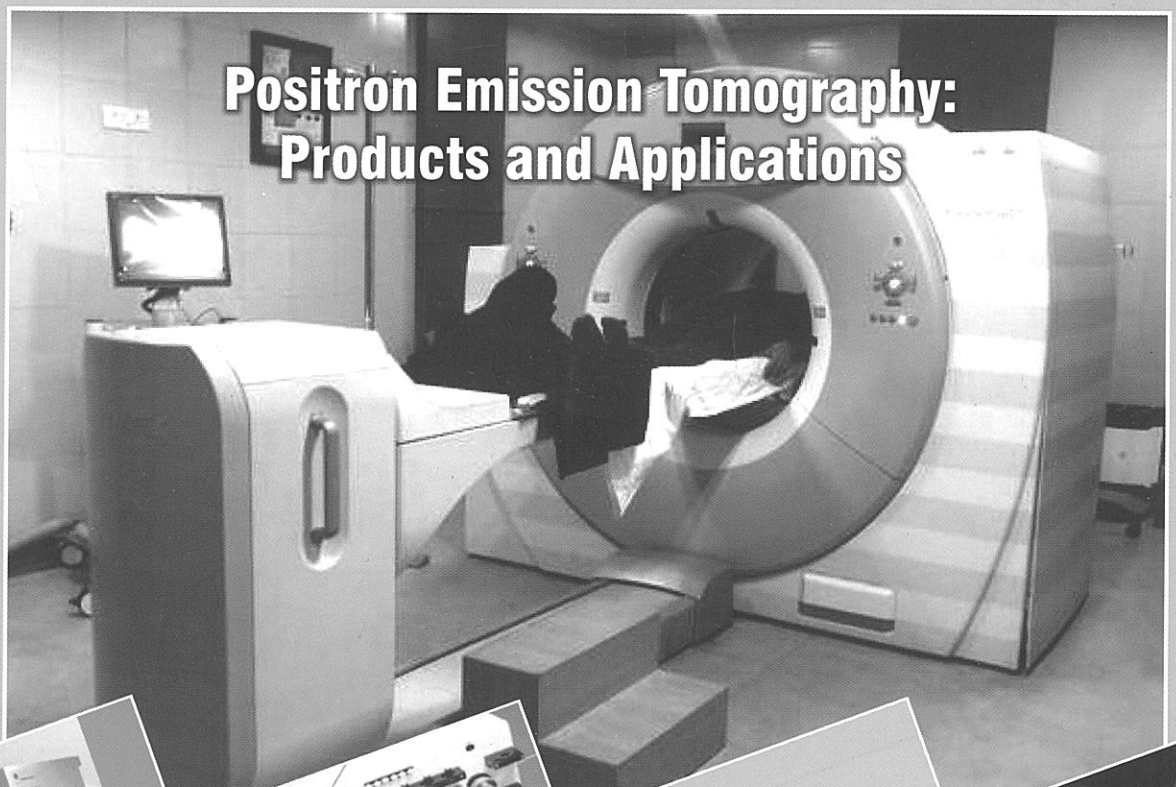
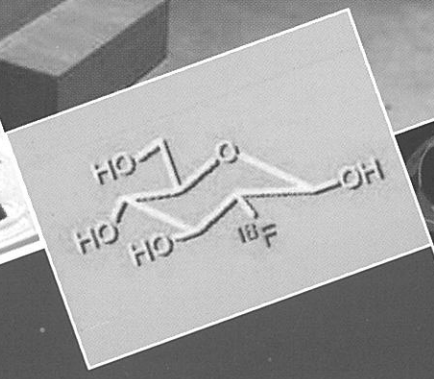
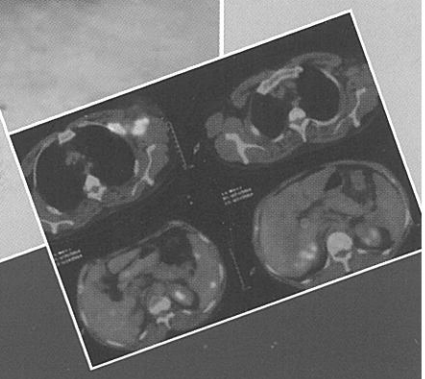
IANCAS Bulletin

INDIAN ASSOCIATION OF NUCLEAR CHEMISTS AND ALLIED SCIENTISTS

Positron Emission Tomography: Products and Applications







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Editorial

One of the most rapidly growing diagnostic imaging modalities of the recent times is the Positron Emission Tomography, popularly known by its acronym, PET. This is mainly due to its high impact in the management of a number of clinical conditions, especially after the development and launch of the hybrid imaging system PET and CT. The application of the findings of PET and PET/CT studies has transformed the management paradigm of patients of cancer in particular. So much so, the field of Nuclear Medicine, which was predominantly based on radionuclides produced in research reactors run by mostly national governments, has witnessed the emergence of an increasing number of medical cyclotrons (MC) operating and delivering day after day the short-lived, positron emitting tracers, Fluorine-18 in particular. The 110 min half-life ^{18}F products produced (often more than once a day) and successfully delivered to users, located at sites requiring several hours of (road/air) transport, has led to a paradigm-shift in the approach to distribution of short-lived radiopharmaceuticals. It goes to the credit of BARC-DAE that the first MC and PET in India became a reality in October 2002. Triggered by this, many centres came up soon thereafter and in quick succession, and toady there are several MC in India supporting nearly 100 PET/CT units rendering regular clinical service.

The major advantages of PET are: use of markers of biological function, tomographic images of very high resolution, accurate quantification, etc. Spurred by the success of the omnipresent tracer in PET clinics, ^{18}F - 2-Fluoro-2-Deoxy Glucose (FDG), marker of glucose metabolism, there has been a surge in seeking more specific PET tracers, including those of radiometals. Currently it is estimated that one PET study takes place every ten seconds somewhere in the world.

PET is then naturally an important theme to cover for dissemination of knowledge and the potential of this technique. I am privileged to have this opportunity to plan and steer the publication of this volume for IANCAS, by taking on an additional role, namely that of one of the two Guest Editors. Dr. M.G.R. Rajan, as Head, RMC and Senior General Manager (MC), BRIT, responsible for the management of BARC's MC Facility and PET Radiopharmacy, became an automatic choice to be the other Guest Editor to help prepare this volume.

