RADIOACTIVE NUCLEI FOR MEDICAL APPLICATIONS*

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(Received December 23, 2011)

The radioisotopes used for labeling the diagnostic and therapeutic radiopharmaceuticals are contemporaneously produced using neutrons in reactors and light charged particles from accelerators (cyclotrons). After the presentation of both methods the commercially available cyclotrons are reviewed. Some examples of the most popular medical radioisotopes are given. The new Radiopharmaceuticals Production and Research Centre at the University of Warsaw is presented.

DOI:10.5506/APhysPolB.43.193
PACS numbers: 87.53.–j, 87.57.–s, 87.57.un, 87.57.uh

1. Introduction

The first radioactive nucleus used for medical applications, ^{226}Ra with a 1600 y half-life was extracted by fractional crystallization from barium chloride contained in uranium ore by Maria Skłodowska-Curie and Pierre Curie in December 1898 (barium and radium belong to the same group in the periodic system) [1]. The gamma radiation of the radioactive series of this isotope was used as the therapeutic agent for cancer cell irradiation from Ra "bombs". In some cases the daughter product of ^{226}Ra, the ^{222}Rn isotope ($T_{1/2} = 3.8$ d) was extracted and placed, similarly to ^{226}Ra in "applicators" in the form of sealed thin tubes and needles used for irradiations [2], ("Curie-therapy", also known as "brachytherapy"). In all cases the source of the energetic gamma-rays was the 20 min β-decay of ^{214}Bi [3]. Besides the U–Ra family indicated above, the thorium radioactive family (alpha-decay products of the 1.4×10^{10} y ^{232}Th) with its gamma-ray emitting ^{228}Ac ($T_{1/2} = 6.1$ h) and ^{208}Tl ($T_{1/2} = 3$ min) members were also sometimes used

* Presented at the XXXII Mazurian Lakes Conference on Physics, Piaski, Poland, September 11–18, 2011.

for Curie-therapy. Today, there is a renewed interest in the Ac/Ra family of isotopes due to their alpha particle emission. These particles are of short range but very effective in cancer cell therapy. The alpha emitters are coupled to monoclonal antibodies that will link uniquely to the cancer cells surface (Targeted Alpha Therapy, TAT).

With the advent of artificially produced radioelements, the radiation from nuclear reactor produced ^{60}Co sources, placed in "cobalt irradiators" successively replaced the gamma-rays of the radium and thorium families. In contemporary cancer therapy with electromagnetic radiation the electron bremsstrahlung radiation issuing from medical linear accelerators is mainly used. The ^{60}Co gamma-rays are, however, still employed in very specialized brain tumor radiosurgery using the so-called Gamma Knife.

An historical perspective of medical radioisotope production and a rich bibliography of this subject can be found in Refs. [3, 4].

2. Radioisotopes and radiopharmaceuticals

The contemporary employment of radioactive nuclei for medical applications is based on two different methods for their production. The first one uses neutron induced reactions with neutrons mainly from nuclear reactors, although accelerator produced neutrons are also considered. The second one employs nuclear reactions induced by accelerated charged particles, mainly using various types of cyclotron.

These two production methods lead to quite different positions of the nuclear reaction product on the nuclear chart. The neutron induced reactions produce unstable neutron-rich nuclei, spontaneously approaching the beta-stability line by the beta-decay process (β^- emission of an electron and a neutrino). The cyclotron accelerated charged particles (p, d, ^{3}He, ^{4}He) impinging on stable targets lead, with some exceptions, to neutron-deficient final products, decaying by positron and neutrino emission (β^+) (two electron–positron annihilation gamma-quanta of 511 keV energy, emitted in opposite directions, promptly follow the nuclear decay by positron emission) and/or the electron capture (EC) process. For heavy nuclei sometimes α-particle emission is possible, also eventually leading toward the beta stability line.

All these radioactive decays may lead to the ground state of the final nucleus or to its excited states which in turn decay by gamma-ray emission or electron internal conversion (IC). The emission of low-energy Auger electrons accompanies the EC and IC processes.

