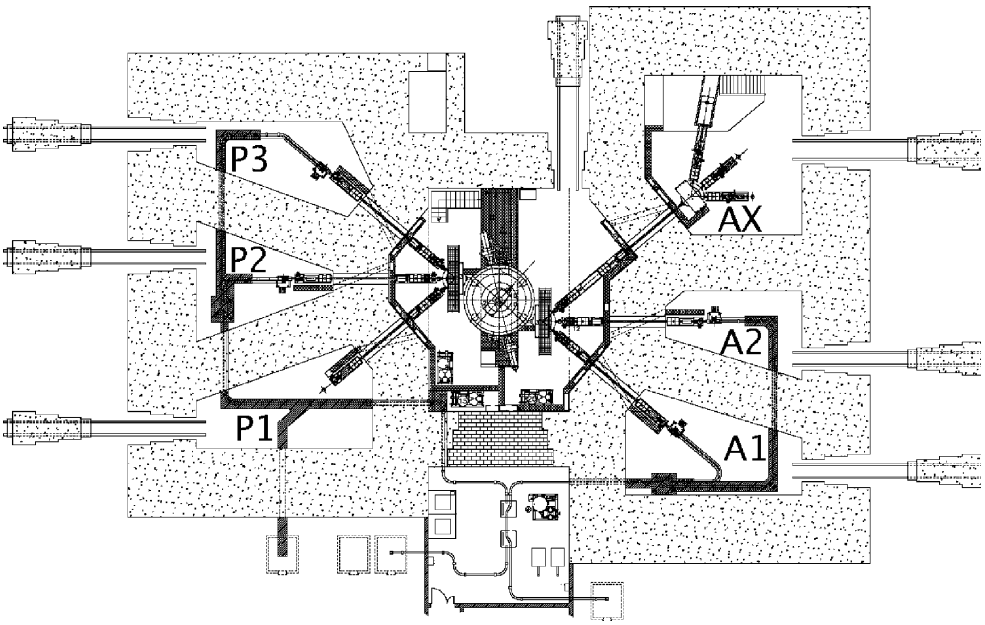

Fig. 1 Schematic view of the ARRONAX facility. The view does not show the different laboratories located around the vaults

Beta+ energy The positron must slow down to rest before it can annihilate with an electron. Thus, annihilation takes place in a spherical volume whose radius depends on the energy. Consequently, the smaller the positron energy is, the better the image.

Associated gamma emission During their decay, most radionuclides emit cascade photons that impact directly on the dose of irradiation delivered to the patient and the medical staff. Gamma exposure rate constants, $\Gamma_{20\ keV}$ (μSv m^2/MBq h), have been calculated for the medical staff and compared with published data, when available (http://www.nchps.org). The calculation takes into account the number of gamma and X-ray emissions per disintegration, their energies and the absorption coefficient of air at these energies. Only gamma and X-rays above 20 keV were considered. Photons of lower energy have low penetrating power and were neglected.

Selection criteria for therapeutic radionuclides

Half-life Half-life should be long enough to allow for radionuclide targeting, from 3 h to 10 days.

Decay scheme Radionuclides must decay to either a stable or rapidly decaying daughter nuclei.

Beam energy Production of a beta− emitter with a cyclotron requires, in general, a high-energy beam. The reaction process has a low occurrence and a highly intense beam is necessary if one wants to make them available at a reasonable cost. ARRONAX will possess all these features.

Beta− energy It is generally considered that short ranges of the order of a few millimetres are best suited to destroy small tumour lesions, thus beta- energies of less than 1 MeV have been favoured.

Associated gamma emission High-energy gammas increase exposure rate; however, gamma or X-rays in the 100 to 200 keV energy range may be useful for imaging.

Results

ARRONAX will make available radionuclides of interest for research in nuclear medicine for both:

Molecular imaging: The number of PET or PET–CT systems as well as system dedicated to small animal imaging is rapidly increasing. This results in an increasing request of positron-emitting radionuclides. Radionuclides with half-lives compatible with long-distance delivery or generator-produced radionuclides will be necessary to reduce costs. In addition, for immuno-PET studies [6, 7] and dosimetry purposes, quantitative imaging studies of radiopharmaceuticals with pharmacokinetics that extend over several hours to a few days, such as antibodies, require radionuclides with half-lives in the same range.
Therapy Targeted radionuclide therapy was extended, over the last 10 years, to a large panel of malignant tumours due to the availability of new carriers, including antibodies and peptides [8, 9], new targeting methods [10] and new radionuclides [11, 12]. ARRONAX will be able to produce both beta and alpha emitters for this therapeutic use.