The design and content of the volume aim to highlight the features and status of, PET tracers (four articles covering both established and emerging products), imaging instrumentation system (one article), and clinical applications (in oncology and other areas, two articles). The volume, in addition, carries the

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Fluorine-18 Radiopharmaceuticals for PET Imaging: FDG and Beyond

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History

The idea that positron emitters would be useful in imaging brain tumours was suggested in 1950 by Dr. Gordon Brownell, hospital physicist of Massachusetts Institute of Technology to Dr. William Sweet a neurosurgeon at the Massachusetts General Hospital, who was injecting phosphorus-32 into patients with suspected brain tumours and inserting small probes into the skull to locate the tumours. Brownell thought of the tactic of using the special radiation that occurs when a positron strikes an electron and the two particles are annihilated, giving rise to a pair of 0.51 MeV annihilation photons, which go off in opposite directions from each other. By means of a coincidence counting circuit, only those pairs of photons that are not scattered are registered. Since collimation will be used for coincidence counting, positron imaging is better able to pinpoint the source of emissions as well as being able to detect smaller amounts of radioactivity, as was published by William Sweet at the end of 1951 [1]. Brownell built a prototype positron scanner, using two opposed sodium iodide detectors mounted on a movable platform (Fig. 1). This scanner was used to image patients with suspected brain tumors, using the radioactive isotope arsenic-72, which could be made by the cyclotron at MIT [2,3]. Sweet and Brownell demonstrated that, in some cases, positron scanning provided clear-cut positive findings, when the standard methods of that time, arteriography and pneumoencephalography, were negative.

^{18}F-2-Fluoro-2-Deoxy-Glucose (FDG)

The concept of FDG-PET using ^{18}F as the positron emitting isotope, which could be made in a cyclotron was developed by Alfred Wolf and Joanna Fowler and their colleagues at the Brookhaven National Laboratory (BNL), New York [4]. This was based on the knowledge that cancer cells consume more glucose than normal cells was known from Warburg's publication in Sciencein 1956 [5]. Further, 2-Deoxy-D-glucose as an analogue of glucose was known as it was developed as a chemotherapeutic agent by Laszlo et al., in 1960but not used, since it blocked glucose metabolism both in normal and cancer cells [6].

Positron emission tomography (PET) imaging is virtually synonymous with ^{18}FDG PET scan and is in the forefront of nuclear medicine for medical and molecular imaging. This product, described as the Molecule of the Millennium, by Prof. Henry Wagner, has made what PET nuclear medicine is today.

In 1976, Ido and co-workers from BNL first synthesized FDG by an electrophilic fluorination method and used it for brain tumours [7]. However, this method was difficult, complex, and required the use of [^{18}F] fluorine gas and was a five steps procedure with 10-12% yield. A three-step nucleophilic approach with [^{18}F] fluoride was first made in 1982 at the Massachusetts General Hospital by Levi, Elmaleh and Livny [8], which gave 20% yield. This approach was later developed by Hamacher et al. at KFA,

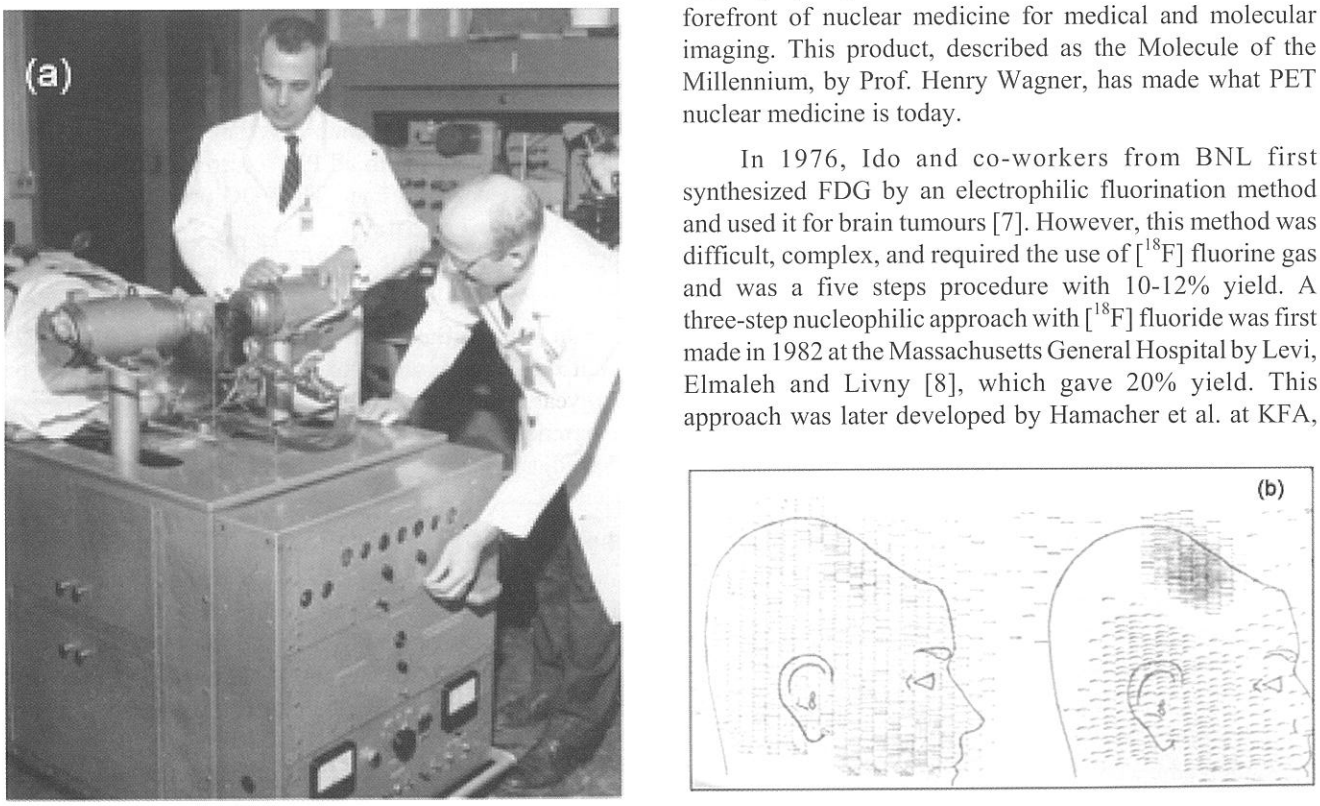


Fig. 1 a: The first clinical positron imaging device using Arsenic-42. This had two positron detectors positioned on either side of the patient's head, was built in 1952 at the MGH by Gordon Brownell (left) and Saul Aronow (right)s pictured on the right. b. images from the positron coincidence scan (positoencephalogram) shows increased uptake in brain under a previous operation site, indicating recurrence of tumor. From Ref. [4]