The nuclear reactor or accelerator produced radioisotopes are used as simple salt solutions or for labeling various compounds, forming so-called diagnostic or therapeutic radiopharmaceuticals [5]. Radiopharmaceuticals

administered to the living organisms of animals or humans selectively localize in various types of tissues or cells, permitting their spatial distribution to be identified, specific physiological processes to be imaged or malignant cells to be destroyed. Radiolabelled molecules are also largely used in research, serving as information agents on the behavior of various metabolic processes. They are also employed in testing of new pharmaceutical products (speeding up the drug discovery process by selecting the new molecules of interest).

The various biomedical properties of labeled radiopharmaceuticals allow the use of the same radioisotope in many applications. Therefore, practically a number of currently used radioisotopes is rather limited whereas the number of labeled compounds is substantially larger and continuously increasing thanks to the radiochemical and radiopharmaceutical research effort all around the world.

3. Production methods of medical isotopes

3.1. Nuclear reactors for radioisotope production

Currently, the prominent part of nuclear medicine diagnostic and therapeutic interventions are based on radioisotopes produced in nuclear reactors [6]. Between them ^{99m}Tc from reactor produced ^{99}Mo generator accounts for more than 80% of all administered radiopharmaceuticals. The principles of the nuclear reactor construction are presented in Refs. [6, 7, 8, 9, 10].

During radioisotope production the reactor neutrons interact with the target material, introduced close to the reactor core in specially designed irradiation capsules. The reactors for radioisotope production (or material science) are specially designed to have a very intense neutron flux in their core with a limited power output to enhance the production process and are not at all comparable to electrical production reactors. Such research high flux reactors were constructed by governmental research groups and heavily funded by grants more than 40 years ago. The actual worldwide problem is the availability of these specific reactors, they are almost all very old and prompt to multiple failures-repairs. The example can be the recent worldwide crisis of the reactor produced ^{99}Mo.

3.2. Accelerators for radioisotope production

At present cyclotrons are, practically, the only accelerators used for medical isotope production. The principle of particle acceleration in a cyclotron can be found in Refs. [10, 11, 12, 13]. Table I gives the updated [12] classification of cyclotrons used in medical applications. Many hundreds of Class I and Class II cyclotrons are presently operating all around the world, producing mainly diagnostic but also some therapeutic radioisotopes. An example

of a Class II cyclotron, a General Electric (GE) PETtrace accelerator is shown in Fig. 1 and its cut is displayed in Fig. 2. Table II gives the list of main manufacturers of Class I and Class II cyclotrons, used mainly for the production of PET radioisotopes.

TABLE I

Classification of accelerators. (Adapted from Ref. [12].)

Accelerator class	Characteristics	Proton energy (MeV)	Comments	Example
Class I	Single particle (p or d)	≤ 11	PET	Siemens Eclipse IBA Cyclone 11
Class II	Single or multiple particle p, d	$11 \leq E_p < 20$	^{3}He, ^{4}He not usually available PET, (SPECT)	GE PETtrace IBA Cyclone 18/9
Class III	Single, two or three particles p, d, α	$20 \leq E_p < 70$	^{3}He, ^{4}He can be available SPECT and PET	IBA Cyclone 30 IBA Cyclone 30XP IBA Cyclone 70 (Arronax)
Class IV	Usually p only	70–500	200 MeV for proton therapy or research	IBA Cyclone 230 Triumf Canada

TABLE II

Cyclotrons with $E_p \leq 20$ MeV for PET radioisotope production. (Adapted from Ref. [11].)

Manufacturer	Feature	Factory localization	Years of operation	Accelerated particles	E_p (MeV)
Siemens	Eclipse	Knoxville, TN (USA)	27	p	11
GE Healthcare	PETtrace	Uppsala (SE)	26	p, d	16.5
	Minitrace		26	p	9.6
Ion Beam Applic. (IBA)	Cyclone 18/9	Louvain-La-Neuve (BE)	25	p, d	18
	Cyclone 11		25	p, d	11
Sumitomo Heavy Ind.	HM-18	Tokio, (JP)	20	p, d	18
	HM-12		20	p, d	12
Advanced Cycl. Syst.	TR-19/9	Vancouver (CA)	17	p, d	19
Best	B-14p	Vancouver (CA)	1	p	14

Fig. 1. The GE Healthcare PETtrace cyclotron, accelerating protons with energy of 16.5 MeV and deuterons with energy of 8.4 MeV with proton current up to 100 μA. This type of cyclotron will be operational at the beginning of 2012 in the Radiofarmaceuticals Production and Research Centre of the Heavy Ion Laboratory, University of Warsaw (courtesy of GE).