The main physical properties of the radionuclides of interest for production on ARRONAX are reported in Table 2, whereas the production route using proton or alpha particle as projectiles are presented in Table 3.

Radionuclides for PET use

Because positron emitters are produced in cyclotrons, we have revisited the entire list of known emitters and have applied the criteria detailed in "Materials and methods" to define a limited priority list.

A special attention was paid to the gamma emission following beta+ decay that may affect the coincidence count rate performance of the PET due to possible triple events, random events and gamma coincidence [13]. Some hints on the contribution of these factors can be obtained through data presented in Figs. 2 and 3. Figure 2 depicts the proportion of gamma emission plus the associated X-ray emission divided by the intensity of beta+ decay. The percentage of gamma emission related to beta+ decay intensity falling into the 350–700 keV energy window, which is commonly used in PET, is also given under brackets above the bar of the histogram. The energy and the intensity (above 10%) of the main gamma emissions are presented in Fig. 3.

Based on the criteria described in "Materials and methods", ten radionuclides have been selected for production by ARRONAX. They have been separated into two groups.

Great interest at short term

The radionuclides for PET imaging, pretherapeutic PET dosimetry of tumour and normal organs (liver, kidney, and lung) and those available through generators have been considered in this group.

^{64}Cu Several studies have demonstrated the high potential of ^{64}Cu for PET imaging [14–16]. Various chelates have been studied to be used for immuno-PET detection with copper radionuclides [15, 16] and ^{64}Cu has been proposed for dosimetry studies performed prior to radioimmunotherapy (RIT) with electron-emitting ^{67}Cu [17]. In addition, in vitro and in vivo studies were recently performed with tracers labelled with ^{64}Cu and other copper isotopes to assess tissue hypoxia [18, 19]. The abundance of positron emission of ^{64}Cu is small (17.40%–E_{mean}=278 keV) due to its ability to decay also via electron emission (39.0%). Nevertheless, ^{64}Cu ($T_{1/2}$= 12.7 h) is considered to be appropriate for PET imaging. Its mean positron energy is small (278 keV). In addition to the 511 keV photons, ^{64}Cu emits a single gamma with E_γ= 1,345.77 keV, likely to have only a minimal influence on image quality. Indeed, it corresponds to a small occurrence (0.473%) and can be rejected by an appropriate energy windowing of the detector. The calculated $\Gamma_{20\ keV}$ constant for ^{64}Cu is 3.51×10^{-2} vs. 1.88×10^{-1} (μSv.m^2)/(MBq.h) for ^{18}F, which makes ^{64}Cu quite similar to ^{18}F in terms of radiation safety. ^{64}Cu can be produced with a high production yield through ^{64}Ni(p,n)^{64}Cu reaction using highly enriched targets.

^{68}Ga Recent in vivo studies have demonstrated the interest of gallium isotopes for PET imaging of somatostatin receptors [20–22]. Feasibility studies of pretargeted immunoscintigraphy using bispecific anti-tumour–anti-metal chelate antibody and peptides labelled with ^{68}Ga have been recently performed in mice [23] and in patients [24]. ^{68}Ga