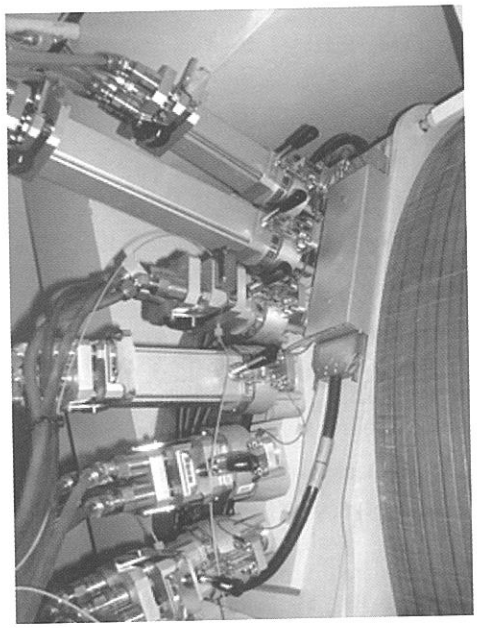


Fig. 2 Targets in medical cyclotron used for producing short-lived PET radioisotopes. Starting from the bottom, Target 1, 2 and 4 are for liquid targets for producing ^{18}F by $^{18}O(p,n)^{18}F$ and can hold between 1 – 2.2 ml. They can also be used for making ^{13}N by $^{16}O(p,\alpha)^{13}N$. Targets 3, 5 and 6 are for irradiating gas targets and have a longer beam path length compared to liquid targets. They are used for making for $^{14}N(d,n)^{15}O$, $^{14}N(p,\alpha)^{11}C$ and $^{20}Ne(d,\alpha)^{18}F_2$respectively.

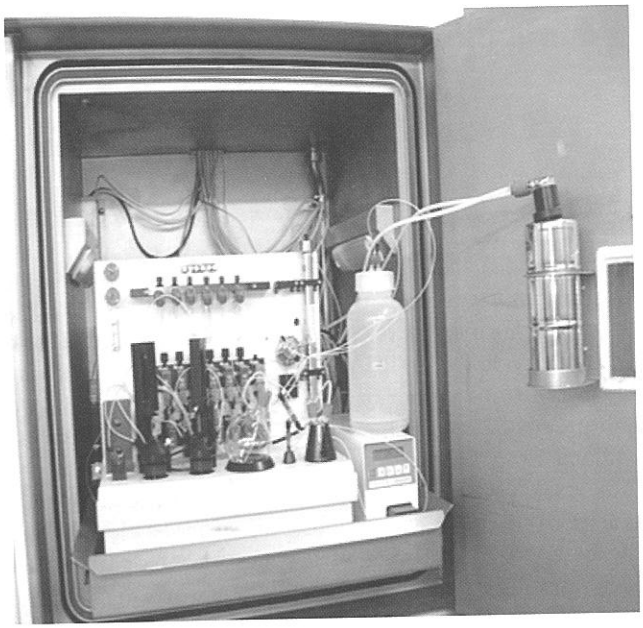


Fig. 3 A general purpose ^{18}F-radiofluorination module for nucleophilic reactions. It is provided with a semi-prep HPLC. The liquid nitrogen trap in a Dewar's flask can be seen on the right. This module can be used for making a variety of ^{18}F-labeled compounds. It has a semi-prep HPLC for purification of the final product, but can be by-passed if solid-phase extraction cartridges are used.

Juelich, Germany into a one-step reaction [9] that gave a labeling yield of over 60%. This is the method that is presently used in all commercial FDG production.

FDG has a wide range of possible clinical imaging applications in neurology, oncology and cardiology.The applications of FDG in oncology and non-oncology are described in articles by Dr. V. Rangarajan and Dr. Sandip Basu in this issue. There is a large difference in the volume of clinical use between these two areas of applications.

The first medical cyclotron was installed in 2002 at the Radiation Medicine Centre (RMC), BARC, located at the Tata Hospital Annexe Building at Parel. This Medical Cyclotron Facility (MCF) has been in successful operation since 2003 mainly producing FDG and, to a lesser extent, [^{18}F] sodium fluoride to meet the requirements of several hospitals in Mumbai. [^{18}F] fluorothymidine (FLT), [^{18}F]fluoromisonidazole (FMISO) are also produced, but the requirement for these are limited.

The FDG produced from the MCF is as per the specifications of the US-Pharmacopoeia and approved by the Radiopharmaceuticals Committee of the Department of Atomic Energy. The reagents and precursors used are of approved quality and used after pre-production runs fulfill all quality control and quality assurance criteria. The production costs are kept low by large production volumes (2 – 2.5 Ci per day) and using synthesis modules which do not use expensive disposables/consumables. To minimize decay losses to the PET-centres using it, the FDG is produced in two batches planned for morning and afternoon use. To ensure the availability to all PET-centres, even one patient dose requirements are met. The FDG produced is used in over 80 patients daily. As in USA and Europe, approximately 95% of all PET studies for patients with cancer are performed with FDG.

In a way, the MCF at RMC was a showcase that medical cyclotrons are viable in our country, since within a few years, several medical cyclotrons were installed in government and private sector hospitals. Presently, there are 15 medical cyclotrons in the country and over 90 PET-CT scanners,

Importance of Fluorine-18 in PET-Radiopharmacy

Fluorine-18 is the radio-isotope of choice in PET-imaging for physical, chemical and biological reasons. Physically, the nuclear reaction $^{18}O(p,n)^{18}F$ can be achieved with protons <9 MeV and its 110 min half-life makes it convenient for making ^{18}F-radiopharmaceuticals and distribute from a centralized radiopharmacy. Chemically, it can be introduced into a variety of molecules by electrophilic and nucleophilic reactions to substitute -H and -OH with minimal perturbation in overall charge distribution in the molecule.Biologically, the mean path of the emitted positrons in tissue before annihilation is 0.3 mm, which assures good spatial resolution.