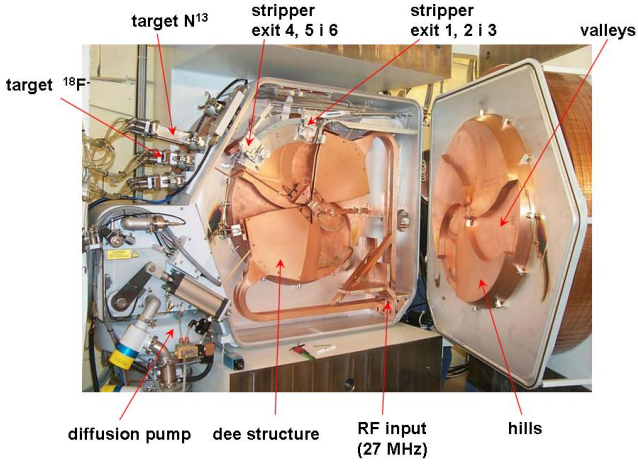

Fig. 2. Interior of the PETtrace cyclotron (courtesy of GE).

The accelerated particles impinge on a cooled target holder, activating the target material. This may be done inside the cyclotron, before the beam extraction (mainly for positively charged ions) as well as after the beam extraction for negatively charged ions, the latter has many benefit with the possibility to have multiple targets around the cyclotron while minimizing internal activation of the machine. Gaseous, liquid or solid target materials are used (see Ref. [13]).

The currently commercially available cyclotrons with proton energies below 20 MeV are, however, generally unable to produce in a reasonable quantity radioisotopes via two nucleon emission (reactions such as $(p, 2n)$, $(d, 2n)$ or (p, pn)). Similarly, the He induced reactions are not accessible in these accelerators. The higher proton energies as well as He beams are presently available in Europe and the US on old Class III Scanditronix accelerators, no longer commercialized. Fortunately, quite recently IBA (Ion Beam Applications) Company launched a new CYCLONE 30XP accelerator delivering protons of variable energy 18–30 MeV, deuterons of energy 9–15 MeV and He^{++} particles of energy 29 MeV. Fig. 3 shows the schematic and cross-sectional view of this cyclotron. Two external ion sources are employed: the multicusp electrical arc device delivering negatively charged protons and deuterons and an ECR ion source for doubly charged He^{++} particles. The negative beams are extracted by stripping and He^{++} by an electrostatic device. The accelerating electric field frequency is also different for these two types of accelerated particles.

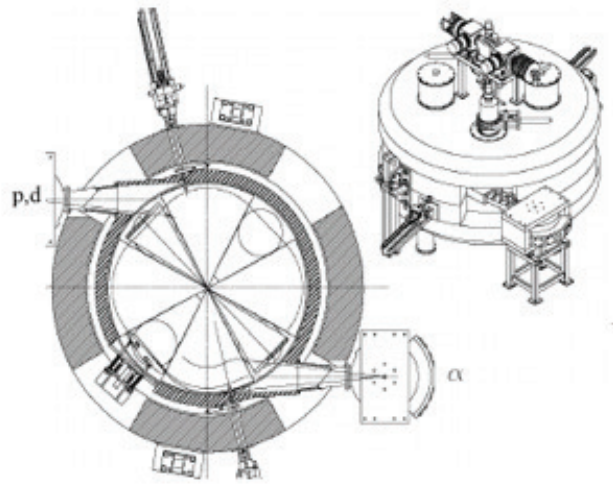

Fig. 3. Schematic and cross-sectional view of the IBA CYCLONE XP 30. Two ion sources (multicusp and ECR) are shown on the top of the cyclotron (courtesy of IBA).

At the upper end of Class III accelerators a currently commercially available cyclotron is again produced by the IBA Company the CYCLONE 70XP, delivering protons of energy 30–70 MeV, deuterons of energy 15–35 MeV and He^{++} particles of energy 70 MeV. Such a cyclotron was recently put into service at Nantes (France), ARRONAX facility [14]. The higher proton energy is desirable for some specific radioisotopes production of generators (^{68}Ge/Ga and ^{82}Sr/Rb) for PET imaging.

