PET Radiopharmaceuticals from Medical Cyclotron Produced Isotopes

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The medical cyclotron facility (MCF) installed at RMC, Parel, is used for producing positron emitting radioactive isotopes for clinical imaging using positron emission tomography (PET). The MCF was commissioned in October 2002, and dedicated to the nation by then Prime Minister of India.

PET provides the most specific and sensitive means for imaging molecular pathways and interactions in the tissues of man. PET images the physiological process at the molecular level, bridging the gap between laboratory science and clinical medicine. Due to its relevance in several diseases, particularly cancer, PET-imaging is making a major scientific as well as financial contribution to drug development, particularly for cancer diagnosis, staging and treatment, and for neurological diseases. PET-imaging requires radiopharmaceuticals (RPs) that are 'true metabolites' i.e., sugars, amino acids, fatty acids etc., essentially made of H, C, N and O which the cells in the body can metabolize. If we look for radioactive isotopes of H, C, N and O, for nuclear medicine imaging, we find only the short lived positron emitters C-11, N-13 and O-15, which are cyclotron produced. A suitable radioisotope of H is not available but, fortunately, F-18 (also cyclotron produced) can substitute for H in several metabolites.

The cyclotron is from GE Medical Systems, Sweden, called PETtrace, which is a compact upright negative-ion cyclotron that features a vertical mid-plane and accelerates protons to 16.5 MeV of energy and deuterons to 8.4 MeV of energy. It supports production of commonly used positron emitting radioisotopes mentioned above. Target beam currents of 75 μA for protons and 60μA for deuterons are achievable. It has the capability to perform simultaneous irradiation of two targets.

Fig. 1 Medical Cyclotron in indigenously designed bunker with ~2 metre thick concrete vault walls and ~1 metre haematite concrete roof. Local shield shielding built to reduce neutron streaming towards vault maze.

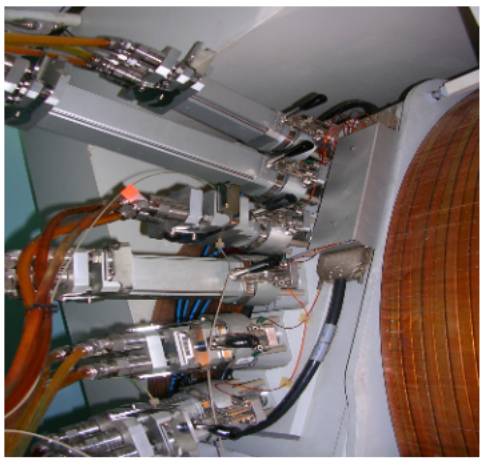

Fig 2. Targets for producing positron emitting isotopes. From below: targets 1, 2 & 4 are for liquid targets for producing F-18, N-13 and F-18 respectively. Targets 3, 5 & 6 are for O-15, C-11 and F-18 gas.

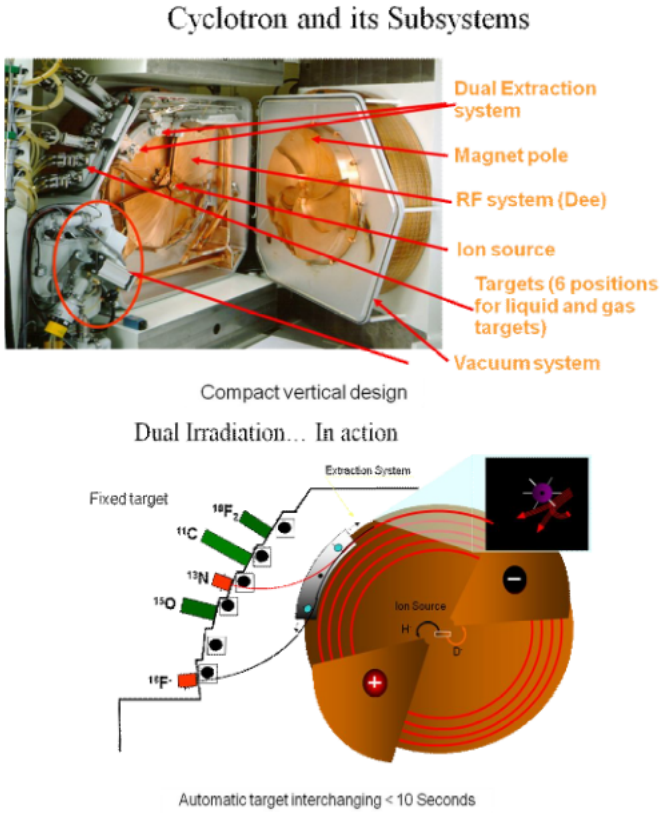

Fig 3. Cyclotron tank opened to show the cyclotron components and the H^- beam can be directed to dual targets as H^+ after stripping away the electrons.