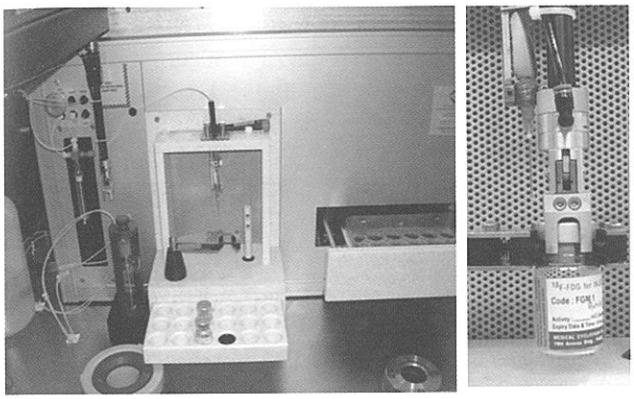


Fig. 4 Sterile dispensing of ^{18}F-radio-pharmaceuticals. The above picture shows the robotic arm moving the sterile vial into the 'Class A' area where a preset amount of activity will be dispensed into the vial.

Over the years, there have been several improvements in medical cyclotrons: (i) configurations that can deliver high proton (H^+) beam currents, (ii) easy availability of >95% enriched [^{18}O]-water used as target for $^{18}O(p,n)^{18}F$ reaction,(iii) niobium cavities for ^{18}O-water targets that can withstand high beam currents with negligible corrosion, by which several Curies of fluorine-18 can be produced in an hour of irradiation. In addition, there are several publications in fluorination chemistry, resulting from much research and development studies,and associated automation that can be used for labeling a variety of molecules for use a [^{18}F]-radiopharmaceuticals. Hot cells with programmable chemistry modules where >185 GBq (>5Ci) of the isotope can be handled with adequate safety features including holding the fluorine-18 waste that is produced till it decays to safe levels.

In addition, there are several proprietary [^{18}F]-radiopharmaceuticals that have been developed by major companies, and these new agents are in different stages of clinical evaluation. These new PET drugs are designed for imaging brain beta amyloid, myocardial perfusion, amino acid transport, angiogenesis, and tumor antigen expression. Some of them have been approved by the US-FDA for use in patients.

Radio-Fluorination approaches with Fluorine-18

The success in making a large number of [^{18}F]-labeled molecules is due to understanding of fluorine chemistry by researchers in this field working inover 600 cyclotron and PET centres. Fluorination of molecules can be carried out by electrophilic or nucleophilic reaction meachanisms, though the latter is the preferred method. In nucleophilic ^{18}F-fluorination: $S_N2$on aliphatic and S_NAr on aromatic compoundsis used. Common leaving groups suited for S_N2 are Br, I and the sulphonyl esters such as triflate, mesylate, tosylate or nosylate. Common leaving groups for S_NAr are F, $NO_2$and NMe^{3+}, with fluorination taking place due to activation by electron withdrawing groups at the ortho or para position, such as CF_3, NO_2, carbonylorcyanide. Typical reaction conditions for ^{18}F-fluorinationinvolve polar aprotic solvents (acetonitrile, DMF, DMSO) with temperatures of 80–180°C and reaction times of 5–30 min. For nucleophilic fluorinations, the [^{18}F]-fluoride from the $^{18}O(p,n)^{18}F$ nuclear reaction in the cyclotron is received in the hot-cell and trapped in an anion-exchange column and usually eluted with $K_2CO_3$and is present as KF. A phase transfer catalyst such as Kryptofix 2.2.2 is required to hold the K^+ and shield its positive charge from the F^-, which otherwise would reduce the latter's nucleophilicity. Alternately, tetrabutyl ammonium carbonate is also used in place of $K_2CO_3$and Kryptofix(2.2.2. Basicity of the reaction mixture can play a role in possible competitive elimination reactions. Examples of such production methods are FDG, FLT,FAZA, FMISO and fluorocholine [66,67]. The use of protic solvents such as tertiary alcohols for the routine production of [^{18}F]- tracers vianucleophilic reactions have also been reported [68].

Electrophilic fluorination, requires elemental [^{18}F]F_2, which is produced by the deuteron irradiation of natural neon $^{20}Ne(d,\alpha)^{18}F$ or proton irradiation of enriched oxygen-18gas $^{18}O(p,n)^{18}F$.

The latter offers the opportunity to produce larger quantities of $^{18}F_2$, however, at the expense of being more complicated. Some carrier F_2 is necessary to prevent $^{18}F_2$ losses and this results in very low specific activity of the labelled product, more so with the former method. The reaction of [^{18}F]F_2 with precursors is accomplished by addition to double bonds or to aromatic rings. This reaction can be carried out either with [^{18}F]F_2 itself or by conversion to [^{18}F]AcOF or N-[^{18}F]F compounds in order to decrease reactivity of the fluorinating reagents and increasethe selectivity of the reaction. Selectivity can further be increased by using the fluoro-demetallation reaction, in which preferentially a trialkyltin group is substituted by electrophilic ^{18}F [69-71]. A classic example of this production method is for producing 6-[^{18}F]fluoro-L-dopa (FDOPA).

Novel approaches to fluorination have been reported recently: Lee et al. [16] has shown a very wherein an palladium complex can trap high specific activity nucleophilic [^{18}F]F^- and by intramolecular electron shifts, the ^{18}F behaves like electrophilic ^{18}F-fluorine with aromatic systems. The future of this novel method requires further studies. Another is by McBride et al, [72] is the 18F-labelling of peptides by NOTA chelation of an AlF^{2+} complex. Usually used for complexation of radiometals, the NOTA-chelatorcan also complex AlF^{2+}. Since azeotropic drying of [^{18}F]-fluoride is not required, the chemistry is quick since the AlF^{2+} complex can be directly added to the NOTA-conjugated peptide. Another strategy is through synthesis of a [^{18}F]-synthon (prosthetic group)followed by coupling to the precursor (at least 2 steps). This is far more difficult than the previous methods, as it requires synthesis of the [^{18}F]-synthon. That could involve several steps and often purification of this synthon before use in the subsequent coupling to precursor. Purification of the intermediates can be done using HPLC, SPE, or distillation, but makes the

procedure very difficult to automate reliably. [^{18}F]fluorocholine, [^{18}F]fluoroRGD, [^{18}F]fluoroannexin, [^{18}F]fluorotropane, several labeled peptides and antibody fragments have been reported to be prepared using synthons.