Table 2 Physical characteristics of radionuclides selected for investigation

Radionuclide	$T_{1/2}$	Branching ratio (beta or alpha)	Mean energy (keV)	Daughter nuclide	$T_{1/2}$ daughter
^{44}Sc	3.97 h	94.27%	632.	^{44}Ca	Stable
^{47}Sc	3.3492 h	100%	162.	^{47}Ti	Stable
^{52}Fe	8.275 h	55.49%	340.	^{52m}Mn	21.1 m
^{55}Co	17.53 h	76%	567.07	^{55}Fe	2.737 years
^{64}Cu	12.7 h	17.4%	278.21	^{64}Ni	Stable
^{67}Cu	61.83 h	100%	141	^{67}Zn	Stable
^{76}Br	16.2 h	55. %	1,180	^{76}Se	Stable
^{86}Y	14.74 h	31.9%	664	^{86}Sr	Stable
^{89}Zr	78.41 h	22.74%	395.5	^{89}Y	Stable
^{124}I	4.176 d	22.8%	819.1	^{124}Te	Stable
^{211}At	7.214 h	41.8% [a]	5,869.5	^{207}Bi	32.9 years
Generator-produced PET radionuclides					
^{82}Sr/^{82}Rb					
^{82}Sr	25.55 days	EC 100%		^{82}Rb	1.273 m
^{82}Rb	1.273 m	95.4%	1,479 keV	^{82}Kr	Stable
^{68}Ge/^{68}Ga					
^{68}Ge	270.95 days	EC 100%		^{68}Ga	67.71 m
^{68}Ga	67.71 m	89.14%	829.5 keV	^{68}Zn	Stable

[a] In the other 58.2% of the case, an alpha particle of 7,594.1 keV is emitted during the ^{211}Po decay to ^{207}Pb

Table 3 Reaction cross sections associated to the main radioisotope production route

Radionuclide	Reaction channel	Target abundance (%)	Cross section maximum value (mb)[a]	Beam energy at maximum (MeV)
^{44}Sc	^{44}Ca(p,n)	2.086	≈700	≈11
	^{41}K(α,n)	6.730	≈200	≥8
^{47}Sc	^{48}Ti(p,2p)	73.72	≈20	≥25
^{52}Fe	^{55}Mn(p,4n)	1.29	≈100	≈54
	^{50}Cr(α,2n)	9.501	≈21	≈29
^{55}Co	^{56}Fe(p,2n)	91.72	≈70	≈25
	^{55}Mn(α,4n)	100	≈11	≈58
^{64}Cu	^{64}Ni(p,n)	0.926	≈700	≈11
	^{61}Ni(α,p)	1.14	≥148	≥15.6
^{67}Cu	^{68}Zn(p,2p)	18.75	≈10	≥40
^{68}Ge	^{69}Ga(p,2n)	60.108	≈558	≈20
	^{66}Zn(α,2n)	27.9	≈550	≈30
^{76}Br	^{76}Se(p,n)	9.36	≈700	≈13
	^{75}As(α,3n)	100	≈480	≈44
^{82}Sr	^{85}Rb(p,4n)	72.165	≈150	≈50
^{86}Y	^{86}Sr(p,n)	9.86	≈800	≈13
	^{88}Sr(p,3n)	82.58	≈470	≈40
	^{85}Rb(α,3n)	72.165	≈800	≈41
^{89}Zr	^{89}Y(p,n)	100	≈780	≈14
	^{86}Sr(α,n)	9.86	≈695	≈17
	^{88}Sr(α,3n)	82.58	≈1,200	≈42
^{124}I	^{124}Te(p,n)	4.816	≈590	≈12
	^{121}Sb(α,n)	57.36	≈557	≈18
	^{123}Sb(α,3n)	42.64	≈1,300	≈36
^{211}At	^{209}Bi(α,2n)	100	≈900	≈31

[a] The maximum value of the cross section is given in millibarn (1 b=10^{-28} m^2) and is extracted from the CSISRS database (http://www.nndc.bnl.gov/exfor3/)

has a short period (67.71 min) and a small amount of associated gamma emission, which have almost no impact on PET images. Despite its high positron energy (E_{mean}= 829.5 keV), the spatial resolution of PET images is not so affected [25] and gallium generators (^{68}Ge/^{68}Ga) are already used worldwide [26]. The $\Gamma_{20\ keV}$ exposure rate constant is 0.179 (μSv.m^2)/(MBq.h) (0.180 (μSv.m^2)/(MBq.h), which makes feasible the use of FDG standard radiation safety automatic infusion system. ^{68}Ga can be obtained using ^{68}Ge/^{68}Ga generator. ^{68}Ga has a long half-life (270.95 days) and a 30 MeV proton beam is adequate to produce ^{68}Ga via a (p,2n) reaction. This radionuclide can be produced using low-energy cyclotrons but there is a strong request for ^{68}Ga generators for clinical use.