4. Nuclear reactions

4.1. Neutron induced reactions

Two quite different nuclear processes are employed to produce medical radioisotopes by neutron interaction with materials introduced into the reactor core: the fission route and the activation route. About 40 radioisotopes are produced by the activation route and at least 5 can be separated from the fission products, including the most widely used ^{99}Mo for the production of ^{99}Mo/^{99m}Tc generator.

In the fission route, after the splitting of the ^{235}U nucleus under the slow neutron capture process two fragments with masses around $A' \approx 95$ and $A' \approx 140$ are produced [15]. By chemical extraction from the irradiated material (always performed in specialized, large separation facilities) the medical radioisotopes are prepared. Currently, highly enriched uranium targets (HEU) are used preferentially, at least for the ^{99}Mo fission product. The target material is inserted in sealed ampules in the high neutron flux core of a special nuclear reactor and removed after a few days of irradiation for further processing. Table III lists the world producers of the ^{99}Mo radioisotope.

In the activation route the compound nuclei, formed after neutron absorption by the irradiated target nuclei, decay via various paths producing final radioactive products. The most common nuclear reaction consists of the absorption of the thermal or epithermal neutron with a subsequent emission of γ rays: the (n, γ) reaction. The production of the famous therapeutic ^{60}Co isotope using neutron absorption by the natural ^{59}Co isotope (100% abundance) is an example. The final reaction product is the same element as the target isotope and cannot be chemically separated. A high neutron flux is, therefore, necessary to produce the final product with high specific activity. In the high neutron flux two consecutive (n, γ) reactions (two neutron captures) on the same target nucleus can also give a reasonable final product activity of the same element two mass units heavier than the target. The neutron absorption reaction of the (n, γ) type may be, however, sometimes employed to produce different element than the target one. If the irradiation products are short-lived beta emitters a final isotope of higher

TABLE III

World producers of ^{99}Mo. (From Ref. [16].)

Reactor	Location	Owner	From	World share of ^{99}Mo
Large producers				
NRU	Canada	AECL	1957	40%
HFR	The Netherlands	European Commission	1961	30%
BR2	Belgium	SCK-CEN	1961	9%
Osiris	France	CEA/CEN Saclay	1966	3%
SAFARI-1	South Africa	NECSA	1965	10%
Small producers				
RA-3	Argentina	CEA	1968	
OPAL	Australia	ANSTO	2007	8%
WWR-TS	Russia	Karpov Institute of Physical Chemistry	1964	

atomic Z number may be formed by β decay. Finally, the (n,p) or (n,α) reactions are also sometimes used employing more energetic (above particle emission threshold) neutrons in the reactor neutron flux.

Some examples of medical radioisotopes formed by fission and activation routes are presented in Table IV. Ref. [17] gives a list of currently operating high flux nuclear reactors as well as a more exhaustive list of therapeutic β-emitters.

4.2. Charged particle induced reactions

Three nuclear reaction mechanisms are of importance when medical radioisotope production with charged particles is considered. For low bombarding particle energies (Class I and Class II cyclotrons) similarly as with thermal or low energy neutrons the compound nucleus (CN) is formed after the fusion of the projectile and target nuclei. Its excitation energy depends mainly on the projectile kinetic energy and the mass difference of the final and initial reaction partners. About 8 MeV of excitation energy is necessary to evaporate one nucleon and less than 3 MeV to evaporate an alpha-particle. With increasing projectile kinetic energy direct reaction processes contribute to the reaction cross-section. Finally, at even higher bombarding energies (Class IV cyclotrons) spallation reactions appear with the emission of a substantial proton and neutron number from the target nucleus.

Similarly as for the reactor produced radioisotopes, the medical radioactive nuclei produced with accelerators can be divided into diagnostic and therapeutic ones.

TABLE IV

Examples of reactor produced medical isotopes.

