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State of the art in cyclotrons for radionuclide production in biomedicine

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State of the art in cyclotrons for radionuclide production in biomedicine

Cyclotrons are one of the most important sources of radionuclides used in bio-medical applications. The production of important radionuclides used in single photon emission tomography techniques such as ^{123}I, ^{67}Ga, ^{201}Tl and ^{111}In has been based for decades on cyclotrons, typically proton machines with an energy up to 30 MeV. The extraordinary growth of positron emission tomography has led to the development of new models, and to the installation of numerous cyclotrons, typically accelerating protons in the energy range 10 - 20 MeV. These have been used for the production of the main PET radionuclides, namely ^{11}C, ^{13}N, ^{15}O and, above all, ^{18}F. Recently, their use has been extended to the production of radiometals, like ^{68}Ga, and even to the direct production of ^{99m}Tc. Moreover, cyclotrons are valuable tool for research and education of new scientists. This review presents the main manufacturers and briefly discuss the characteristics of the models they currently offer on the market.

Keywords: cyclotron; positron emission tomography; radionuclide production; nuclear medicine; particle accelerators.

I. INTRODUCTION

A review on the use of cyclotrons cannot fail to consider the technological and industrial evolution induced by these accelerators.

The accelerating machines on the research front-line are usually complex general-purpose structures designed for fundamental physics research such as particle or nuclear physics. These devices, as already seen in the past, then find a new life in more applied research fields, such as solid state or materials science. Subsequently, differentiation begins where dedicated machines are designed and built for a more

specific research field or process such as synchrotron radiation, pulsed neutrons, generation of particles, and production of radionuclides. Finally, devices are optimized for a single purpose such as compact cyclotrons for the production of positron-emitting radionuclides or cyclotrons for hadrontherapy: these systems are produced on an industrial basis rather than designed and built by or for a research laboratory [1] .

Cyclotrons are now one of the most important sources of radionuclides used in biomedical applications [2,3, 4] . For decades, the production of important radionuclides used in Single Photon Emission Tomography (SPECT) techniques, such as ^{123}I, ^{67}Ga, ^{201}Tl and ^{111}In, has been based on cyclotrons, typically accelerating protons up to an energy of 30 MeV [4] .

In the last 20-25 years, the extraordinary growth and diffusion of positron emission tomography (PET) all over the world has led to the development of new cyclotrons models and to the installation of numerous of these PET cyclotrons, capable of accelerating protons in the energy range 10-20 MeV. These machines have been extensively used in the production of the main PET radionuclides, namely ^{11}C, ^{13}N, ^{15}O and above all ^{18}F, in hospitals, research centers, and commercial radiopharmacies [5] .

Recently, it has been proved that PET cyclotrons can also be used effectively for the direct production of important radionuclides that were originally available only by means of generation systems, such as ^{68}Ga, and even the most important radionuclide for SPECT, the ^{99m}Tc [6,7,8] . This took place as part of a research and development process for new targets; initially dedicated above all to the development of new solid, effective and relatively cheap targets, to be installed on cyclotrons essentially dedicated to PET. Subsequently, an important impulse came from the targets designed for the

production of radiometals in liquid solution. This has led, at least in some cases, such as that of ^{68}Ga, to important achievements .

There is a variety of established PET/SPECT cyclotron manufacturers offering a wide range of solutions to meet the diverse needs of what is now a mature sector of the health technology market.

This review intends to present the main manufacturers and briefly discuss the characteristics of the models they currently offer on the market.

II. IBA

This company was founded by Yves Jongen aiming at the development of high intensity, energy-efficient cyclotrons, combining the advantages of compact and separated sector cyclotrons. The first manufactured system was a 30 MeV high-bean current H^- machine, later called Cyclone 30, whose design included many innovations [9, 10] . This was a highly successful system so that for many years it has been the system of choice for the producers of SPECT radionuclides, and beyond. From a downscale of the Cyclone 30, the Cyclone 18/9 and the Cyclone 10/5 were conceptualized. These negative ion cyclotrons, capable of accelerating H^- and optionally D^-, have had a great diffusion and in the critical years of the development of clinical PET and they have been the workhorse of many PET centers and local radiopharmacies[11] .

The Cyclone 30 was not actually the first negative ion cyclotron to be proposed, but it was probably the first to experience commercial success, which then led to the development of all the family. The stripping foil-based beam extraction that characterizes negative ion cyclotrons has been one of the keys to the success and

diffusion of such systems. Positive ion cyclotrons could count on a much simpler source of ions, compared to those needed to generate negative ions, for example of Hydrogen; it is clear that this is preferably an electron donor and creating negative hydrogen ions requires sophisticated technology. On the other hand, beam extraction in positive ion cyclotrons is very inefficient. The deflector magnets and the septum necessary for this purpose are inevitably hit, at least in part, by the accelerated beam. This determines their activation, which in high current systems can be significant, such as to constitute a significant source of radiation during maintenance operations. Furthermore, in high-current systems, such as those for radionuclide production, cooling of the deflector and septum is required, which increases the complexity of the system. The stripping foils are installed on a system that allows them to be quickly replaced in case of breakage. This system is isolated, thus allowing in a simple way the real-time measurement of the current flowing through the foil, which allows the adjustment of the irradiation parameters.

Continuing its path of innovation, IBA has profoundly revised and modernized the Cyclone 18 in recent years, by introducing the Cyclone KIUBE in 2016 [12] (Fig. 1).

The KIUBE is a very compact machine, significantly smaller with respect to the 18/9. It is optimized for high extracted current exceeding 200 μA and includes several innovations in the design and geometry of the poles and deep valleys. The internal ion source has been redesigned and is now motorized, making possible fine tuning of the position for optimal beam shape and transmission during the period of use between periodical source rebuilding. The new design also makes maintenance, e.g. cathode replacement and source body cleaning, very simple. The innovation of the conformation of the valleys and the adoption of high-performance diffusion pumps make the vacuum system fast and efficient, allowing to obtain a very high transmission of the negative ion

beam, of the order of 80%, while typical values for cyclotrons with internal ion sources are hardly higher than 55 – 60%. The KIUBE maintains the arrangement of the 8 installable targets all around the magnet, as in the Cyclone 18/9, but it offers the possibility of extracting the beam with a predetermined energy between 13 and 15 Mev on a specific target port per side. In this case we are not talking about variable energy, but about the possibility of setting a suitable energy value for the production of some radionuclides, such as ^{68}Ga, without having to resort to a degrader.. The KIUBE is therefore a new success and since its introduction in 2016, already over 20 units have been installed worldwide.

Following the line drawn with the KIUBE, in 2021 the successor of the Cyclone 30, called Cyclone IKON, was presented [11]. The IKON is compact, versatile and capable of working over a variable energy in the range 13-30 MeV. This make possible irradiating a target with the appropriate energy to limit the production of impurities and avoiding the need to degrade the beam by means of absorbers. The Cyclone IKON has an external multicusp ion source, optimized for accelerating H^- , with the capacity of an extracted beam current of 500 µA for the base model and up to 1500 µA for the top of scale. The Cyclone 30 XP remains available for applications in which D^- or alphas shall be accelerated.

The vacuum system is based on cryogenic pumps. The IKON has 3 exit ports per side, 2 of which can be fitted with beam lines. One port per side is dedicate for PET radionuclides production, with a maximum beam energy of 18 MeV, and can be fitted with a 5 position switching magnet providing a great flexibility.

Taking into consideration the needs of small PET centers, in 2022 IBA presented the Cyclone KEY [11], one of the H^- ion cyclotrons with the smallest footprint. The KEY has a maximum energy of 9.2 MeV, and a maximum extracted current of

about 80 μA. It has one single extraction port, on which is fitted a 3 positions target changer. The KEY is the only cyclotron manufactured by the IBA with a vertical acceleration plane. It is rated to produce 111 GBq of $^{18}F^-$ in a 2 hours irradiation, and has a very simple and user friendly software interface, making possible also to small sized hospitals to independently produce ^{18}F-FDG. The overall dimensions of the self-shield version are 3.6 x 3 x 2.2 m (L x W x H).

On the other extreme of the range, IBA is producing also the Cyclone 70 [13,14] for industrial production of all sort of radionuclides, including parents for isotope generators. The "Proton" version is H^- minus only, with variable energy 30 – 70 MeV and maximum extracted current of 750 μA, while the "XP" version can accelerate also D^- and alphas. The Cyclone 70 has been the first 70 MeV cyclotron industrially manufactured and, from 2007, at least 4 units have been already installed and are dedicated to the industrial production of two important PET generators parents ^{82}Sr, ^{68}Ge and other radionuclides for SPECT or therapy.

III. General Electric

In the second half of the '80s, the staff at Scanditronix, leaded by Stig Lindbäck, started to design an evolution of the MC-17. The new system was thought as more compact than is predecessor and based on accelerating negative ions. The project was considered so promising that, also in light of the growing interest in PET in the clinical setting, at the end of 1989 General Electric took over the entire business. This, in short, was the origin of PETtrace, one of the most successful cyclotrons on a world scale (Fig. 2).

