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Experience and Challenges during Establishment of a Cyclotron and PET-CT facility at National Institute of Nuclear Medicine & Allied Sciences (NINMAS)

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National Institute of Nuclear Medicine and Allied Sciences (NINMAS) is the ‘Center of Excellence’ and a leading institute amongst all other Nuclear Medicine (NM) facilities in Bangladesh. It is a sister concern of Bangladesh Atomic Energy Commission (BAEC) running under Ministry of Science and Technology (MOST) and located in Bangabandhu Sheikh Mujib Medical university (BSMMU) campus. The Institute started its journey back in 1980 and now it has well equipped Scintigraphy, Nuclear Cardiology, Thyroid, In-Vitro and Ultrasound & Color Doppler division. Besides it has well established Research & Development and Medical Physics division that ensures future advancement of NM at the Institute. The seeking and thinking of an establishment of Cyclotron and Positron Emission Tomography-Computed Tomography (PET-CT) facility at the institute initiated inthe year 2003. At that time, Prof. Dr. M. A. Karim, the then Director and now ex-chairman of BAEC, Prof. Dr. Lutfun Nisa, head of scintigraphy division and chief scientific officer Prof. Dr. Kamila Afroj inspired me to plan and submit an annual development project (ADP) on the establishment of Cyclotron and PET-CT facility at NINMAS. Accordingly, the project was submitted and finally approved by MOST on October 09, 2011 as a project titled *“Establishment of PET-CT with Cyclotron Facilities”*. Three latest model PET-CT sytems and one modern medical Cyclotron with Radiochemistry facility were procured for this project.We could successfully install a model of GE Discovery 710 as the first PET-CT scanneron November 2014. This model of GE Discovery 710 used Lutetium based scintillator (LBS) (1) for detection of positron emission and Time of Flight (TOF) (2) technique for data acquisition. A 128 slice CT was included with this PET-CT scanner with a resolution of approximately 0.625 mm and low radiation exposure as measured with CT Dose Index e.g. $CTDI_{vol}$ –Helical head 17.0mGy/100 mAs and $CTDI_{vol}$ –Helical body 8.8mGy/100 mAs (1). Second PET-CT scanner was installed at Institute of Nuclear Medicine and Allied Sciences (INMAS), Dhaka Medical College Hospital (DMCH) campus on April 2018 and the third one at NINMAS on January 2019. Both the second and third ones were supplied by Philips Medical Systems and their model was ‘Ingenuity TF’ having Yttrium doped Lutetium Ortho-silicate (LYSO) crystal detector and modern Time of Flight (TOF) technique for data acquisition (3). A 128 slice CT was included with these PET-CT scanners having a resolution of approximately 0.6mm and low radiation exposure as measured with CT Dose Index e.g.$CTDI_{vol}$ – head 11.0 mGy/100 mAs and $CTDI_{vol}$ – body 5.6 mGy/100 mAs (3).

Cyclotron is a device that accelerates charged atomic or subatomic particles in a constant magnetic field. This type of particle accelerator was very first developed in the early 1930s by two American physicists Ernest Orlando Lawrence and M. Stanley Livingston at the University of California, Berkeley (4, 5). On March 2018, main equipment of cyclotron and radiochemistry (Model: Cyclone®18/9 from IBAS. A., Belgium) reached NINMAS premises having the ability to accelerate both proton at energy of 18 MeV and deuteron at 9 MeV. Enormous hurdles and challenges were faced with the placement of a 100 tons crane during the rigging of the cyclotron in the cyclotron bunker as the space was narrow with high voltage electricity cables right in front of the oncology building (Block-F, BSMMU). Breaking down a part of the boundary walls and some already constructed parts of the oncology building and plugging out high voltage electricity connections were way too cumbersome a process. Another big challenge was to slide the 27 tons (approx.) cyclotron in the appropriate place of the cyclotron bunker. Indian experts helped us to get four super strong sliding rollers suitable for the four legs of this heavy machine and place it at the appropriate place. Arranging and solving these undue and uncalculated issues were time consuming and at last on January 07, 2019, it was possible to rig the cyclotron at the designated bunker of oncology basement. Simultaneously the installation of two chillers, four air handling units (AHU), clean room, radiochemistry unit, quality control equipment and radiation safety equipment was completed during this period.

The main objective of this cyclotron establishment is to produce conventional ^{18}F, ^{11}C, ^{13}N and ^{15}O PET radionuclides. This cyclotron has eight target ports. Primarily four target ports will be chosen for the ^{18}F, one for ^{11}C, one for ^{13}N, one for ^{15}O and one for solid target.