First Generation [^{18}F]-radiopharmaceuticals other than FDG

Though it is not specific for any one disease, FDG's ability to show abnormalities in energy metabolism in a wide range of diseases has made it very useful when interpreted with other relevant information. Radiochemists and nuclear medicine physicians looking for specific PET-tracers have prepared several tens of [^{18}F]-radiopharmaceuticals (other than FDG), that have been described and evaluated as diagnostic tracers in oncology, neurology, cardiology and other illnesses. Pre-clinical studies in laboratory animals and limited human volunteer and patient studies have been carried out. The availability of small-animal PET-CT machines have made possible studying bio-distribution, pharmaco-kinetics in real time, thereby making [^{18}F]-radiopharmaceutical evaluation and pre-clinical studies more reliable.

There are several publications [10-14] reviewing the potential of [^{18}F]-radiopharmaceuticals, other than FDG and are unanimous about the need to propagate their use in nuclear medicine. Among the reviews, a comprehensive one was published by a group of senior PET-radiochemists, invited by the International Atomic Energy Agency for a Consultants' Meeting on the subject and make their recommendations [14]. The [^{18}F]-RPs that have been clinically used at several centres and are likely to be used routinely are the ones with known pharmacology and accepted clinical application, lack of toxicity, availability of precursors and ease of automated synthesis, which include [^{18}F]fluoride, (FLT), (FMISO, [^{18}F]Fluoroazomycinarabinoside (FAZA), [^{18}F]Fluoroestradiol (FES), [^{18}F]fluoroethyl)-L-tyrosine (FET), [^{18}F]fluoromethylcholine (FCh). There are several more [^{18}F]-RPs where precursors are not readily available and/or ease of automated synthesis is not there, and so it would be some time before these are in widespread clinical use. Hence, [^{18}F]-Sodium Fluoride (NaF), FLT, FMISO, FAZA, FES, FET, FCholine and FDOPA may be considered first generation non-FDG PET tracers that have been studied by numerous workers and are also part of currently on-going multi-centre phase-II and phase-III clinical trials coordinated by the National Cancer Institute, Society of Nuclear Medicine Clinical Trials Network, and the American College of Radiology Imaging Network. Similar approvals are also there in countries in Europe under the European Medicine Agency (EMA).

All new PET radiopharmaceuticals, must be manufactured under current good manufacturing practices as required by the US-FDA, the EMA or the local regulatory authority before used or distributed to nuclear medicine centres for clinical evaluation (phases I, II, and III) and submission of new drug application to the appropriate approving authority.

[^{18}F]NaF

NaF for bone-imaging was first introduced in 1962 and was the first US-FDA approved radiopharmaceutical. Blauet al.1962, used it for skeletal imaging with early gamma cameras [15] since NaF has a biodistribution similar to [^{99m}Tc]-polyphosphonates, but with less protein binding. It is rapidly cleared since like the latter there is no serum binding and <10% is in circulation after 1h, hence, giving low background scans. Fluoride is firmly attached at sites of osteoblastic activity and remains in the bone and gives twice the target-to-background ratio of [^{99m}Tc] MDP and accumulation is higher at sites of new bone formation due to the greater availability of binding sites and regional hyperemia.The fluoride ion is exchanged for a hydroxyl group on the hydroxyapatite crystal in the bone matrix to form fluorapatite and, hence, is very sensitive for the detection of bothlytic and sclerotic bone lesions. [16,17] (Fig. 6). Co-registration with CT as in PET-CT increases specificity and has a resolutionof 4–6 mm versus 10–15 mm for [^{99m}Tc]MDP imaging. NaF PET-CT has been shown to be moresensitive for detecting skeletal metastases than planaror [^{99m}Tc]MDPSPECTbone imaging. Benignbone lesions like fractures, Paget disease, enchondroma, and osteoid osteomas also demonstrateincreased NaFuptake [18]. NaF is easily produced from the irradiated [^{18}O]water by trapping the [^{18}F]F$^-$ on an anion column as in the initial

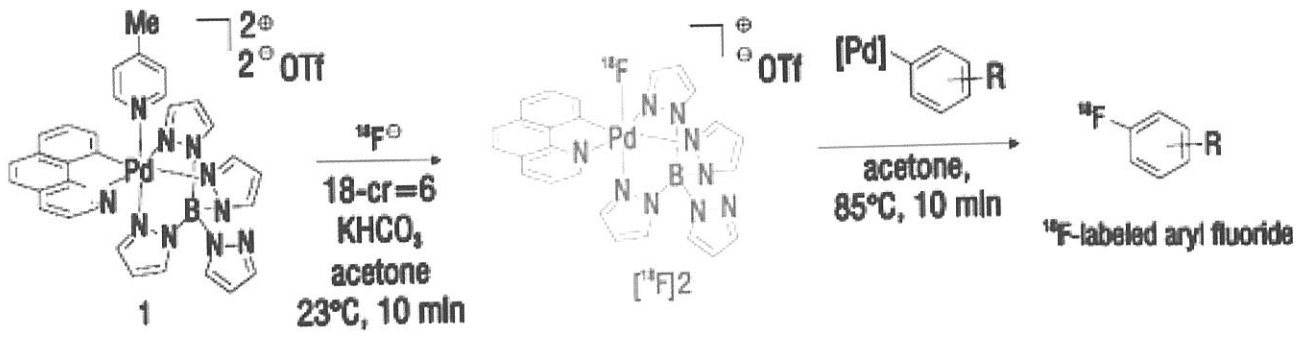


Fig. 5 Use of palladium complex to trap high specific activity nucleophilic [^{18}F]-fluoride for electrophilic fluorination From Ref [16].

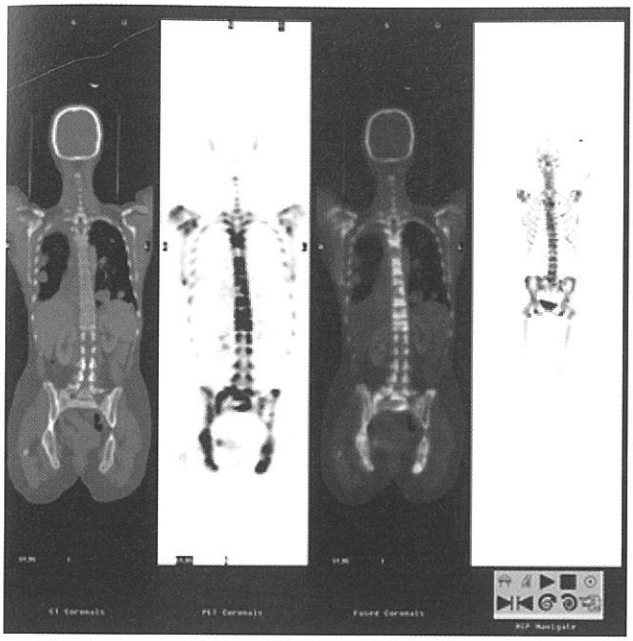


Fig. 6 *^{18}F-Sodium Fluoride (NaF) PET scan for evaluating skeletal metastasis. NaF PET/CT is an extremely sensitive method for detecting bony metastases in patients with known malignancy. NaF normally accumulates in the bones and areas of active soft tissue calcification with renal excretion into the bladder*

step of FDG synthesis, and eluting NaF with sterile isotonic saline and dispensing into sterile vials [19].