The PETtrace is an isochronous cyclotron, with a vertical acceleration plane, which makes maintenance operations very simple. It can accelerate H^- ions up to 16.5 MeV and optionally D^- ions to 8.4 MeV [15] . It has 6 target ports, all on the same side. The extraction system, based on two carousels with graphite stripping foils, allows two targets to be irradiated simultaneously according to combinations target slots. The ion source is internal, Penning type with two different chimneys, for the H^- ions and, optionally, for the D^- contained in the same assembly. The maximum beam current for single beam irradiation has been gradually increased, from 75 µA of the initial versions up to 100 µA, introducing improvements in the ion source itself and in its positioning [16] . The vacuum system includes a single diffusion pump, plus a rotary pump. As for all cyclotrons with an internal ion source, during the irradiation phase there is a certain pressure of the hydrogen gas: the residual molecules of the gas involve the neutralization, and therefore the loss of control, of a part of the H^- ions of the beam. The transmission of the beam is typically of the order of 60%.

The technology used to allow the change of stripping foils in negative ion cycltrons is very important for their functionality and all the systems of the different manufacturers have functional solutions. The strippingo foils, carbon sheets with a thickness of 10 µm or less, are in fact relatively fragile and, under the action of the accelerated beam, can break with use. Their rapid replacement, without the need to open the acceleration chamber under vacuum, is therefore an aspect of considerable importance for practical operation.

The PETtrace was the first system to present a mechanism based on a carousel, which carries 6 stripping foils, and by rotating it allows rapid replacement in case of breakage.

An important aspect in the PETtrace is its extreme ease of use: when it was introduced, for the first time, a cyclotron of this class and productivity level had such a simple and user friendly operator software. The control system automatically prepares the cyclotron and the targets, tunes the beam and manages the target irradiation, adjust the beam current to the desired value. Such software was later adopted for all other GE cyclotrons.

Following the success of the PETtrace, in the year 2000 GE introduced the MINItrace [17] . This is a 9.6 MeV H^- cyclotron designed essentially to be sold in self-shielded configuration. The MINItrace was not conceptualized as a downscale of the PETtrace: even if it shares the vertical orientation of the acceleration plane, the design of the magnet and of the dees of the radiofrequency system is independent. The internal ion source is of Penning type. The first series of the MINItrace had a fixed ion source, which alignment was somewhat cumbersome, being the root cause of problems in keeping optimal performance during a period of use between maintenance. Latest version are equipped with a motorized adjustment system, manually controlled, which makes possible a fine alignment of the ion source without the need of venting the vacuum chamber.

The maximum extracted beam current if 50 μA . The standard configuration features 5 target ports. The extraction system is based on a single stripping foil installed on an arm that can move radially (in and out) and tangentially to the magnet poles allowing for the selection of the target to be irradiated. Dual beam irradiation can be achieved by involving the irradiation of a 6th target in a fixed position and by adding a dedicated additional stripping foil. The vacuum system is similar to that of the PETtrace.

The MINItrace has an efficient self-shield configuration consisting of a stationary part with an internal cavity in which the cyclotron fits while the front part can be opened through two doors. The self-shielding is essentially made up of borated concrete with some additional components in borated polyethylene and lead. This allows for a substantial reduction of the prompt dose rate during irradiation, with a contained level of activation of the self-shielding itself. An interesting feature is that the self-shielding also contains a system for the collection of gaseous waste: this is essentially a delay line, i.e. a long plastic pipe that allows for the physical decay of radioactivity in the gaseous effluents and provides a single outlet, located on the upper part of the self-shield, which can then be connected to the ventilation system and appropriate filtration prior to release.

To complete the range of cyclotrons [18] , GE introduced the GENtrace [19,20] . This is an extremely compact, sector focused, 7.8 MeV negative ion cyclotron. The internal ion source allows for the irradiation at 35 – 50 μA of one of the 3 production targets, mounted on a short beamline. An interesting feature is that the GENtrace is supplied with a dedicated hydrogen generator for the ion source. The vacuum system is based on a turbomolecular pump. The extraction system has a carousel entirely in graphite, to reduce activation, with 8 interchangeable stripping foils. The carousel is driven by a piezoelectric driver granting a very precise movement and optimal beam control. The footprint of the cyclotron, including its self-shielding is just 4 x 2.3 m, while it is rated to produce 28 GBq of $^{18}F^-$ in a 2 hours irradiation.

IV. Advanced Cyclotron Systems Inc (ACSI)

Advanced Cyclotron Systems Inc (in short, ACSI) produces a full range of variable energy cyclotrons: the TR-19 (12-19MeV), the TR-24 (15-25MeV), the TR-FLEX (12-30 MeV), and the TR-30 (15 -33 MeV) [21]. The technologies used in the ACSI cyclotrons are based on the knowledge developed at TRIUMF, Canada's particle accelerator centre based in Vancouver (BC), initially established as a consortium of three Universities to which other partners gradually joined. The commercial models of cyclotrons were initially built by the EBCO Tech Company, which was later transformed into ACSI. The first model made was the TR-30, introduced in 1989, a system capable of accelerating protons up to 30 MeV with a maximum current of 750 μA[22,23] . The maximum energy was then raised to 33 MeV, introducing minor changes to the design, while the current was raised firstly to 1200 and later on to 1600 μA[24] . The TR-30 has been a successful system, particularly on the North American continent.

In the PET cyclotrons industry, the TR-19 [25] has a number of cutting edge features (Fig. 3). It is a system with a vertical acceleration plane and allows to vary the energy of the extracted beam thanks to the extraction system consisting of a stripping foil mounted on a rod. The rod can be moved radially in order to intercept the beam at different distances with respect to the geometric center of the poles of the magnet. Therefore, it is possible to extract the beam at the desired and optimal energy value for a given production process, without requiring the use of absorbers to degrade the energy of the beam. The rod carries a single stripping foil, mounted on a frame. In case of breakage, this can be extracted through an intercept valve, thus allowing to maintain the vacuum in the acceleration chamber; the frame with the stripping foil can be replaced quickly and easily and the system is up and running in a few minutes.

The maximum energy for H^- ions is 19 MeV; optionally, D^- ions can also be accelerated up to a maximum energy of 9 MeV. The TR-19 has two target stations on

opposite sides, on each of which a revolving carousel is installed accommodating 4 targets for a total of 8 targets available.

The multicusp ion source is external, an almost unique feature among PET cyclotrons. This makes it possible to have no neutral gas pressure, as in the case of internal ion sources. The vacuum level during acceleration is therefore only slightly different from the baseline value and the beam transmission is higher than 95%.

Furthermore, the fact that the ion source is external allows it to be maintained, e.g. change the filament, without having to break the vacuum in the acceleration chamber.

The vacuum system is based on cryopumps, which allow for a "cleaner" vacuum without any oil release and, in general, better performance than classic diffusion pumps. The basic version of the TR-19 has a maximum current of 150 μA which can be increased up to 400 μA with an upgrade of the ion source.

Building on the expertise of TR-19, TR-24 was introduced as a bridge between PET cyclotrons and those used for the production of SPECT radionuclides. The acceleration plane of this system, which accelerates only H- ions, is horizontal and the energy varies between 12-25 MeV. Beam currents range from 300 μA, of the baseline model up, to 750 μA, with the possibility of upgrading on the field.

The TR-Flex cyclotron is built from the TR-24 concept[26] by extending the beam energy range from 12 MeV to 30 MeV. However, it is necessary to consider that in order to provide optimal conditions for both PET and SPECT radioisotope production, the TR-Flex beam profile and output is typically optimized at ~18 MeV and ~29 MeV for the low and high energy regime respectively. The high current model of the TR-Flex cyclotron can operate at a higher current, up to 1000 μA beam, offering a higher production capability compared to the TR-24. On the other hand, the TR-Flex is a

compact, cost-efficient accelerator, offering high production capacity at a fraction of the cost of the larger TR-30 cyclotron installations.

V. Sumitomo

Sumitomo Heavy Industries produced the first cyclotron for the Research Center for Nuclear Physics at Osaka University in the first 1970s, having no previous experience in the field[27] . The collaboration with the researchers at the University of Osaka was essential to realize a powerful research tool. In the following years, Sumitomo first partnered with the French company CGR-MeV, which had extensive experience with accelerators, then introduced his own line of cyclotrons for radionuclide production[28] . This approach was successful, with more than 100 installations mostly in Japan and Eastern Asia.

Sumitomo currently offers several models, the Cypris HM-20, HM 18 and HM-12. These are systems with a vertical acceleration plane, capable of accelerating H^- and D^- ions. The HM20 at 20/10 MeV with a maximum beam current of 100 µA for H^- and 50 µA for D^-; the HM12 at 12/6 MeV with a maximum beam current of 100/40 µA . The HM18 is offered in the HC version, H^- only, that can reach up to 400 µA of beam current. Two beam extraction ports are available, each one allowing for the installation of 4 targets.

In the past, another Japanese company, Japan Steel Works (JSW), has produced a positive ion Baby cyclotron in different models, from 10 to 17 MeV of maximum energy, which have had some diffusion. Some of these are still in operation but JSW has long since ceased to develop new products and abandoned this market.