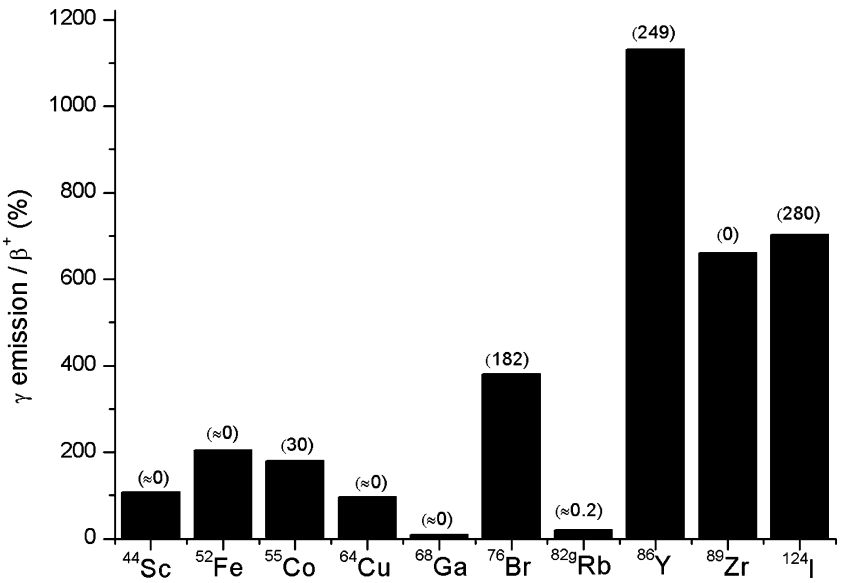

Fig. 2 Proportion of gamma and X-ray emission normalised to the intensity of beta+ decay for each radionuclide. Under brackets: percentage of gamma emission related to beta+ decay intensity falling into the 350–700 keV energy window which is commonly used in PET

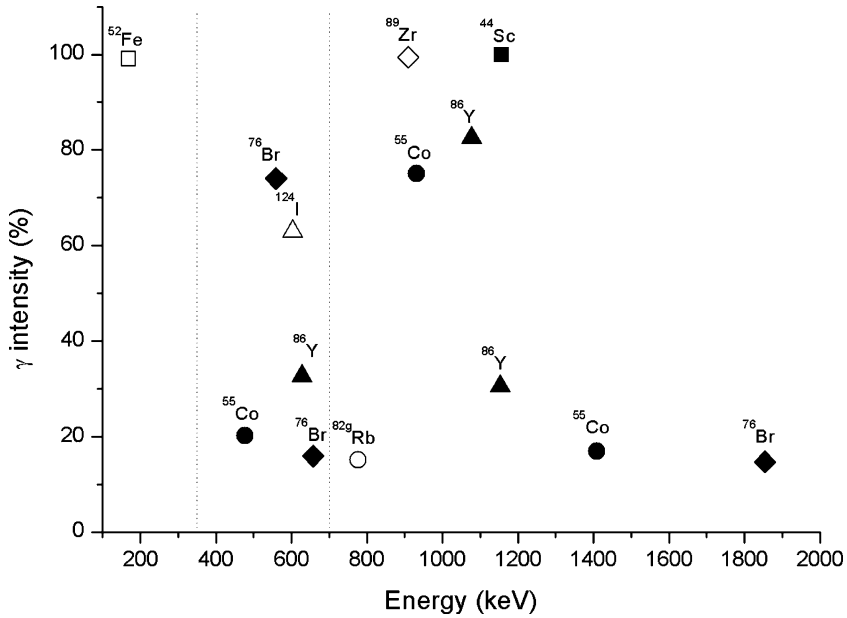

Fig. 3 Intensity and energy of gamma emission greater than 10% for each radionuclide. The *dotted lines* correspond to the commonly used PET energy window (350–700 keV)

^{82}Rb ^{82}Rb can be produced either in its ground state, which has a half-life of 1.273 min, or in an isomeric state with a half-life of 6.472 h. A generator from ^{82}Sr, which has a long half-life (25.55 days) and decays to ^{82}Rb, has been used in the US for many years. The $\Gamma_{20\ keV}$ exposure rate constant is 0.208 (μSv.m^2)/(MBq.h). As an analogue of potassium, it is used in cardiology for myocardial perfusion imaging [27, 28]. ^{82}Sr can be produced from rubidium or RbCl targets at high energy (above 30 MeV) using (p,4n) reaction. The cross section of this process is small and it is necessary to use highly intense beams to produce high activities of ^{82}Sr at a reasonable cost.