[^{18}F]FLT

FLT as PET tracer has been evaluated at many centres and has a proven utility for studying cell proliferation in tumors [20,21].The comparative biochemistry of thymidine and its analogue FLT and are similar to that of glucose and its analogue FDG. Thymidine is completely metabolized in vivo. FLT and thymidine are both phosphorylated by a specific kinase, however, unlike thymidine, FLT is not incorporated into DNA [21] and is stable in vivo and since it acts as a false substrate for thymidine kinase, its metabolism is limited and is retained for sufficiently long period of time in the tumour.Increased mitotic rate, cell multiplication and lack of differentiation are characteristics of the tumors and correlate with FLT uptake in these cells.FLT uptake can help differentiate between benign and malignant tissues and assess tumor aggressiveness and early prediction of treatment response. FLT uptake does not increase with infection or inflammation like FDG.In brain tumors, FLT provides highly reliable prognostic information, by noninvasively grading their biological behavior judged by the activity of the enzyme thymidine kinase closely associated with the tumor mitotic activity, shown to be superior to FDG imaging [22]. Similar results have been shown in patients with sarcoma or osteosarcoma [23]. Figure 7 shows normal FLT scan with no brain uptake. The radiosynthesis of FLT is by Sn2 fluorination and several

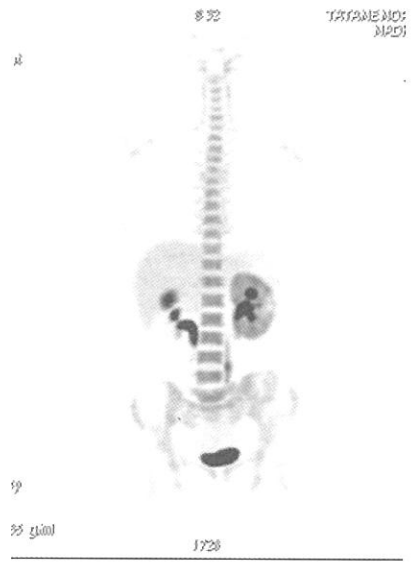
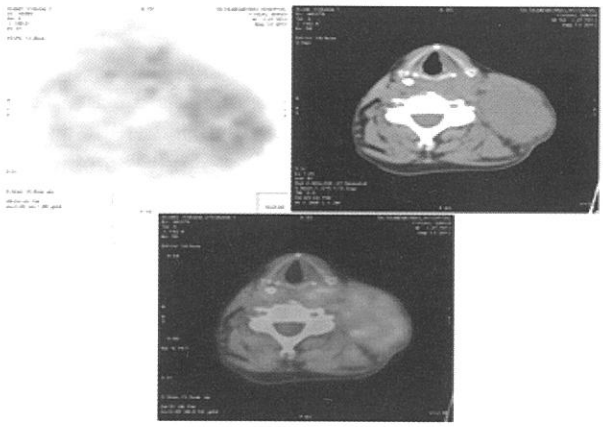


Fig. 7 *^{18}F-FLTused for assessing cell-proliferation in a tumour. Fast growing tumours will pick up more FLT. FLT normally passes accumulates in the liver and bone marrow and is excreted through the bladder.*



FMISO PET of tumour in neck: Top-left-PET image Top-right-CT image Bottom-PET-CT fusion image

Fig. 8 *^{18}F-FMISO) is used for imaging hypoxic areas in a tumour. FMISO PET is extremely useful in head and neck cancer patients undergoing radiotherapy. FMISO normally accumulates in the liver with renal excretion into the bladder.*

methods using different precursors have been described. The 3-N-Boc-5'-O-dimethoxytrityl-3'-O-nosyl thymidine precursor is reported to give good yields (~20%) but requires semi-HPLC purification [24]. In our experience the use of anhydro-precursor or benzoyl anhydro-precursor is practical to use, albeit the yields are about 5% since the purification can be achieved by solid-phase extraction using standard Sep-Pak® cartridges [25].

[^{18}F]FMISO and [^{18}F]FAZA

FMISO was developed as a PET-tracer for imaging hypoxia in oncology and is clinically gaining importance in

planning radiotherapy since hypoxic areas within a tumour are radiation resistant. Hypoxia occurs in rapidly growing tumors as their need for oxygen exceeds the supply available from blood and tissue diffusion [26]. The anoxic center of tumors typically undergoes cell death and necrosis In the borderline zones of the tumor, hypoxia inhibits cell growth and division but often leads to adaptive changes as the tumor cells struggle to survive in the harsh environment and evolve into radiation resistant cells. As shown in Fig. 8, PET/CT with FMISO is able to assess the evolving hypoxia level in tumors during radiotherapy [27]. Its limitation is high background and significant liver uptake requiring delayed imaging (of up to 4 h post injection).

FMISO can be easily made (like FDG) with good yield. The most widely used precursor is 1-(2-nitro-1 -imida-zolyl)2-O-tetrahydropyranyl-3-O-toluenesulphonyl -propane-diol (commonly known as NITTP), and following SN2 substitution, hydrolysis of leaving groups is carried out and purification is on a solid phase extraction column [28,29].

The limitations seen with FMISO lead to the development of a new hypoxic cell marker FAZA with improved properties. FAZA is also easily prepared by SN2 nucleophilic substitution [^{18}F]F$^-$ to the precursor 1-(2,3-di-O-acetyl-5-O-tosyl-α-D-arabinofuranosyl)-2-nitr oimidazolefollowed by hydrolysis of the protective acetyl groups and purification using Sep-Pak and HPLC [30]. A method using a commercially available combination column, like that used for FDG, is also described [31].