VI. Efremov Institute

The Scientific Research Institute of Electrophysical Apparatus (NIIEFA in Russian) D.V. Efremov has a long tradition in the design of several type of accelerators, lasers and other systems for research, and in particular of cyclotrons. Through the Rosatom Corporation, a state organization that comprises many Russian enterprises in the sector of nuclear and high-tech products, the cyclotrons designed in the St. Petersbug Institute are also sold outside of Russia.

The offer of cyclotrons for producing medical radionuclides includes the CC-12, CC-18/9 and MCC-30/15.

These are negative ions systems, with an external ion source multicusp type. The CC-18/9 (Fig. 4) has nominal extracted currents of 100/50 μA respectively for H^- and D^-, while the MCC-30/15 has been upgraded up to 500/250 μA [29, 30] . No up-to-date performance parameters are published for the CC-12, which should be able to operate with a beam current of at least 50 μA.

VII. Others

In addition to the main producers that have been described above, there is a variety of smaller producers, whose production was limited to a few units, or companies that had a significant production but then left the market.

Among the first we can remember the Korean group Kotron, which took over the technology developed by the Korea Institute of Radiological and Medical Sciences (KIRAMS). Currently, the maintenance of the approximately 10 units installed between Korea, Vietnam and China is offered by the radiopharmaceutical company Samyoung Unitech and it is not clear whether the accelerators are still in production.

The CTI company, based in Knoxville (USA), has played a very important role in the development of PET by producing scanners, cyclotrons and synthesis modules for radiopharmaceuticals until it was taken over by Siemens. More than 200 RDS 112, RDS 111 and Eclipse cyclotrons were installed worldwide. However, following market evaluations, in 2015 Siemens decided to stop the production and research in this sector.

Ronald Nutt, one of the co-founders of CTI, later also founded the firm ABT Molecular Imaging which produced compact cyclotrons of reduced energy: 7.5 MeV, operating with positive ions and with relatively low currents. ABT aimed to create simple systems intended for small productions accordingly to the concept of producing a dose of radiopharmaceutical on the spot, following the request (dose on demand). In practice, this concept has not turned out to be a success. Some systems have been installed to meet the needs of small centers. ABT was later taken over by the BEST Group. The latter announces itself on the web as a manufacturer of various models of cyclotrons. However, to the best of the authors' knowledge, it manufactured only one 70 MeV prototype, not yet entered in routine use for radionuclide production. The French company PMB-Alcen has revived a model of 12 MeV proton only cyclotron based on superconductive magnet, that was already market in the ‘90s by the company Oxford Instruments, and it is now called iMiTRACE. Finally, the US company Ionetix offers a very compact 12 MeV cyclotron model, essentially designed for the production of ^{13}N ammonia and to support the spread of cardiological PET.

VIII. Conclusions and outlook

In this review the most relevant manufacturers of cyclotrons used in the production of medical radionuclides have been presented. As illustrated, they offer a

wide range of solutions to meet the diverse needs of what is now a mature sector of the health technology market (Table I).

Cyclotrons with an energy range for hydrogen ions from about 7 MeV up to 20 MeV are widely diffused for the production of PET radionuclides. Most of these systems are installed within hospitals and proven to be reliable as they made possible the diffusion of a clinically important methodology as Positron Emission Tomography worldwide. A number of the accelerators in the range 16 – 20 Mev are also installed in centralized commercial radiopharmacies, which have contributed to the capillary distribution of 18F-FDG and other relevant radiopharmaceuticals on a local scale. Cyclotrons accelerating hydrogen ions up to 30 MeV have contributed to the production of a variety of SPECT radionuclides, like ^{123}I, ^{67}Ga, ^{201}Tl and ^{111}I as well as to the distribution of ^{18}F. A limited number of cyclotrons operating up to 70 MeV is present in selected production and research sites, to make possible the production of some radionuclides which have very low cross section or "exotic" radionuclides, such as ^{47}Sc, ^{67}Cu or ^{211}At. The experience of the Arronax research center in Nantes (France) is worthy of particular mention [31, 32] ; also worth mentioning is the INFN project in Legnaro (Italy)[33].

Cyclotrons for biomedical use also prove to be safe: a correct design and appropriate operational radiation protection make possible minimal risk for operators and the environment [34, 35, 36, 37, 38, 39, 40] .

The IAEA maintains a database of cyclotrons for the production of radionuclides[41] : until recently, it counted 1286 entries. At the current time, the database is being revised, to verify the number of centers actually still in operation and to complete the data; the confirmed entries are at the moment 683. Cross checking with the information reported in the web sites of the main manufacturers gives a number of

1145, which is quite consistent with the 1286 figure. Above all, it must be remembered that these statistics are dynamic: the number of systems produced and sold does not necessarily correspond to those that are actually active or does not take into account those whose installation is about to be completed.

However, the order of magnitude of the number of these devices is indicative. Finally, it must be remembered that in many countries around the world PET has not yet been introduced due to economic, logistic and organization reasons. It is foreseeable that in the next few years, after the crisis due to the pandemic, the cyclotrons market will continue its growth, although the number of installed units per year will probably not be comparable with what occurred in the period 2000 – 2015 (Fig. 5).

Unfortunately, it is necessary to comment on how in different areas of the globe the main limitation to the diffusion of PET and the installation of the necessary equipment is not of an economic nature, but rather derives from the difficulty in finding and maintaining human resources with the necessary qualification and competence.

It is also very important to remember how a cyclotron, even if dedicated to a practical purpose, such as the production of radionuclides within a health facility, is still a particle accelerator that offers numerous possibilities for research, development and also for the education of young scientists. .

These range from the realization of new components for the accelerator itself, as new beam lines[42], new targets[43,44] , measurement of cross section of activation reactions[45, 46], production of new radionuclides or whose generation is not standardized, particularly in the field of theranostic applications[47, 48, 49], to the use of radiation beams for different purposes (neutron beams production, resistance tests of materials, ...)[50,51], to operational radiation protection[34, 35, 40,52] .

All these possibilities should be considered right from the start of each project. We have already seen how it is possible to combine an efficient routine activity, with active research programs that have produced and continue to provide important innovations.

In conclusion, the market for cyclotrons for the production of radionuclides is nowadays a mature industrial sector, with a variety of systems with excellent characteristics able to satisfy different needs and to operate reliably, delivering daily relevant amount of clinically needed radionuclides worldwide. A large number of cyclotrons allows to support Nuclear Medicine activities, with great benefit for patients, and operating safely for operators and for the environment.

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Tables and Figures

Manufacturer	Model	Particles	Energy (MeV)	Variable energy	Beam current (μA)	Type of Ion source	N. of targets
IBA	Cyclone KEY	H-	9.2	N	80	Int. PIG	3
IBA	Cyclone 18/9	H- (D-)	18 (9)	N	150 (65)	Int. PIG	8
IBA	KIUBE	H-	18	Y	>200	Int. PIG	8
IBA	IKON	H-	30	Y	>500	Ext. Cusp	3 ports per side, one of which dedicated to PET can fit up to 5 targets
IBA	Cyclone 30 XP	H- (D-) (α)	30 (15) (30)	Y	400 (50) (50)	Ext. Cusp	2 ports, can fit beam lines and target stations
IBA	Cyclone 70P	H-	70	Y	750	Ext. Cusp	2 ports, can fit beam lines and target stations
IBA	Cyclone 70XP	H- (D-) (α)	70 (30) (70)	Y	750 (50) (50)	Ext. Cusp	2 ports, can fit beam lines and target stations
GE	GENtrace	H-	7.8	N	50	Int. PIG	3
GE	MINITrace	H-	9.6	N	50	Int. PIG	5
GE	PETtrace	H- (D-) (α)	16.5 (8.4)	N	100	Int. PIG	6
ACSI	TR19	H- (D-)	19 (9)	Y	> 150 (100)	Ext. Cusp	2 ports, each can fit up to 4 targets
ACSI	TR24	H-	25	Y	up to 750 (300)	Ext. Cusp	2 ports, can fit beam lines and target stations
ACSI	TR24FLEX	H- (D-)	30 (15)	Y	up to	Ext. Cusp	2 ports, can fit beam lines and target stations
ACSI	TR30	H- (D-)	30 (15)	Y	> 750 (50)	Ext. Cusp	2 ports, can fit beam lines and target stations
Sumitomo	Cypris HM12	H- (D-)	12 (6)	N	100 (40)	Int. PIG	2 ports, each can fit up to 4 targets / optionally 1 single por
Sumitomo	Cypris HM18	H-	18	N	400	Int. PIG	2 ports, each can fit up to 4 targets
Sumitomo	Cypris HM20	H- (D-)	20 (10)	N	100 (50)	Int. PIG	2 ports, each can fit up to 4

Table I. Summary of the most diffused types of cyclotron currently available on the market.

Figure 1. the IBA Cyclone KIUBE, 18 MeV, H- cyclotron. Courtesy of mr. J.M. Geets.