^{124}I ^{124}I has been used to estimate absorbed doses to thyroid or thyroid lesions in thyroid cancer treatment [3, 29–30]. A variety of tracers, including monoclonal antibodies [31–33] that target processes such as apoptosis [34] or receptors involved in tumourigenesis, such as HER-2/neu [35] or other epidermal growth factor receptors [36], are currently being labelled with ^{124}I and used in vitro or in animals. Indeed, its relatively long half-life ($T_{1/2}$= 4.176 days) is very suitable for monoclonal antibody labelling and dosimetry studies. Despite its low positron emission percentage (22.8%), its relative high mean positron energy (820 keV) and the large amount of gamma emission (e.g. 602.7 keV, 62.9%), PET system performances make it possible to perform quantitative imaging and dosimetry studies [3, 29–30]. The numerous cascade photons are responsible for a relatively high exposure radiation constant (0.218 vs. 0.205 (μSv.m^2)/(MBq.h)), 20% higher than that of ^{18}F. The production of ^{124}I can be performed using low-energy cyclotrons and a guide of good practice for the production of both ^{131}I and ^{124}I has been published by the International Atomic Energy Agency [37].

^{44}Sc Scandium offers the opportunity to use two different isotopes with similar half-lives and high positron abundance: ^{43}Sc ($T_{1/2}$=3.891 h with 88.1%–E_{mean}=476 keV) and ^{44}Sc ($T_{1/2}$=3.97 h with 94.27%–E_{mean}=632 keV). These radionuclides can be used to for dosimetry studies of ^{47}Sc-targeted radionuclide therapy. ^{44}Sc has an isomeric state ^{44m}Sc ($T_{1/2}$=58.6 h) that decays mainly to the ground state (98.80%) by isomeric transition emitting a 270.91 keV photon. The small amount of recoil energy delivered to ^{44}Sc by the isomeric transition is not expected to alter the carrier molecule and to dissociate the daughter nuclei from it. Due to its long period, the isomeric state acts like a generator of ^{44}Sc and should allow us to monitor the kinetics over long periods of time (a few days). The databases [38] show that the ratio of isomeric to ground state varies between 0.05 and 0.2 below 20 MeV when using (p,n) reaction on an enriched ^{44}Ca target. Each decay of ^{44}Sc is followed by the emission of a 1.1 MeV gamma. On the one hand, it has an effect on the exposure dose (0.434 (μSv.m^2)/(MBq.h)), but on the other hand this third gamma may offer the opportunity to work on a new concept of imaging based on three gamma correlation [39, 40].

Potential interest at middle term

^{86}Y This radionuclide has been used to quantify the kinetics of ^{90}Y-labelled antibodies and peptides and to perform dosimetry calculations for targeted radionuclide therapy [41–44]. More frequently, therapeutic injections are carried

out with the pure electron emitter ^{90}Y whereas quantitative images are recorded with ^{111}In. ^{86}Y can be obtained with low-energy cyclotron with an enriched ^{86}Sr target [45]. Its half-life ($T_{1/2}$=14.74 h), its positron abundance (31.9%) and its mean positron energy (650 keV) are well suited for antibody labelling and PET imaging. However, the numerous photons emitted during its decay may result in imaging and quantification problems, which have been addressed by phantom measurements [46–49]. Today, only a few patients have been studied with ^{86}Y PET imaging [50, 51]. Regardless of imaging considerations, the photon cascade severely impacts this radionuclide gamma exposure rate constant (0.614 (μSv.m2)/(MBq.h)), which is 3.3 times higher than that of ^{18}F. To limit radiation exposure of medical staff, injected activity must be low leading to less informative and quantitative images.