[^{18}F]FET

PET-tracers of amino acids or its analogues are of considerable interest in brain imaging mainly because of their high uptake in biologically active tumor tissue but low uptake in normal brain tissue [32]. [^{18}F]-FDG is expectedly unreliable at predicting the nature of brain lesions because of high uptake in normal brain and, in addition, the unspecific uptake in inflammation and in relatively benign tumors [33,34]. The diagnosis and staging of brain tumours, particularly, gliomas is very important due to their high morbidity and mortality. Presently, clinicians rely largely on MRI imaging, which provides very satisfactory morphologic assessment of the tumour but very little information on its metabolic activity.

l-[methyl-^{11}C]methionine would be the ideal choice but the 20 min T1/2 of ^{11}C makes it less available to PET-centres for imaging [33]. Further, it is rapidly incorporated into proteins and metabolized and also taken up by inflammatory cells. FET is an artificial amino acid taken up into upregulatedtumoral cells, and is found to correlate very well with ^{11}C-methionine uptake, but is not incorporated into proteins, and, hence, remains trapped in the tumour cells [33]. The lower uptake of FET by inflammatory cells helps to differentiate tumor from treatment-induced necrosis, and its 110 min T1/2 makes it readily available for use [32, 35, 36].

FET most useful fluoroamino acid can be prepared by a direct substitution, one-pot synthesis with high batch yields for broader clinical use [37]. The procedure involves the fluorination of O-(2-tosyloxyethyl)-N-trityl-L-tyrosine tertiary butylester to get enantiomerically pure O-(2-[18F] fluoroethyl)-N-trityl-L-tyrosine tert-butyl ester which is deprotected under non-aqueous conditions using a mixture of trifluoroacetic acid in 1,2-dichloroethane and the crude [^{18}F]FET is adsorbed on a solid phase extraction column. A final purification by reverse-phase HPLC on a C18 column is done to get clinically useful product. FET is made in RMC for research applications and efforts are on for supply after RPC approvals. Hence no patient study scans are available.

[^{18}F]FCh

The uptake and phosphorylation of choline forming choline phosphate which is used in the biosynthesis of cell membrane phospholipids are increased in tumor cells. In fact the enhanced rate of proliferation of tumor cells necessitates an increased synthesis of this phospholipid membrane inducing a higher uptake of choline. Also a high level of choline in prostate cancer cells has been proved by magnetic resonance spectroscopy. 11C-choline has been confirmed to be particularly effective as PET tracer for the imaging of prostate, brain, lungs, esophagus, rectum and urinary bladder cancers for which ^{18}FDG is less useful [38]. As with all ^{11}C-compounds, [^{11}C]Choline has serious limitations due to it half-life and hence, labeling of choline with 18F, longer half-life ($T_{1/2}$ = 110 min) will facilitate its distribution to PET centers that do not have cyclotron.

PET studies on patients with prostate cancer and with breast cancer and brain tumor support further studies to evaluate the usefulness of FCH as an oncologic probe [39]. Recent studies have shown that FCH imaging plays a more relevant role in detection of prostate cancer relapse [40].

An automated method for synthesis of Fchwas achieved by the reaction of [^{18}F]fluoromethyltriflate with dimethylethanolamine on a Sep-Pak column. The total timerequired for obtaining the finished radiotracer was 30 min with radiochemical yield around 80% and radiochemical purity and chemical purity of >98% [41]. FChT is being made in RMC for research applications and efforts are on for supply after RPC approvals. Hence no patient study scans are available.

[^{18}F]FES

The staging of breast cancers and their metastasis into whether they are estrogen receptor positive or not, is very important since it decides their management. PET scan with FES helps in determining this hormonal status. [42]. A onepot synthesis of [^{18}F]FES is reported by fluorinating theprecursor, 3-O-Methoxymethyl-16, 17-O-sulphuryl-16-epiestriol [43].

[^{18}F]FDOPA

FDOPA, a radiolabelled analogue of L-DOPA, was first introduced in 1980s as a radiotracer for the assessment the central dopaminergic function of presynaptic neurons

[44,45] On further developments of PET technique, the FDOPA study has become highly relevant research and clinical tool allowing evaluate the changes of dopaminergic function in progress of the Parkinson's disease and in the course of various other central nervous system and movement disorders [46]. In 2000, other clinical applications for FDOPA have arisen in the field of oncology. The radiotracer has shown a great potential for accurate detecting primary and recurrent high- and low- grade cerebral gliomas effecting the patient management and treatment [47,48]. In addition FDOPA has been extensively used in PET/CT investigations to image a variety of neuroendocrine tumours (NETs) - gastroenteropancreatic NETs, pheochromocytomas and paragangliomas, medullary thyroid carcinoma (MTC) [49,50]. More recently FDOPA has proved to be useful radiotracer for evaluation of primary hyperinsulinemia in pediatric patients and adults [50]. As a result, in the recent years the number of requests for clinical FDOPA PET studies has been dramatically increasing, despite of relatively high cost of single patient dose and study itself.

However in a recent study, ^{68}Ga-DOTA-TATE, a somatostatin receptor-targeting peptide showed superior result as compared to FDOPA for staging of patients with NET [51]. In general FDOPA tends to be less sensitive in identifying non-secreting neuroendocrine tumors. Together with receptor imaging, FDOPA could be useful for to assist the management of NETs. The report of a carcinoid crisis induced by [^{18}F]FDOPA, however, points to the necessity of a practical n.c.a. labeling method for this tracer [52]. Electrophilic methods are generally applied to produce FDOPA [53], however, with the disadvantages of relatively low specific activity and batch yields and thus limited availability. Although nucleophilic procedures were established for the routine production of FDOPA, they are, however, difficult to implement because they involve multistep synthesis. Electrophilic radiofluorination by destannylation of an FDOPA precursor reaction appears to be the best option for labeling with satisfactory yields [54]. In the automated procedure, 4,5-di-[(1,1-dimethylethoxycarbonyl)oxy]-N-formyl-2-trimethylstannyl-L-phenylalanine ethyl ester is fluorinated with F2, the intermediate is hydrolysed and the final product is purified by HPLC to get FDOPA in high yields.

Second Generation [^{18}F]-radiopharmaceuticals other than FDG

These are [^{18}F]-labeled compounds identified to be for a very specific clinical use and there is much interest in them now. The numbers of centres producing and evaluating them are much smaller than the first generation tracers listed above. These appear to be more industry driven and are covered by patents or proprietary licensing.