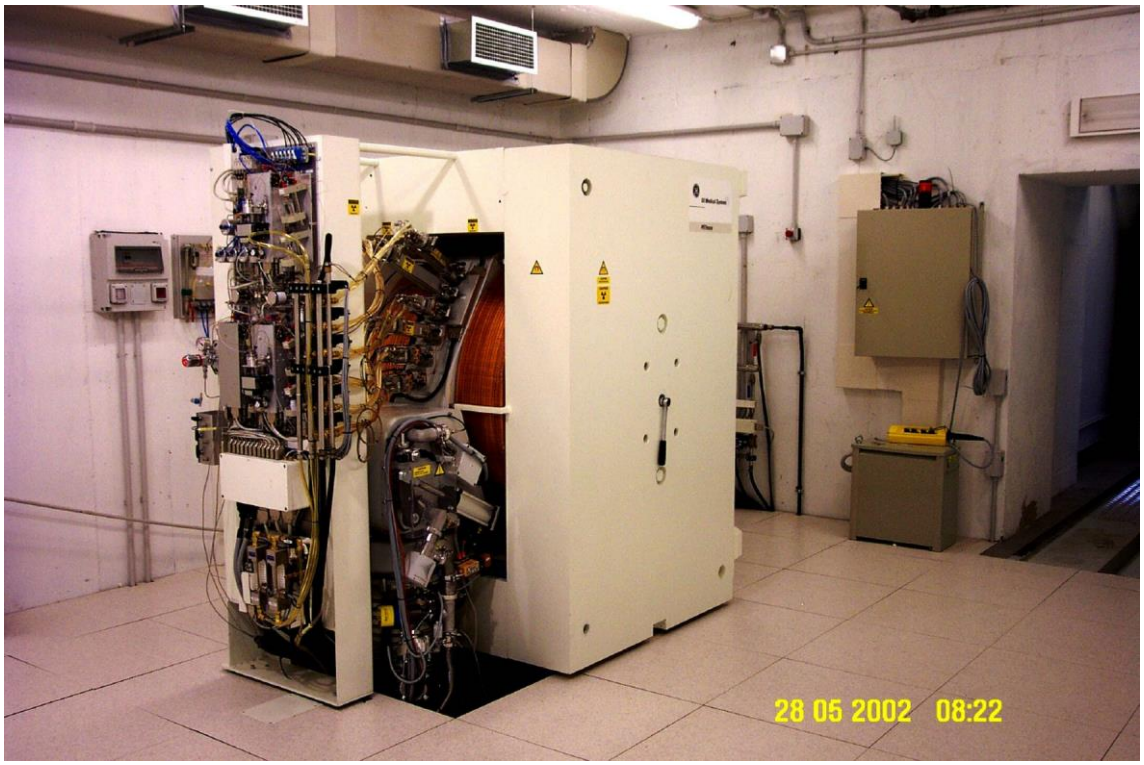

Figure 2. The GE PETtrace cyclotron installed at the University Hospital S.Orsola – Malpighi, Bologna (Italy).

Figure 3. The ACSI TR-19 cyclotron , shown in a configurations with local shields on the target stations. Courtesy of mr. B. Kovacs.

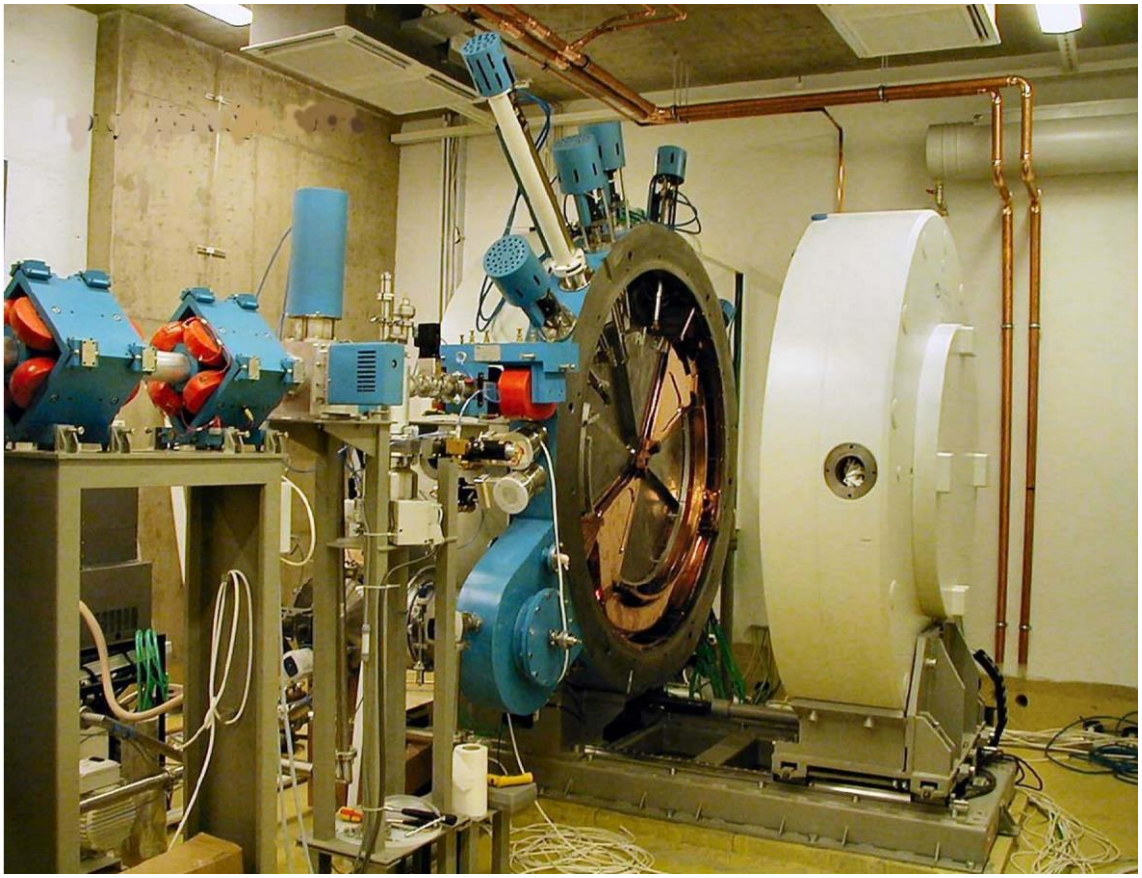

Figure 4. The NIIEFA Efremoc CC-18/9 cyclotron , installed in Turku (Finland). Courtesy of mr. M.F. Vorogushin .

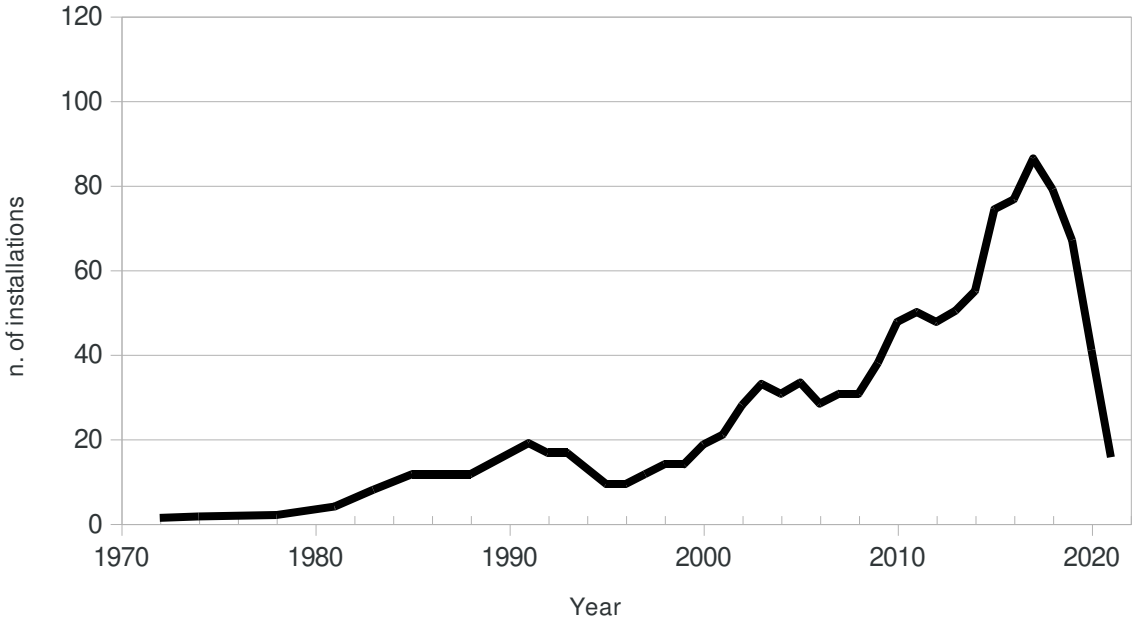

Figure 5. Number of cyclotrons installation per year.

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State of the art in cyclotrons for radionuclide production in biomedicine

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State of the art in cyclotrons for radionuclide production in biomedicine

Cyclotrons are one of the most important sources of radionuclides used in bio-medical applications. The production of important radionuclides used in single photon emission tomography techniques such as ^{123}I, ^{67}Ga, ^{201}Tl and ^{111}In has been based for decades on cyclotrons, typically proton machines with an energy up to 30 MeV.