^{55}Co ^{55}Co seems well suited for PET imaging due to its high abundance of positron decay (76%), its relatively long half-life (17.5 h) and its mean positron energy (E_{mean}= 570 keV). Among gamma rays accompanying the decay, two photons (E_γ=930 keV (≈75%) and E_γ=1.4 MeV (≈17%)) have an impact on the gamma exposure rate (0.361 (μSv.m2)/(MBq.h)). As a surrogate for calcium, ^{55}Co allows the study of degenerative process in tissues. A number of clinical studies mainly related to brain [52–54] and blood [55, 56] have been performed with this radionuclide. The effect of the high gamma energy was evaluated and it was concluded that images were slightly altered by the diffusion of these photons [57]. High production yield of cobalt can be obtained through the (p,2n) reaction on an ^{56}Fe target which requires a beam energy around 30 MeV whereas high purity of ^{55}Co is achieved using the ^{54}Fe(d,n) reaction [58]. The long half-life (2.732 years) of its unstable daughter nuclei (^{55}Fe) may limit its usefulness.

^{52}Fe Iron-52 is a positron emitter with a half-life of $T_{1/2}$= 8.275 h, a high abundance of positron decay (55.49%) and a mean positron energy of E_{mean}=340 keV. Among gamma rays accompanying its decay, only the 168.69 keV photon is present in a significant amount (99%). It would have negligible effect on the image quality and on the gamma exposure rate constant (0.136 (μSv.m2)/(MBq.h)—without taking into account the decay of the daughter nuclide). ^{52}Fe has been used in nuclear medicine mainly for imaging in haematology [59–62]. It can be obtained through a (p,4n) reaction at high energy (greater than 40 MeV) on ^{55}Mn which is naturally monoisotopic. However, the production cross section is very small (a few millibarn) and long-lived ^{55}Fe ($T_{1/2}$=2.737 years) is also produced during the irradiation. To limit the production of this isotope, it is possible to use 30 MeV alpha particles and an enriched ^{50}Cr target [63]. ^{52}Fe decays into ^{52m}Mn ($T_{1/2}$=21.1 m), which has been suggested as a candidate for myocardial imaging [64]. However, the positron emission (98.25%) of the daughter isotope complicates the interpretation of ^{52}Fe PET [65].

^{76}Br Over the last years, several studies reported on the use of ^{76}Br to label monoclonal antibodies [66, 67]. As a halogen, the labelling chemistry is close to that of iodine. ^{76}Br has a half-life of 16.2 h and it decays through positron emission (E_{mean}=1,180 keV) in 55% of the decay. A low-energy proton beam bombarding an enriched target can be used to produce it. One of the main drawbacks of this radionuclide is the large number of associated gamma rays that will generate a proportionally high radiation dose (0.448 (μSv.m2)/(MBq.h)) [68] and induce a large number of false coincidences.

^{89}Zr Meijs et al. [69] have quantified the biodistribution of zirconium-labelled monoclonal antibodies. However, up to now, it has been found that Zr-labelled antibodies may be unstable [70]. ^{89}Zr has a $T_{1/2}$=78.41 h and a branching ratio of 22.74%. Its positron energy, E_{mean}=470 keV, as well as the gamma emission which is mostly outside the energy window of the PET camera should not alter the image quality. Indeed, the 909.15 keV (99.04%) can be rejected by an appropriate gating. The cascade photons are responsible for a relatively high exposure radiation constant (0.209 (μSv.m^2)/(MBq.h)). ^{89}Zr can be obtained at low energy from an yttrium target.

Radionuclides for targeted beta therapy

Based on the criteria described in "Materials and methods", ^{47}Sc and ^{67}Cu have been selected as radionuclides of interest. They can both be obtained through a (p,2p) reaction and thus require a proton beam energy above 30 MeV. In both cases, the production cross section is of the order of few tens of millibarns.