Table 1: Some basic uses of the cyclotron produced PET radiopharmaceuticals

TRACER	IMAGING	CLINICAL USE
^{18}F-FDG	Glucose metabolism	Oncology, neurology
^{18}F-FMISO	Hypoxic cell tracer	Oncology, stroke
^{18}F-FLT	DNA synthesis	Oncology
^{18}F-FCH	Biosynthesis of phospholipids	Oncology (prostate)
^{18}F-FDHT	Androgen receptor expression	Oncology (prostate)
^{18}F-NaF	Bone Seeking Agent	Oncology
^{18}F-FDOPA	Dopaminergic function	Neurology, (Parkinson's)
^{18}F-AV1	Amyloid plaque	Neurology (Alzheimer's)
^{11}C-Methionine	Metabolic (Amino acid transport)	Oncology
^{11}C-Acetate	Oxidative Metabolism	Cardiology/ oncology
^{11}C-Choline	Biosynthesis of phospholipids	Oncology
^{11}C-Flumazenil	Benzodiazepine antagonist	Psychiatry, neurology
^{11}C-PK11195	Perif Benzodiazepine antagonist	Neurology, psychiatry
^{11}C-PIB	Amyloid plaque	Neurology (Alzheimer's)
^{13}N-NH3	Blood flow	Cardiology
^{15}O-O2	O2 metabolism	Metabolism
^{15}O-H2O	Blood flow	Brain activation
^{68}Ga-Dotatate	Neuroendocrine tumor	Oncology
^{68}Ga-PSMA	Prostate specific membrane	Oncology (prostate)
^{124}I-antibody	Tumor	Oncology
^{89}Zr-antibody	Tumor	Oncology

The radiochemistry for ^{18}F is designed for the radiopharmaceuticals (RPh) of ^{18}F-FDG, ^{18}F-FLT, ^{18}F-FMISO and ^{18}F-NaF (6-10). On the other hand, radiochemistry for ^{11}C is designed for the ^{11}C-Methionine, ^{11}C-Acetate and^{11}C-Choline (11-14) and radiochemistry for ^{13}N is only for ^{13}N-NH$_3$(15). The target for ^{15}O is not included in this project right now but kept in hand for future use.

Solid target in this cyclotron is included for the research & development and also for advanced tumor imaging in oncology. In recent years, there has been increased interest in nonconventional positron emitters as ^{89}Zr. Since the introduction of the long-lived positron emitter 89Zr as a residual radionuclide for immuno-PET, procedures have been developed for large-scale production of ^{89}Zr and its stable coupling to monoclonal antibodies (mAbs) (16, 17). It is expected in the future that PET imaging with ^{89}Zr-based tracers will constantly progress, and more promising ^{89}Zr-based tracers should be into clinical use. To diagnose malignant tumors with ^{68}Ga using PET-CT, global demand for positron emitters like ^{68}Ge/^{68}Ga generators have increased but low number of manufacturing sites are making it hard to meet the demands. So,a cyclotron-based production of ^{68}Ga via the nuclear reaction ^{68}Zn(p,n) ^{68}Ga (from the stable isotope ^{68}Zn) will provide an opportunity to ensure patient care with ^{68}Ga radiopharmaceuticals (18,19). Thus alternative production method for ^{68}Ga using solid targets is also possible.

Table 2: Production reaction and characteristics of some conventional PET isotopes

Radionuclide	Half-life	β+ decay*	Production
Oxygen-15	2.0 min	100%	^{14}N(d,n)15O
Nitrogen-13	10.0 min	100%	^{16}O(p,α)13N
Carbon-11	20.4 min	100%	^{14}N(p, α)11C
Fluorine-18	109.6 min	98%	^{18}O(p,n)18F

Table 3: Production reaction and characteristics of some other PET isotopes from solid targets

Other PET isotopes - Solid target

Radionuclide	Half-life	Nuclear reaction	+ decay*	Other emissions
Copper-64	13 hour	64Ni(p,n)64Cu	18%	-, γ (578keV)
Yttrium-86	14.7 hour	86Sr(p,n)86Y	34%	γ (1075keV)
Zirconium-89	3.3 day	89Y (p,n) 89Zr	23%	γ (909keV)
Iodine-124	4.2 day	124Te(p,n)124I	23%	γ (603, 1691keV)
Gallium-68	68 min	68Zn(p,n)68Ga	90%	γ (1075keV)
GENERATORS:				
Gallium-68	68 min	**68Ge--- 68Ga generator	90%	γ (1075keV)γ

Figure 1: a) Current view of the installed cyclotron at the basement section of oncology building, BSMMU.

Figure 1: b) Philips Ingenuity TF PET-CT located at the 2nd floor of same building.

The Cyclotron facility at NINMAS is finally established as a project and renamed as "*Establishment of Positron Emission Tomography-Computed Tomography (PET-CT) with Cyclotron facilities*" and aimed to develop modern services and innovative research in NM with two major agendas a) diagnostic and therapeutic service to patients and b) Physical and biomedical research. Vibrant research activities are a demand of time in the era of precision medicine where NM focuses on theranostics and diagnostics using the state of the art technologies. Cyclotron produced radio-pharmaceuticals are very efficient for molecular imaging and targeted therapy. This project created the possibility of oncologic research in animals and humans ensuring maximum use of the cyclotron produced RPh. The scientists of NINMAS have long been working to address these issues with international experts of these fields. It is highly recommended to provide the opportunity for a successive project for the clinical trials of the applications of different RPh in biomedical fields which would help create a research environment for the multidisciplinary team of physicians, scientists and engineers as well as trained technologists. Development of manpower, research opportunities and patient services will definitely earn more wages and cut down the costs of cancer management in near future. So, the establishment of cyclotron and PET-CT facility will rapidly reduce our dependence on other suppliers and efficiently alleviate patient's burden of disease. It is highly recommended to provide an opportunity for a future project in order to approach for the applications of the cyclotron and radio-chemistry of new RPh to clinical trials.

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