The extraordinary growth of positron emission tomography has led to the development of new models, and to the installation of numerous cyclotrons, typically accelerating protons in the energy range 10 - 20 MeV. These have been used for the production of the main PET radionuclides, namely ^{11}C, ^{13}N, ^{15}O and, above all, ^{18}F. Recently, their use has been extended to the production of radiometals, like ^{68}Ga, and even to the direct production of ^{99m}Tc. ~~Moreover, cyclotrons are valuable tool for research and education of new scientists.~~Moreover, cyclotrons are valuable tool for research and education of new scientists. This review presents the main manufacturers and briefly discuss the characteristics of the models they currently offer on the market.

Keywords: cyclotron; positron emission tomography; radionuclide production; nuclear medicine; particle accelerators.

I. INTRODUCTION

A review on the use of cyclotrons cannot fail to consider the technological and industrial evolution induced by these accelerators.

The accelerating machines on the research front-line are usually complex general-purpose structures designed for fundamental physics research such as particle or nuclear physics. These devices, as already seen in the past, then find a new life in more

applied research fields, such as solid state or materials science. Subsequently, differentiation begins where dedicated machines are designed and built for a more specific research field or process such as synchrotron radiation, pulsed neutrons, generation of particles, and production of radionuclides. Finally, devices are optimized for a single purpose such as compact cyclotrons for the production of positron-emitting radionuclides or cyclotrons for hadrontherapy: these systems are produced on an industrial basis rather than designed and built by or for a research laboratory [1] .

Cyclotrons are now one of the most important sources of radionuclides used in biomedical applications [2,3, 4] . For decades, the production of important radionuclides used in Single Photon Emission Tomography (SPECT) techniques, such as ^{123}I, ^{67}Ga, ^{201}Tl and ^{111}In, has been based on cyclotrons, typically accelerating protons up to an energy of 30 MeV [4] .

In the last 20-25 years, the extraordinary growth and diffusion of positron emission tomography (PET) all over the world has led to the development of new cyclotrons models and to the installation of numerous of these PET cyclotrons, capable of accelerating protons in the energy range 10-20 MeV. These machines have been extensively used in the production of the main PET radionuclides, namely ^{11}C, ^{13}N, ^{15}O and above all ^{18}F, in hospitals, research centers, and commercial radiopharmacies [5] .

Recently, it has been proved that PET cyclotrons can also be used effectively for the direct production of important radionuclides that were originally available only by means of generation systems, such as ^{68}Ga, and even the most important radionuclide for SPECT, the ^{99m}Tc [6,7,8] . ~~This took place as part of a research and development process for new targets; initially dedicated above all to the development of new solid, effective and relatively cheap targets, to be installed on cyclotrons essentially dedicated~~

~~to PET. Subsequently, an important impulse came from the targets designed for the production of radiometals in liquid solution. This has led, at least in some cases, such as that of ^{68}Ga, to important achievements~~ This took place as part of a research and development process for new targets; initially dedicated above all to the development of new solid, effective and relatively cheap targets, to be installed on cyclotrons essentially dedicated to PET. Subsequently, an important impulse came from the targets designed for the production of radiometals in liquid solution. This has led, at least in some cases, such as that of ^{68}Ga, to important achievements ~~(mettere ref)~~.

There is a variety of established PET/SPECT cyclotron manufacturers offering a wide range of solutions to meet the diverse needs of what is now a mature sector of the health technology market.

This review intends to present the main manufacturers and briefly discuss the characteristics of the models they currently offer on the market.

II. IBA

This company was founded by Yves Jongen aiming at the development of high intensity,

energy-efficient cyclotrons, combining the advantages of compact and separated sector cyclotrons. The first manufactured system was a 30 MeV high-bean current H^- machine, later called Cyclone 30, whose design included many innovations [9, 10] . This was a highly successful system so that for many years it has been the system of choice for the producers of SPECT radionuclides, and beyond. From a downscale of the Cyclone 30, the Cyclone 18/9 and the Cyclone 10/5 were conceptualized. These

negative ion cyclotrons, capable of accelerating H^- and optionally D^-, have had a great diffusion and in the critical years of the development of clinical PET and they have been the workhorse of many PET centers and local radiopharmacies[11] .

The Cyclone 30 was not actually the first negative ion cyclotron to be proposed, but it was probably the first to experience commercial success, which then led to the development of all the family. The stripping foil-based beam extraction that characterizes negative ion cyclotrons has been one of the keys to the success and diffusion of such systems. Positive ion cyclotrons could count on a much simpler source of ions, compared to those needed to generate negative ions, for example of Hydrogen; it is clear that this is preferably an electron donor and creating negative hydrogen ions requires sophisticated technology. On the other hand, beam extraction in positive ion cyclotrons is very inefficient. The deflector magnets and the septum necessary for this purpose are inevitably hit, at least in part, by the accelerated beam. This determines their activation, which in high current systems can be significant, such as to constitute a significant source of radiation during maintenance operations. Furthermore, in high-current systems, such as those for radionuclide production, cooling of the deflector and septum is required, which increases the complexity of the system. The stripping foils are installed on a system that allows them to be quickly replaced in case of breakage. This system is isolated, thus allowing in a simple way the real-time measurement of the current flowing through the foil, which allows the adjustment of the irradiation parameters.

Continuing its path of innovation, IBA has profoundly revised and modernized the Cyclone 18 in recent years, by introducing the Cyclone KIUBE in 2016 [12] (Fig. 1).

The KIUBE is a very compact machine, significantly smaller ~~of~~with respect to the 18/9. It is optimized for high extracted current exceeding 200 μA and includes

several innovations in the design and geometry of the poles and deep valleys. The internal ion source has been redesigned and is now motorized, making possible fine tuning of the position for optimal beam shape and transmission during the period of use between periodical source rebuilding. The new design also makes maintenance, e.g. cathode replacement and source body cleaning, very simple. The innovation of the conformation of the valleys and the adoption of high-performance diffusion pumps make the vacuum system fast and efficient, allowing to obtain a very high transmission of the negative ion beam, of the order of 80%, while typical values for cyclotrons with internal ion sources are hardly higher than 55 – 60%. The KIUBE maintains the arrangement of the 8 installable targets all around the magnet, as in the Cyclone 18/9, but it offers the possibility of extracting the beam with a predetermined energy between 13 and 15 Mev on a specific target port per side. In this case we are not talking about variable energy, but about the possibility of setting a suitable energy value for the production of some radionuclides, such as ^{68}Ga, without having to resort to a degrader.. The KIUBE is therefore a new success and since its introduction in 2016, already over 20 units have been installed worldwide.

Following the line drawn with the KIUBE, in 2021 the successor of the Cyclone 30, called Cyclone IKON, was presented [11]. The IKON is compact, versatile and capable of working over a variable energy in the range 13-30 MeV. This make possible irradiating a target with the appropriate energy to limit the production of impurities and avoiding the need to degrade the beam by means of absorbers. The Cyclone IKON has an external multicusp ion source, optimized for accelerating H^- , with the capacity of an extracted beam current of 500 µA for the base model and up to 1500 µA for the top of

scale. The Cyclone 30 XP remains available for applications in which D^- or alphas shall be accelerated.

The vacuum system is based on cryogenic pumps. The IKON has 3 exit ports per side, 2 of which can be fitted with beam lines. One port per side is dedicate for PET radionuclides production, with a maximum beam energy of 18 MeV, and can be fitted with a 5 position switching magnet providing a great flexibility.

Taking into consideration the needs of small PET centers, in 2022 IBA presented the Cyclone KEY [11], one of the H^- ion cyclotrons with the smallest footprint. The KEY has a maximum energy of 9.2 MeV, and a maximum extracted current of about 80 µA. It has one single extraction port, on which is fitted a 3 positions target changer. The KEY is the only cyclotron manufactured by the IBA with a vertical acceleration plane. It is rated to produce 111 GBq of $^{18}F^-$ in a 2 hours irradiation, and has a very simple and user friendly software interface, making possible also to small sized hospitals to independently produce ^{18}F-FDG. The overall dimensions of the self-shield version are 3.6 x 3 x 2.2 m (L x W x H).

On the other extreme of the range, IBA is producing also the Cyclone 70 [13,14] for industrial production of all sort of radionuclides, including parents for isotope generators. The "Proton" version is H^- minus only, with variable energy 30 – 70 MeV and maximum extracted current of 750 µA, while the "XP" version can accelerate also D^- and alphas. The Cyclone 70 has been the first 70 MeV cyclotron industrially manufactured and, from 2007, at least 4 units have been already installed and are dedicated to the industrial production of two important PET generators parents ^{82}Sr, ^{68}Ge and other radionuclides for SPECT or therapy.

III. General Electric

In the second half of the ‘80s, the staff at Scanditronix, leaded by Stig Lindbäck, started to design an evolution of the MC-17. The new system was thought as more compact than is predecessor and based on accelerating negative ions. The project was considered so promising that, also in light of the growing interest in PET in the clinical setting, at the end of 1989 General Electric took over the entire business. This, in short, was the origin of PETtrace, one of the most successful cyclotrons on a world scale (Fig. 2).