^{47}Sc ^{47}Sc is a promising candidate for RIT as, associated to favourable average beta energy (162 keV), its physical half-life (3.35 d) fits well with antibody kinetics. However, despite these attractive characteristics, ^{47}Sc has not yet been used in the clinic. This may be explained, at least in part, by the limited availability of that radionuclide, because, to our knowledge, the Brookhaven National Laboratory has been the only source of production [71]. A few publications from this laboratory describe the potential of ^{47}Sc in targeted radionuclide therapy, mentioning that its reactivity is close to that of ^{90}Y. Classical chelating agents (diethylene triamine pentaacetic acid, 4-ICE) should satisfactorily bind scandium for targeted radionuclide therapy [11].

^{67}Cu ^{67}Cu-2IT-BAT-Lym1 has been studied in the context of non-Hodgkin's lymphoma [12, 72–75] and ^{67}Cu is considered to be a good alternative to ^{131}I due to its suitable physical half-life (62 h) and moderate beta particle energy (141 keV on average) associated with low-energy photons (185 keV, 47%; 93 keV, 17%). Preliminary results indicate that higher doses can be delivered with ^{67}Cu-2IT-BAT-Lym1 compared with ^{131}I-Lym1 without significant toxicity. Targeting of colon carcinoma or bladder cancer has been also mentioned in the literature. A good review of these applications can be found in [76].

Radionuclides for targeted alpha therapy

The use of alpha particle in therapy is a promising approach in oncology. The high linear energy transfer and short path length in tissues which characterise alpha particles should result in very localised irradiations while preserving the surrounding tissues. There are many alpha-emitting radionuclides but only few of them are available for clinical use. Their characteristics have been described in numerous reports [77–79]. Among them, it will be possible to produce ^{211}At with the alpha-particle beam delivered by ARRONAX using the ^{209}Bi(α,2n) ^{211}At reaction.

^{211}At has many attractive features for targeted radiotherapy. With a half-life of 7.2 h, it permits complex labelling strategies and is compatible with the pharmacokinetics of molecular entities such as peptides or monoclonal antibody fragments. Locoregional administration has also been considered.

Each decay of ^{211}At leads to an alpha emission directly or through ^{211}Po. The first route of disintegration is by alpha emission to ^{207}Bi (42%), followed by electron capture to stable ^{207}Pb. ^{207}Bi has a long half-life (31.6 years), but decay-generated activities and dosimetry are considered acceptable. The second is by electron capture and leads to ^{211}Po (58%), followed by an alpha emission to stable ^{207}Pb. Interestingly, the ^{211}Po daughter has a short half-life (0.5 s) and emits X-rays of 77–92 keV that can be used for imaging [80]. The toxicity of ^{211}At for human cancer cells has been demonstrated with a wide variety of ^{211}At-labelled compounds in cell cultures and in animal models [81, 82]. A clinical trial has been initiated at Duke University and other trials are in the planning stage.

Discussion

ARRONAX will allow the extraction of proton and alpha particles up to 70 MeV. The number of open reaction channels increasing with the particle incident energy, such high beam energy offers the possibility to explore a wide variety of processes to produce the desired isotopes. A wider zone in the vicinity of stable isotopes that constitute the target materials can be explored. Processes in which many neutrons are emitted can be used to produce positron emitters such as the (p,4n) reactions involved in ^{82}Sr or ^{52}Fe production. Unlike low-energy cyclotrons which only provide positron emitters, a high-energy cyclotron is also able to produce beta emitters with high specific activity. For example, ^{67}Cu and ^{47}Sc may be produced through a (p,2p) reaction. Finally, alternative production routes for well-defined isotopes can be followed such as that described by Szelecsényi et al. [83] for ^{64}Cu. In addition, by its ability to accelerate different kinds of ions (protons, deuterons and alpha particles), ARRONAX will offer the possibility to widen even more the isotope zone of interest by selecting the most appropriate particle. As an example, ^{52}Fe can be obtained using a proton beam through the ^{55}Mn(p,4n)^{52}Fe reaction or an alpha-particle beam through ^{50}Cr(α,2n)^{52}Fe. The latter reaction must be preferred in order to lower the ^{55}Fe contamination.