Isotopes	$T_{1/2}$	Production route	Decay characteristics	Applications
^{99m}Tc	6.0 h	^{235}U(*n*,fission)^{99}Mo ^{99}Mo(β^-,66 h)^{99m}Tc	γ 142 keV (95%)	imaging, scintigraphy and SPECT
^{60}Co	5.3 y	^{59}Co$(n,\gamma)^{60}$Co	γ 1173 keV (100%) 1333 keV	Therapy Co irradiators, Gamma knife
^{131}I	8.0 d	^{130}Te$(n,\gamma)^{131m}$Te ^{131m}Te(β^-,30 h)^{131}I	β^- γ 364 keV (89%)	Imaging and therapy thyroid, carcinomas
^{177}Lu	6.7 d	(a) ^{176}Lu(2.6%,$n,\gamma)^{177}$Lu (b) ^{176}Yb(13%,$n,\gamma)^{177}$Yb ^{177}Yb(β^-,1.9 h)^{177}Lu	β^- 498 keV (79%) γ 208 keV (11%)	Short range β Targeted cancer therapy
^{90}Y	2.7 d	(a) ^{89}Y$(n,\gamma)^{90}$Y (b) ^{235}U(*n*,fission)^{90}Y	β^- 2.28 MeV (99%)	Therapy, long range β part
^{192}Ir	73 d	^{191}Ir$(n,\gamma)^{192}$Ir	β^- and EC γ 296 keV (29%) 308 keV (31%)	High dose rate brachytherapy
^{186}Re	3.7 d	^{185}Re$(n,\gamma)^{186}$Re	EC, β^- 1077 keV (93%) γ 137 keV (9%)	Therapy with imaging

Radioisotope imaging in contemporary nuclear medicine uses two different approaches. The first one is based on the detection of a single gamma-ray line from the appropriate radiotracer. The planar 2D scintigraphy (gamma-cameras) and 3D SPECT scanners represent this approach. The second approach is based on the β^+ radioactive decay consisting of a successive positron emission and annihilation followed by the simultaneous production of two annihilation quanta (511 keV energy). The sensitivity of 3D Positron Emission Tomography (PET) significantly exceeds the SPECT sensitivity due to the auto-collimation of the coincident annihilation quanta emitted almost antiparallely. Currently more and more SPECT and PET scanners are equipped with X-ray CT devices giving, during the same examination, the superposition of morphological and anatomic images. In PET+CT stems the CT data are also used to derive the attenuation corrections. Recently, nuclear magnetic resonance imaging (MRI) devices have begun to be coupled with PET scanners (barely commercially available) and, most probably, SPECT-MRI devices will be also accessible soon on the market.

We begin with the enumeration of the radioisotopes used for PET techniques. The most popular and convenient PET radiopharmaceuticals are based on short lived radioactive nuclei, presented in Table V. Their robust representative, fluorodeoxyglucose, a Fluor-18 marked glucose that will bind to glucose avid cancer cells, besides local production by hospital-owned small cyclotrons, is often produced in specialized centers and transported to distant diagnostic PET cameras.

TABLE V

Short lived radioisotopes for PET.

Radio-isotope	$T_{1/2}$ (min)	$E_{\max\ \beta^+}$ (mm)	Effective range β^+ (mm)	Target	Nuclear reaction
^{18}F	109.7	0.635	0.2	^{18}O — water Ne — gas	$^{18}O(p,n)^{18}F$ $[^{20}Ne(d,\alpha)^{18}F]$
^{11}C	20.4	0.96	0.4	N_2 — gas	$^{14}N(p,\alpha)^{11}C$ $[^{10}B(d,n)^{11}C]$
^{13}N	9.96	1.72	0.8	^{16}O — water	$^{16}O(p,\alpha)^{13}N$
^{15}O	2.07	1.19	0.5	N_2 — gas	$^{14}N(d,n)^{15}O$ $[^{15}N(p,n)^{15}O]$

Another solution for PET radioisotopes is their extraction from the long lived generator systems utilizing parent nuclides, also produced with accelerators. Examples can be ^{82}Sr/^{82}Rb or ^{68}Ge/^{68}Ga generators, discussed in more details in Ref. [10, 13].

Finally, in a number of applications it is necessary to follow labeled compounds in slow pharmacokinetic processes *in vivo* for times substantially longer than the decay time of classic, short lived PET radioisotopes. Examples can be 13 h ^{64}Cu, 3 d ^{89}Zr or 4 d ^{124} I discussed in more details in Refs. [10, 13].

Gamma camera and SPECT imaging is dominated by the use of ^{99m}Tc, extracted from the 66 h ^{99}Mo generators, produced in nuclear reactors. However, a recent "reactor crisis", due to the unexpected shut-down of a few high flux reactors in Europe and Canada prompted the Canadian Government to launch a research program allowing the efficient production of ^{99}Mo or ^{99m}Tc by the accelerator route. The considered nuclear reactions are indicated at the top of Table VI. In the same table other accelerator produced SPECT radioisotopes are also shown.