Table 1.
PET-radioisotopes that are commonly produced in a medical cyclotron

Nuclide	T1/2	Mode of γ-ray production method (%)	Abundance energy(%) *(kev)*	Production methods and the common production method (**in bold font**)
^{11}**C**	20.4min	β+ (100)511	200	^{10}B(d,n) ^{11}C, **^{14}N(p.α) ^{11}C**
^{13}**N**	10min	β+ (100)511	200	^{12}C(d,n) ^{13}N, **^{16}O(p,α) ^{13}N**, ^{11}C(p,n) ^{13}N
^{15}**O**	2min	β+ (100)511	200	^{14}**N(d.n)** ^{15}**O** ^{15}N(p,n) ^{15}O
^{18}**F**	110min	β+ (97) 511	194	^{18}**O(p,n)** ^{18}**F**

The H^- and D^- ion sources are contained in the same assembly. With the existing operation within 75 μA of target current, the ion source has an excellent life (typically over six months). The H- source operates on an internal H_2 gas whose pressure is maintained in the range 4-8 Torrs. To maintain this pressure a continuous flow of H_2 of about 5 ml per minute into the ion source is necessary. With a nominal beam current on the O-18 target is 40-50 μA, a production capacity of 3 Ci of $18F^-$ after 1 hour of proton bombardment is achievable. Larger quantities may be prepared by irradiating dual targets simultaneously.For e.g., targets 1 and 2 can be filled with O-18 water and bombarded simultaneously. The PETtrace ion source is of cold cathode Penning discharge type.

Three key sub-systems for yield improvement in PETtrace are: ion source, RF system and the target (Fig.2). Effective 18F- yield is determined by these cascaded factors, specifically, the level of ion-beam current generated by the ion source and the target design with optimal thermal and operating parameters. The RF system has to support the alternating acceleration voltage and should be capable of providing the power needed for acceleration of ions. The nominal beam

current on the standard 18F- target is 35-40μA with a specified production capacity of 2.5 Ci of 18F- after 1 hour of proton bombardment.

Fig 5. Shows on left, the FDG synthesis module, to which the F-18 produced in the cyclotron is sent. The F-18 is conerted to [F-18] FDG. On the right is the radioactive- waste gas compression system, which maintains the synthesis at a –ve pressure, and compresses the sucked air in cyclinders. After overnight decay the stored air is released to the atmosphere.

Radiological safety is ensured by the design and construction parameters that went into the system at the time of construction, reviewed periodically by the DSRC at that time. Fail-safe interlocks, search and clear operations, administrative controls, appropriate placement of area gamma radiation monitors, use of adequately shielded equipment, personnel protection have ensured that there were very few radiological hazards. The operations are monitored by the RSO on duty and a record is maintained of all the operations.

Equally important is the care required in producing [F-18] radiopharmaceutials since they will be injected into patients. The air quality in the environment is controlled to be Class 10,000 and there is a strict adherence to good manufacturing practices (GMP). Since the $T_{1/2}$ is 110 min, all the QC tests on the [F-18] FDG produced cannot be completed before dispatch. Hence, all the production procedures are validated before they are put to routine use. This ensures that any production batch will be safe for patient use with a very high level of confidence.

The MCF began by producing only [F-18] FDG in 2002 and was the first in the country to make available [F-18] NaF, [F-18] FLT and [F-18] FMISO to hospitals. Two other F-18 Radiopharmaceuticals, FET and FAZA are in the pipeline.

Till date, in the 12 years of MCF operations, nearly 5000 batches of [F-18] FDG and over 1000 batches of [F-18] sodium fluoride, has been produced and supplied to various hospitals.