Table 4 Potential production capacity on ARRONAX

Radionuclide	Reaction channel	Target material	Irradiation duration (h)	Beam energy interval of interest (MeV)	Theoretical activity (Ci)
^{44}Sc	(p,n)	$^{44}CaCO_3$	1	8–13	2.8
^{47}Sc	(p,2p)	TiO_2	8	23–53	1.2
^{52}Fe	(p,4n)	^{55}Mn	8	40–70	1
	(α,2n)	^{50}Cr	4	20–38	0.018
^{55}Co	(p,2n)	^{56}Fe	1	20–30	1
^{64}Cu	(p,n)	^{64}Ni	1	8–13	3.3
^{67}Cu	(p,2p)	^{68}Zn	8	40–70	1.5
^{68}Ge	(p,2n)	^{69}Ga	8	15–40	0.21
^{76}Br	(p,n)	^{76}Se	1	10–15	2.7
^{82}Sr	(p,4n)	RbCl	20	40–70	1.3
^{86}Y	(p,n)	SrO	1	10–15	1.7
^{89}Zr	(p,n)	^{89}Y	1	10–15	0.7
^{124}I	(p,n)	$^{124}TeO_2$	8	9–14	0.58
^{211}At	(α,2n)	^{209}Bi	4	21–28	0.069

These estimates correspond to theoretical activities for the maximum available beam intensity. The expected target composition, irradiation time and energy beam of interest are also reported

By working at high energy, it is possible to produce elements very different from the target element, which cannot be produced by low-energy cyclotrons. However, more impurities are formed by the allowed reaction channels and more important efforts must be applied to the chemical extraction. This effect may be reduced by carefully defining the range of particle energies that will be used and by using monoisotopic or highly enriched targets.

The production yield of a radionuclide is proportional to the cross section of the selected reaction channel, to the irradiation time as long as it does not exceed the half-life of the radionuclide to be produced and to the beam intensity. Even if a cyclotron like ARRONAX offers the possibility to explore alternative production routes, optimising the reaction channel will not increase production rates by much. Irradiation time may be increased within the limit of the radionuclide half-life but this increases production costs. The real breakthrough will be to increase the beam intensity. This is the reason why cyclotrons are now designed to deliver more and more intense beams. However, an increase of the beam intensity also results in an increase of the heat deposited in the target. As an example, it will be necessary to evacuate 25 kW deposited on a small spot in the target to use the proton beam delivered by ARRONAX at full intensity and full energy. This remains a challenge [84].

However, we have determined the potential production capability of ARRONAX when running at maximum intensity (350 μA for proton and 35 μA for alpha particles). These estimates, made using formulas from [85], are reported in Table 4. They correspond to theoretical yields and are based on data presented in Tables 2 and 3. Theses values are still speculative because targets have not been tested under the high currents available with this machine. However, these data show that high activities (up to Curies of radionuclides) can be obtained within reasonable irradiation time. This is especially true when it comes to production through processes with low cross sections as, for example, (p,2p) reactions.

To conclude, ARRONAX will accelerate both protons and alpha particles at high energy (up to 70 MeV) and high intensity (two simultaneous proton beams with intensity up to 350 μA each and 35 μA for alpha particles). It is dedicated to research in radiochemistry and nuclear medicine. ^{82}Sr/^{82g}Rb generators, routinely used in the USA for cardiology PET imaging, are in the priority list established for ARRONAX, as well as ^{68}Ge/^{68}Ga generators. For radionuclide therapy, reliable dosimetry estimates are needed. Quantification of the in vivo distribution of radionuclides may be performed efficiently using PET imaging, which explains the high priority given to ^{124}I, ^{64}Cu and ^{44}Sc and to the beta+/beta− pairs of the same element (^{124}I/^{131}I, ^{64}Cu/^{67}Cu and ^{44}Sc/^{47}Sc). Several other beta+ radionuclides may have potential for medical research or diagnostic. However, they have some drawbacks that explain their ranking in a second-priority category. ^{67}Cu is considered as an attractive option in targeted radionuclide therapy. Production of large activities of ^{67}Cu using a cyclotron remains a challenge and a major development project for ARRONAX because high energy and high intensity are required. ^{47}Sc is another attractive option. Finally, ARRONAX will also produce ^{211}At which seems particularly appropriate for targeted alpha therapy. Associated with appropriate carriers, these radionuclides will respond to a maximum of unmet clinical needs.

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