At this point a comment about accelerator produced ^{99m}Tc should be made. The cross-sections of the $(p, 2n)$ reaction for this production were recently investigated theoretically using the nuclear reaction models and

the optimal irradiation conditions discussed [18]. Surprisingly, taking into account the impurities activation, the optimal bombarding energy for this reaction was found to be only between 16 and and 19 MeV, thus accessible for Class II accelerators. However, the analysis of Ref. [19] indicates, that the cyclotron generated ^{99m}Tc is not an economically viable alternative to the well established ^{99}Mo/^{99m}Tc generator. The question of the accelerator replacement of the reactor produced ^{99m}Tc is still open.

TABLE VI

Examples of accelerator produced SPECT radioisotopes. Accelerator production of ^{99m}Tc and ^{99}Mo is considered by Canadian Government and recently by IAEA within a Coordinated Research Project.

Isotope	$T_{1/2}$	Nuclear reaction	Target abund. %	Decay charact.	Applications/ comments
^{99m}Tc	6.0 h	^{100}Mo$(p,2n)$	9.6	γ	project
^{99}Mo	66 h	^{100}Mo(p,pn)	9.6	β^-	^{99m}Tc generator (project)
^{99}Mo	66 h	$^{\text{nat}}$U(γ,fission)	—	β^-	project
^{67}Ga	3.3 d	^{67}Zn(p,n) ^{68}Zn$(p,2n)$	4 19	EC (93, 184, 300 keV)	Tumors imag.
^{111}In	2.8 d	^{111}Cd(p,n) ^{112}Cd$(p,2n)$ ^{109}Ag$(\alpha,2n)$	12 24 48	EC γ (171, 245 keV)	(nat. Cd comerc. used) Methastases
^{123}I	13 h	^{124}Te$(p,2n)$ ^{124}Xe$(p,2n)$ ^{123}Cs$\rightarrow{}^{123}$Xe$\rightarrow{}^{123}$I	5 0.1	EC γ (159 keV)	Thyroid functions. Can replace ^{131}I in imaging
^{201}Tl	9 h$\rightarrow$ 73 h	^{203}Tl$(p,3n)$ ^{201}Pb ^{201}Tl	30	EC γ (167 keV)	Cardiology

It is evident that their production often involves nuclear reactions with the emission of more than one nucleon. As discussed previously, the bombarding energies of Class I and Class II cyclotrons are too low for an efficient production of these isotopes. Class III accelerators are necessary. Presently, 95% of accelerator produced medical radioisotopes are used for imaging purposes. In the remaining 5% of therapeutic applications [20] a substantial part is still in the preclinical stage of development. We mention here two of them with great therapeutic potential in a new field of so-called Targeted Alpha Therapy (TAT). The alpha particle emitters, if linked to the cancer cells, efficiently destroy the malignant cells by their double strand breaking without great damage to the surrounding healthy cells. The large energy deposited by short range alpha particles is the basis of TAT. Two isotopes are

of particular interest ^{213}Bi and ^{211}At; ^{213}Bi is obtained from the ^{225}Ac/^{213}Bi generator [21, 22] and ^{211}At is produced by the 28 MeV $(\alpha, 2n)$ reaction on a natural Bi target [23]. Their radiopharmaceuticals are based on peptides or monoclonal antibodies, actively investigated in many laboratories.

5. Medical radioisotopes from the Heavy Ion Laboratory of the University of Warsaw

The production of radioisotopes and radiopharmaceuticals for Positron Emission Tomography is in the preparatory phase at HIL–UW. Fig. 4 and Fig. 5 show the layout of the Radiopharmaceuticals Production and Research Centre of this Laboratory [24].