The PETtrace is an isochronous cyclotron, with a vertical acceleration plane, which makes maintenance operations very simple. It can accelerate H^- ions up to 16.5 MeV and optionally D^- ions to 8.4 MeV [15] . It has 6 target ports, all on the same side. The extraction system, based on two carousels with graphite stripping foils, allows two targets to be irradiated simultaneously according to combinations target slots. The ion source is internal, Penning type with two different chimneys, for the H^- ions and, optionally, for the D^- contained in the same assembly. The maximum beam current for single beam irradiation has been gradually increased, from 75 µA of the initial versions up to 100 µA, introducing improvements in the ion source itself and in its positioning [16] . The vacuum system includes a single diffusion pump, plus a rotary pump. As for all cyclotrons with an internal ion source, during the irradiation phase there is a certain pressure of the hydrogen gas: the residual molecules of the gas involve the neutralization, and therefore the loss of control, of a part of the H^- ions of the beam. The transmission of the beam is typically of the order of 60%.

The technology used to allow the change of stripping foils in negative ion cycltrons is very important for their functionality and all the systems of the different manufacturers have functional solutions. The strippingo foils, carbon sheets with a thickness of 10 µm or less, are in fact relatively fragile and, under the action of the

accelerated beam, can break with use. Their rapid replacement, without the need to open the acceleration chamber under vacuum, is therefore an aspect of considerable importance for practical operation.

The PETtrace was the first system to present a mechanism based on a carousel, which carries 6 stripping foils, and by rotating it allows rapid replacement in case of breakage.

An important aspect in the PETtrace is its extreme ease of use: when it was introduced, for the first time, a cyclotron of this class and productivity level had such a simple and user friendly operator software. The control system automatically prepares the cyclotron and the targets, tunes the beam and manages the target irradiation, adjust the beam current to the desired value. Such software was later adopted for all other GE cyclotrons.

Following the success of the PETtrace, in the year 2000 GE introduced the MINItrace [17] . This is a 9.6 MeV H^- cyclotron designed essentially to be sold in self-shielded configuration. The MINItrace was not conceptualized as a downscale of the PETtrace: even if it shares the vertical orientation of the acceleration plane, the design of the magnet and of the dees of the radiofrequency system is independent. The internal ion source is of Penning type. The first series of the MINItrace had a fixed ion source, which alignment was somewhat cumbersome, being the root cause of problems in keeping optimal performance during a period of use between maintenance. Latest version are equipped with a motorized adjustment system, manually controlled, which makes possible a fine alignment of the ion source without the need of venting the vacuum chamber.

The maximum extracted beam current if 50 μA . The standard configuration features 5 target ports. The extraction system is based on a single stripping foil installed

on an arm that can move radially (in and out) and tangentially to the magnet poles allowing for the selection of the target to be irradiated. Dual beam irradiation can be achieved by involving the irradiation of a 6th target in a fixed position and by adding a dedicated additional stripping foil. The vacuum system is similar to that of the PETtrace.

The MINItrace has an efficient self-shield configuration consisting of a stationary part with an internal cavity in which the cyclotron fits while the front part can be opened through two doors. The self-shielding is essentially made up of borated concrete with some additional components in borated polyethylene and lead. This allows for a substantial reduction of the prompt dose rate during irradiation, with a contained level of activation of the self-shielding itself. An interesting feature is that the self-shielding also contains a system for the collection of gaseous waste: this is essentially a delay line, i.e. a long plastic pipe that allows for the physical decay of radioactivity in the gaseous effluents and provides a single outlet, located on the upper part of the self-shield, which can then be connected to the ventilation system and appropriate filtration prior to release.

To complete the range of cyclotrons [18] , GE introduced the GENtrace [19,20] . This is an extremely compact, sector focused, 7.8 MeV negative ion cyclotron. The internal ion source allows for the irradiation at 35 – 50 μA of one of the 3 production targets, mounted on a short beamline. An interesting feature is that the GENtrace is supplied with a dedicated hydrogen generator for the ion source. The vacuum system is based on a turbomolecular pump. The extraction system has a carousel entirely in graphite, to reduce activation, with 8 interchangeable stripping foils. The carousel is driven by a piezoelectric driver granting a very precise movement and optimal beam control. The

footprint of the cyclotron, including its self-shielding is just 4 x 2.3 m, while it is rated to produce 28 GBq of $^{18}F^-$ in a 2 hours irradiation.

IV. Advanced Cyclotron Systems Inc (ACSI)

Advanced Cyclotron Systems Inc (in short, ACSI) produces a full range of variable energy cyclotrons: the TR-19 (12-19MeV), the TR-24 (15-25MeV), the TR-FLEX (12-30 MeV), and the TR-30 (15 -33 MeV) [21]. The technologies used in the ACSI cyclotrons are based on the knowledge developed at TRIUMF, Canada's particle accelerator centre based in Vancouver (BC), initially established as a consortium of three Universities to which other partners gradually joined. The commercial models of cyclotrons were initially built by the EBCO Tech Company, which was later transformed into ACSI. The first model made was the TR-30, introduced in 1989, a system capable of accelerating protons up to 30 MeV with a maximum current of 750 μA[22,23] . The maximum energy was then raised to 33 MeV, introducing minor changes to the design, while the current was raised firstly to 1200 and later on to 1600 μA[24] . The TR-30 has been a successful system, particularly on the North American continent.

In the PET cyclotrons industry, the TR-19 [25] has a number of cutting edge features (Fig. 3). It is a system with a vertical acceleration plane and allows to vary the energy of the extracted beam thanks to the extraction system consisting of a stripping foil mounted on a rod. The rod can be moved radially in order to intercept the beam at different distances with respect to the geometric center of the poles of the magnet. Therefore, it is possible to extract the beam at the desired and optimal energy value for a given production process, without requiring the use of absorbers to degrade the energy of the beam. The rod carries a single stripping foil, mounted on a frame. In case of

breakage, this can be extracted through an intercept valve, thus allowing to maintain the vacuum in the acceleration chamber; the frame with the stripping foil can be replaced quickly and easily and the system is up and running in a few minutes.

The maximum energy for H^- ions is 19 MeV; optionally, D^- ions can also be accelerated up to a maximum energy of 9 MeV. The TR-19 has two target stations on opposite sides, on each of which a revolving carousel is installed accommodating 4 targets for a total of 8 targets available.

The multicusp ion source is external, an almost unique feature among PET cyclotrons. This makes it possible to have no neutral gas pressure, as in the case of internal ion sources. The vacuum level during acceleration is therefore only slightly different from the baseline value and the beam transmission is higher than 95%. ~~Furthermore,~~

Furthermore, the fact that the ion source is external allows it to be maintained, e.g. change the filament, without having to break the vacuum in the acceleration chamber.

~~t~~The vacuum system is based on cryopumps, which allow for a "cleaner" vacuum without any oil release and, in general, better performance than classic diffusion pumps. The basic version of the TR-19 has a maximum current of 150 µA which can be increased up to 400 µA with an upgrade of the ion source.

Building on the expertise of TR-19, TR-24 was introduced as a bridge between PET cyclotrons and those used for the production of SPECT radionuclides. The acceleration plane of this system, which accelerates only H- ions, is horizontal and the energy varies between 12-25 MeV. Beam currents range from 300 µA, of the baseline model up, to 750 µA, with the possibility of upgrading on the field.

The TR-Flex cyclotron is built from the TR-24 concept[26] by extending the beam energy range from 12 MeV to 30 MeV. However, it is necessary to consider that in order to provide optimal conditions for both PET and SPECT radioisotope production, the TR-Flex beam profile and output is typically optimized at ~18 MeV and ~29 MeV for the low and high energy regime respectively. The high current model of the TR-Flex cyclotron can operate at a higher current, up to 1000 µA beam, offering a higher production capability compared to the TR-24. On the other hand, the TR-Flex is a compact, cost-efficient accelerator, offering high production capacity at a fraction of the cost of the larger TR-30 cyclotron installations.

V. Sumitomo

Sumitomo Heavy Industries produced the first cyclotron for the Research Center for Nuclear Physics at Osaka University in the first 1970s, having no previous experience in the field[27] . The collaboration with the researchers at the University of Osaka was essential to realize a powerful research tool. In the following years, Sumitomo first partnered with the French company CGR-MeV, which had extensive experience with accelerators, then introduced his own line of cyclotrons for radionuclide production[28] . This approach was successful, with more than 100 installations mostly in Japan and Eastern Asia.

Sumitomo currently offers ~~two~~several models, the Cypris HM-20, HM 18- and HM-12. These are ~~two~~ systems with a vertical acceleration plane, ~~both~~ capable of accelerating H^- and D^- ions. The HM20 at 20/10 MeV with a maximum beam current of 100 µA for H^- and 50 µA for D^-; ~~and~~ the HM12 at 12/6 MeV with a maximum beam current of ~~8~~100/~~43~~0 µA . The HM18 is offered in the HC version, H^- only, that can

reach up to 400 µA of beam current. Two beam extraction ports are available, each one allowing for the installation of 4 targets.