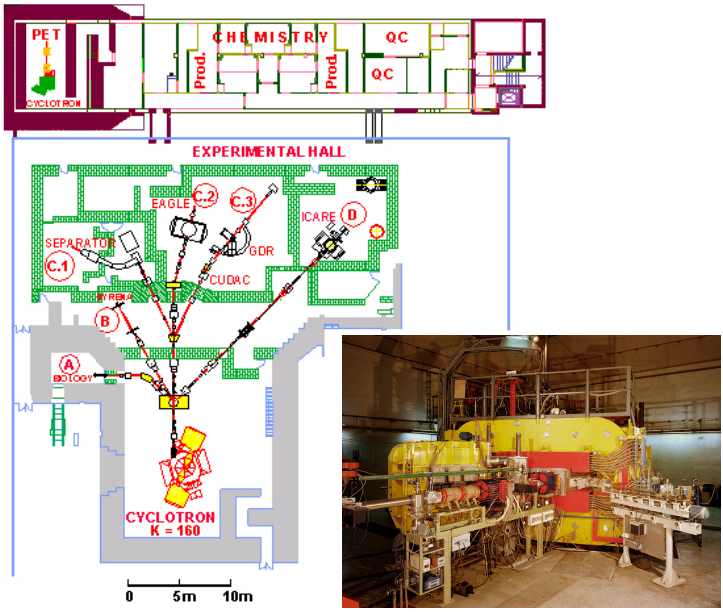

Fig. 4. Layout of the ground floor of the HIL building. Lower part of the layout shows the heavy ion cyclotron, the beam lines and the nuclear physics experimental stations. Upper part shows the Radiopharmaceuticals Production and Research Centre, placed underground (−7 m), see also `www.slcj.uw.edu.pl/pet`.

The Centre will be operational at the beginning of 2012 , with a PET-trace, $k = 16$ cyclotron (see Fig. 1). Using the large, $k = 160$, heavy ion cyclotron the ^{211}At isotope ($T_{1/2} = 7$ h) is produced and will be used by a large collaboration [25] for applications in Targeted Alpha Therapy (TAT).

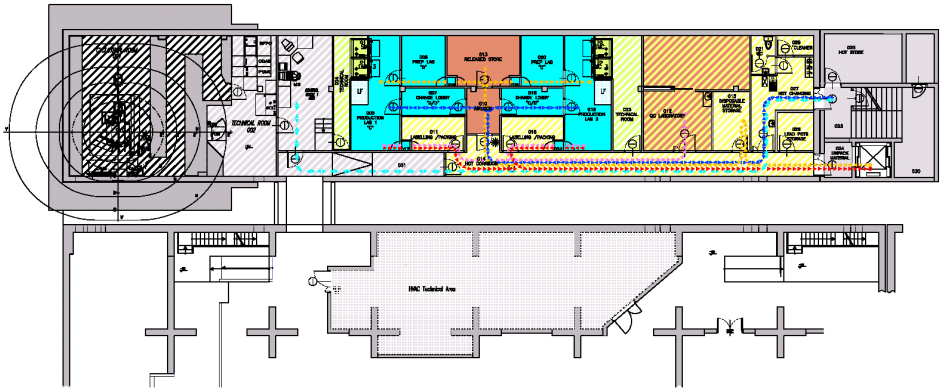

Fig. 5. Layout of the RPRC. Proton/deuteron cyclotron and its control room is placed on the left part of the figure. Two independent production rooms are placed in the middle of the figure (The first one for the routine production of FDG and the second one for other radiopharmaceuticals). The Quality Control room is placed in the right part of the figure.

6. Summary and outlook

Radioactive isotopes are currently indispensable in the contemporary health service all around the world. They are produced using nuclear reactors and more and more with particle accelerators. In Poland during the last decade substantial progress in imaging modalities may be noted. To the currently operating about 50 scintigraphic gamma cameras, 60 SPECT and 8 SPECT/CT devices the 12 PET-CT scanners were added during last years both in public and private establishments [26]. Two Class I and Class II cyclotrons are operating and three others should be operational at the end of 2011. Whereas the PET radioisotopes seem soon to be adequately provided, the new, less common accelerator produced SPECT isotopes are not available in Poland yet, due to the lack of an appropriate accelerator. Some therapeutic radioisotopes produced via the reactor route are available thanks to the high flux research reactor in Świerk near Warsaw. Also, some α-emitting therapeutic radioisotopes are produced for research purposes at the Heavy Ion Laboratory of the University of Warsaw. However, the current everyday practice of nuclear medicine in Poland needs also a dedicated Class III accelerator.

Author highly appreciates the discussions and critical reading of the manuscript by Jean-Michel Geets, Leszek Królicki, Renata Mikołajczak, Ludwik Pieńkowski, Józef Sura and Anna Teresińska.

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