In the past, another Japanese company, Japan Steel Works (JSW), has produced a positive ion Baby cyclotron in different models, from 10 to 17 MeV of maximum energy, which have had some diffusion. Some of these are still in operation but JSW has long since ceased to develop new products and abandoned this market.

VI. Efremov Institute

The Scientific Research Institute of Electrophysical Apparatus (NIIEFA in Russian) D.V. Efremov has a long tradition in the design of several type of accelerators, lasers and other systems for research, and in particular of cyclotrons. Through the Rosatom Corporation, a state organization that comprises many Russian enterprises in the sector of nuclear and high-tech products, the cyclotrons designed in the St. Petersbug Institute are also sold outside of Russia.

The offer of cyclotrons for producing medical radionuclides includes the CC-12, CC-18/9 and MCC-30/15.

These are negative ions systems, with an external ion source multicusp type. The CC-18/9 (Fig. 4) has nominal extracted currents of 100/50 µA respectively for H^- and D^-, while the MCC-30/15 has been upgraded up to 500/250 µA [29, 30] . No up-to-date performance parameters are published for the CC-12, which should be able to operate with a beam current of at least 50 µA.

VII. Others

In addition to the main producers that have been described above, there is a variety of smaller producers, whose production was limited to a few units, or companies that had a significant production but then left the market.

Among the first we can remember the Korean group Kotron, which took over the technology developed by the Korea Institute of Radiological and Medical Sciences (KIRAMS). Currently, the maintenance of the approximately 10 units installed between Korea, Vietnam and China is offered by the radiopharmaceutical company Samyoung Unitech and it is not clear whether the accelerators are still in production.

The CTI company, based in Knoxville (USA), has played a very important role in the development of PET by producing scanners, cyclotrons and synthesis modules for radiopharmaceuticals until it was taken over by Siemens. More than 200 RDS 112, RDS 111 and Eclipse cyclotrons were installed worldwide. However, following market evaluations, in 2015 Siemens decided to stop the production and research in this sector.

Ronald Nutt, one of the co-founders of CTI, later also founded the firm ABT Molecular Imaging which produced compact cyclotrons of reduced energy: 7.5 MeV, operating with positive ions and with relatively low currents. ABT aimed to create simple systems intended for small productions accordingly to the concept of producing a dose of radiopharmaceutical on the spot, following the request (dose on demand). In practice, this concept has not turned out to be a success. Some systems have been installed to meet the needs of small centers. ABT was later taken over by the BEST Group. The latter announces itself on the web as a manufacturer of various models of cyclotrons. However, to the best of the authors' knowledge, it manufactured only one 70 MeV prototype, not yet entered in routine use for radionuclide production. The French company PMB-Alcen has revived a model of 12 MeV proton only cyclotron based on superconductive magnet, that was already market in the ‘90s by the company Oxford

Instruments, and it is now called iMiTRACE. Finally, the US company Ionetix offers a very compact 12 MeV cyclotron model, essentially designed for the production of ^{13}N ammonia and to support the spread of cardiological PET.

VIII. Conclusions and outlook

In this review the most relevant manufacturers of cyclotrons used in the production of medical radionuclides have been presented. As illustrated, they offer a wide range of solutions to meet the diverse needs of what is now a mature sector of the health technology market (Table I).

Cyclotrons with an energy range for hydrogen ions from about 7 MeV up to 20 MeV are widely diffused for the production of PET radionuclides. Most of these systems are installed within hospitals and proven to be reliable as they made possible the diffusion of a clinically important methodology as Positron Emission Tomography worldwide. A number of the accelerators in the range 16 – 20 Mev are also installed in centralized commercial radiopharmacies, which have contributed to the capillary distribution of 18F-FDG and other relevant radiopharmaceuticals on a local scale. Cyclotrons accelerating hydrogen ions up to 30 MeV have contributed to the production of a variety of SPECT radionuclides, like ^{123}I, ^{67}Ga, ^{201}Tl and ^{111}I as well as to the distribution of ^{18}F. A limited number of cyclotrons operating up to 70 MeV is present in selected production and research sites[31,32,33], to make possible the production of some radionuclides which have very low cross section or "exotic" radionuclides, such as ^{47}Sc, ^{67}Cu or ^{211}At. The experience of the Arronax research center in Nantes (France) is worthy of particular mention [31, 32] ; also worth mentioning is the INFN project in Legnaro (Italy)[33].

Cyclotrons for biomedical use also prove to be safe: a correct design and appropriate operational radiation protection make possible minimal risk for operators and the environment [34, 35, 36, 37, 38, 39, 40] .

The IAEA maintains a database of cyclotrons for the production of radionuclides[41] : until recently, it counted 1286 entries. At the current time, the database is being revised, to verify the number of centers actually still in operation and to complete the data~~The database is continuously reviewed and updated and has now 683 entries, probably following the dismantling or discontinuation of numerous outdated units~~; the confirmed entries are at the moment 683. Cross checking with the information reported in the web sites of the main manufacturers gives a number of 1145, which is ~~very~~quite consistent with the 1286 figure. Above all, it must be remembered that these statistics are dynamic: the number of systems produced and sold does not necessarily correspond to those that are actually active or does not take into account those whose installation is about to be completed.

However, the order of magnitude of the number of these devices is indicative. Finally, it must be remembered that in many countries around the world PET has not yet been introduced due to economic, logistic and organization reasons. It is foreseeable that in the next few years, after the crisis due to the pandemic, the cyclotrons market will continue its growth, although the number of installed units per year will probably not be comparable with what occurred in the period 2000 – 2015 (Fig. 5).

Unfortunately, it is necessary to comment on how in different areas of the globe the main limitation to the diffusion of PET and the installation of the necessary equipment is not of an economic nature, but rather derives from the difficulty in finding and maintaining human resources with the necessary qualification and competence.

It is also very important to remember how a cyclotron, even if dedicated to a practical purpose, such as the production of radionuclides within a health facility, is still a particle accelerator that offers numerous possibilities for research, development and also for the education of young scientists. .

These range from the realization of new components for the accelerator itself, as new beam lines[42], new targets[43,44] , measurement of cross section of activation reactions[45, 46], production of new radionuclides or whose generation is not standardized, particularly in the field of theranostic applications[47, 48, 49], to the use of radiation beams for different purposes (neutron beams production, resistance tests of materials, ...)[50,51], to operational radiation protection[34, 35, 40,52] .

All these possibilities should be considered right from the start of each project. We have already seen how it is possible to combine an efficient routine activity, with active research programs that have produced and continue to provide important innovations.

In conclusion, the market for cyclotrons for the production of radionuclides is nowadays a mature industrial sector, with a variety of systems with excellent characteristics able to satisfy different needs and to operate reliably, delivering daily relevant amount of clinically needed radionuclidies worldwide. A large number of cyclotrons allows to support Nuclear Medicine activities, with great benefit for patients, and operating safely for operators and for the environment.

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Tables and Figures

Manufacturer	Model	Particles	Energy (MeV)	Variable energy	Beam current (μA)	Type of Ion source	N. of targets
IBA	Cyclone KEY	H-	9.2	N	80	Int. PIG	3
IBA	Cyclone 18/9	H- (D-)	18 (9)	N	150 (65)	Int. PIG	8
IBA	KIUBE	H-	18	Y	>200	Int. PIG	8
IBA	IKON	H-	30	Y	>500	Ext. Cusp	3 ports per side, one of which dedicated to PET can fit up to 5 targets
IBA	Cyclone 30 XP	H- (D-) (α)	30 (15) (30)	Y	400 (50) (50)	Ext. Cusp	2 ports, can fit beam lines and target stations
IBA	Cyclone 70P	H-	70	Y	750	Ext. Cusp	2 ports, can fit beam lines and target stations
IBA	Cyclone 70XP	H- (D-) (α)	70 (30) (70)	Y	750 (50) (50)	Ext. Cusp	2 ports, can fit beam lines and target stations
GE	GENtrace	H-	7.8	N	50	Int. PIG	3
GE	MINITrace	H-	9.6	N	50	Int. PIG	5
GE	PETtrace	H- (D-) (α)	16.5 (8.4)	N	100	Int. PIG	6
ACSI	TR19	H- (D-)	19 (9)	Y	> 150 (100)	Ext. Cusp	2 ports, each can fit up to 4 targets
ACSI	TR24	H-	25	Y	up to 750 (300)	Ext. Cusp	2 ports, can fit beam lines and target stations
ACSI	TR24FLEX	H- (D-)	30 (15)	Y	up to	Ext. Cusp	2 ports, can fit beam lines and target stations
ACSI	TR30	H- (D-)	30 (15)	Y	> 750 (50)	Ext. Cusp	2 ports, can fit beam lines and target stations
Sumitomo	Cypris HM12	H- (D-)	12 (6)	N	100 (40)	Int. PIG	2 ports, each can fit up to 4 targets / optionally 1 single por
Sumitomo	Cypris HM18	H-	18	N	400	Int. PIG	2 ports, each can fit up to 4 targets
Sumitomo	Cypris HM20	H- (D-)	20 (10)	N	100 (50)	Int. PIG	2 ports, each can fit up to 4 targets

Table I. Summary of the most diffused types of cyclotron currently available on the market.

Figure 1. the IBA Cyclone KIUBE, 18 MeV, H- cyclotron. Courtesy of mr. J.M. Geets.

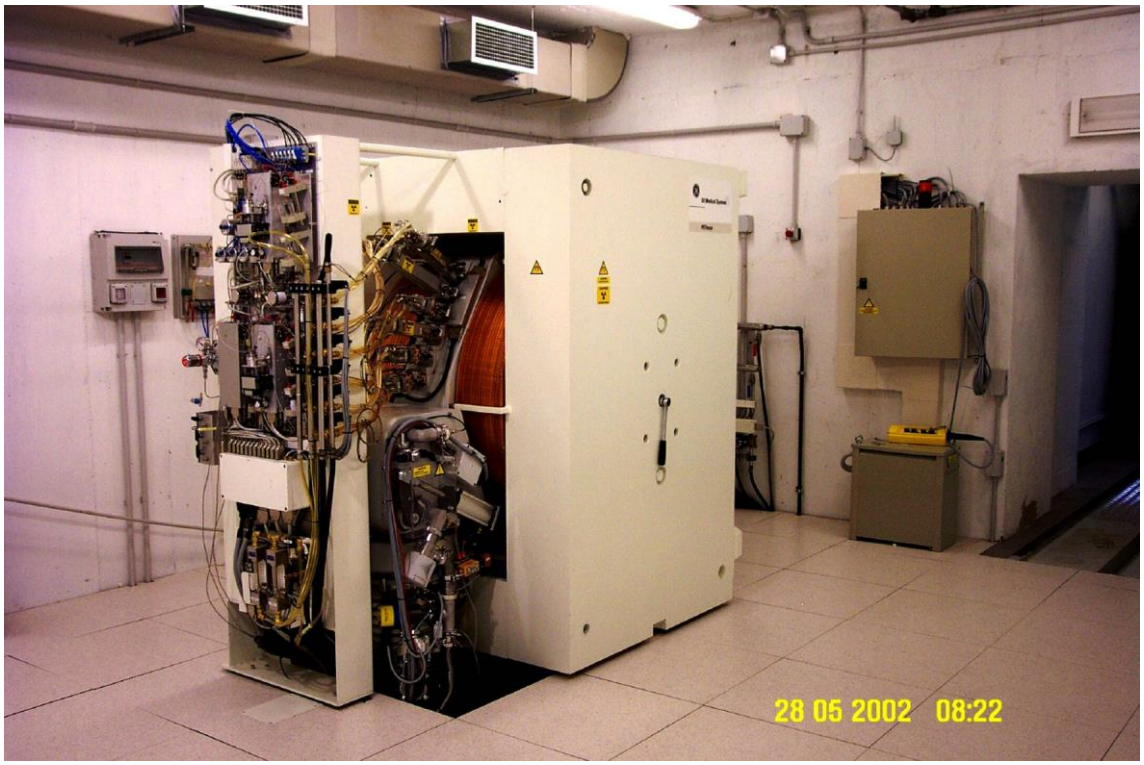

Figure 2. The GE PETtrace cyclotron installed at the University Hospital S.Orsola – Malpighi, Bologna (Italy).

Figure 3. The ACSI TR-19 cyclotron , shown in a configurations with local shields on the target stations. Courtesy of mr. B. Kovacs.

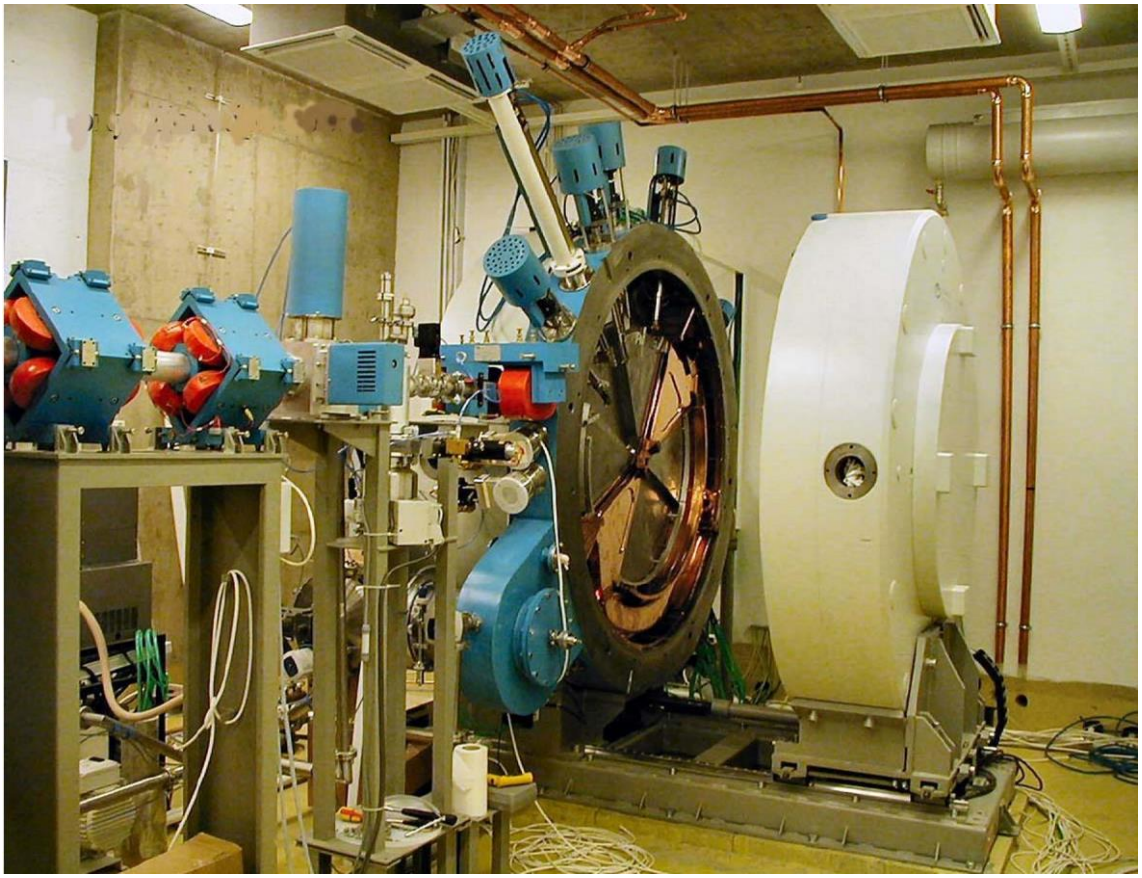

Figure 4. The NIIEFA Efremoc CC-18/9 cyclotron , installed in Turku (Finland). Courtesy of mr. M.F. Vorogushin .

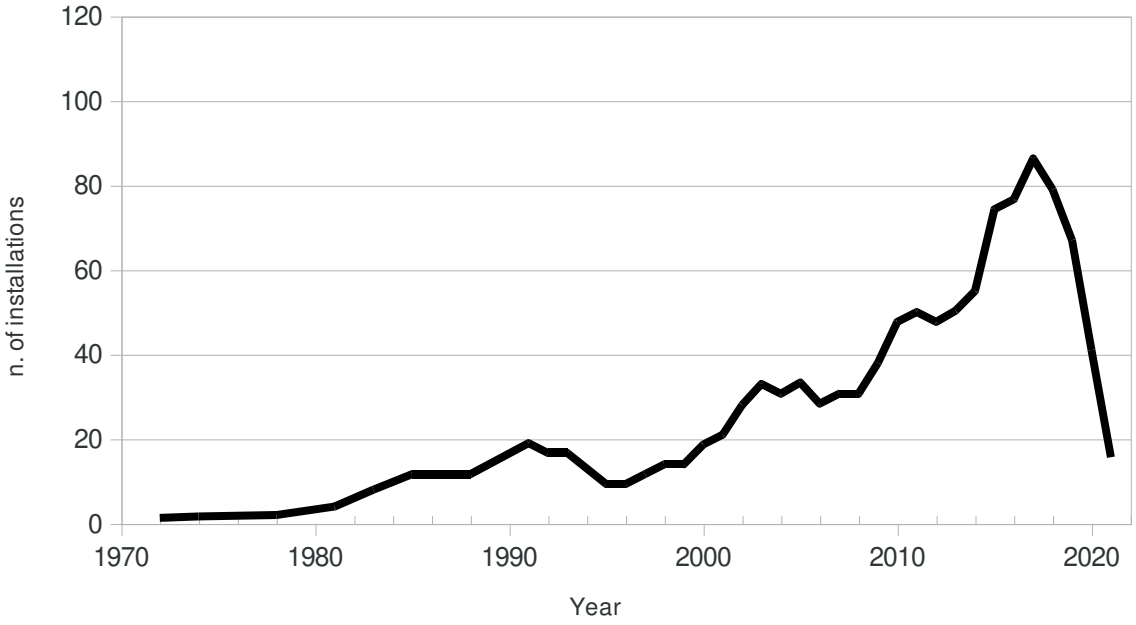

Figure 5. Number of cyclotrons installation per year.