^{18}F-Fluoro-5-dihydrotestosterone(FDHT)

FDHT is a fluorinatedanalog of dihydrotestosterone (DHT), the native androgen receptor-binding ligand.FDHT is reported to target the androgen receptors (ARs), which are the principal components along the pathway to prostate cancer [55]. FDHT is currently under clinical trials. The synthesis of FDHT by Liu et al [56,57] reported way back in 1992 is still the standard method of preparation, with only minor modifications. An automated protocol for ^{18}F-FDHT with a plastic cassette-type ^{18}F-FDG synthesizer was developed by Mori etal., [58].

^{18}F-Galacto-arginine-glycine Aspartic Acid (^{18}F-RGD) (RGD)

RGD was the first ^{18}F-labeled RGD-containing glycopeptidedescribedfor noninvasive imaging of ávâ3integrin expressionwith PET; the design, synthesis, and radiolabeling of ^{18}FGalacto-RGD was reported by Haubner et al., [59, 60]. The receptor αvβ3 is an integrin implicated in metastasis, angiogenesis,and proliferation; faint expression is observed in restingendothelial cells and normal organs. The biodistribution of ^{18}F-Galacto-RGD shows tracer uptake in many human cancers, including musculoskeletal, melanoma, colon, breast, head or neck, sarcoma, and osseous metastases [61].

Haubner et.al., designed first-generation radioiodinated cyclic RGD peptidesto image αvβ3 integrin expression, showing receptorspecifictumor accumulation in various mouse models. Limitations of the tracers, however, included high liver and intestinal retention. Therefore, pharmacokinetic considerations led the authors to investigate conjugating the RGDmonomercyclo (-Arg-Gly-Asp-D-Tyr-Lys-) with a galactosugar amino acid in an approach known for improving peptidepharmacologic properties [59].

Anti-^{18}F-Fluoro-cyclobutyl-1-carboxylic Acid (FACBC)

^{18}F-FACBC was used by Shoupet.al., as a brain tumor imaging agent alternative to L-methyl-^{11}C-methionine because of longer half-life of ^{18}F (109.8 minutes). FACBC, as well as othernon-naturally occurring amino acids, is metabolically stable(versus naturally occurring amino acids) and capable of radiolabel by longer-lived isotopes [62]. Amino acid measurementin protein synthesis might be able to be used as a sensitiveand specific target for malignancy.The synthetic L-leucine anti-1-amino-3-^{18}F-fluoro-cyclobutyl-1-carboxylic acid (anti-^{18}F-FACBC) is an analog of 1-aminocyclobutane-1-^{11}C-carboxylic acid (^{11}C-ACBC) [63]. Thesynthesis of anti-^{18}F-FACBC was first reported by Shoupet.al., [64,65] in an 11-step formulation (from epichlorohydrin) ofthe triflate precursor syn-1-(tert-butoxycarbonyl)amino-3-[[(trifluoromethyl) sulfonyl] oxy]-cyclobutane-1-carboxylicacid methyl ester. Radiosynthesis and deprotectionby acid hydrolysis were performed with a self-developed remotemanual system. The synthetic route was performed in 60 minutes, with a RCY of 12% (end of bombardment) afterpurification.

^{18}F-radiopharmaceuticals for Alzheimer's Disease

This requires a special mention as the early diagnosis of This disease is an urgent need.The U.S. Food and Drug

Administration (FDA) approved a third beta-amyloid plaque positron emission tomography (PET) imaging radiotracer to identify Alzheimer's disease. The FDA's approval of Piramal Imaging's Neuraceq ([^{18}F]florbetaben injection) came withinfour weeks after receiving marketing authorization in Europe. It is the third radiotracer to gain FDA clearance for beta amyloid plaque imaging. In October 2013, the FDA-cleared Vizamyl([^{18}F]flutemetamol injection) developed for GE Healthcare by Medi-Physics Inc. The first agent to gain approval was Amyvid (([^{18}F] florbetapir Injection) in April 2012. Amyvid was developed by Eli Lilly & Co. and Avid Radiopharmaceuticals Inc. Prior to these agents, the only clear diagnosis of Alzheimer's was by post-mortem autopsy.

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Bibliography

[1] Sweet WH. The uses of nuclear disintegration in the diagnosis and treatment of brain tumor. New Engl J Med 1951; 245:875-8.

[2] Brownell, GL and Sweet, WH. Localization of Brain Tumors with Positron Emitters. Nucleonics11: 40-45, 1953

[3] Sweet WH, Brownell GL. (1955) Localization of intracranial lesions by scanning with positron-emitting arsenic. J Am Med Assoc 157:1183-8.

[4] Miller JC Radiopharmaceutical Development at the Massachusetts General Hospitalhttp://www2.massgeneral.org/imagingintranet/pdf/news/miller_janet_4_17_09.pdf

[5] Warburg O On the origin of cancer cells. Science1956; 123:309–314

[6] Laszlo J, Humphreys SR, GoldinA Effects of glucose analogues (2-deoxy-D-glucose, 2-deoxy-D-galactose) on experimental tumors. J Natl Cancer Inst1960; 24:267–281

[7] Ido T, Wan CN, Casella JS et al Labeled 2-deoxy-Dglucose analogs: 18F labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and 14C–2-deoxy-2-fluoro-Dglucose.J Label Compd Radiopharmacol 1978; 14:175–183

[8] Levy, S, Elmaleh, DR and Livni, E. A new method using anhydrous [18F] fluoride to radiolabel 2-[18F] fluoro-2-deoxy-D-glucose. J Nucl Med 1982; 23: 918-22

[9] Hamacher K, Coenen HH, Stöcklin G. Efficient stereospecific synthesis of no-carrier-added 2-[^{18}F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 1986; 27:235–8

[10] Vallabhasojula S. ^{18}F-Labelled positron emission tomographic radiopharmaceuticals in oncology: an overview of radiochemistry and mechanism of tumor localization. Semin Nucl Med 2007; 37: 400–19.

[11] Mercer JR. Molecular imaging agents for clinical positron emission tomography in oncology other than fluorodeoxyglucose (FDG): applications, limitations and potential. J Pharm Pharmaceut Sci 2007; 10:180–202.

[12] Vallabhajosula S, Solnes L, Vallabhajosula B: A broad overview of PET radiopharmaceuticals and clinical applications: What is new? Semin Nucl Med 41:246-264, 2011.

[13] Rice SL, Roney CA, Daumar P, et al: The next generation of PET radiopharmaceuticals in oncology. Semin Nucl Med 41:265-282, 2011.

[14] Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr, Zaknun JJ; Fluorine-18 radiopharmaceuticals beyond [^{18}F]FDG for use in oncology and neurosciences. Nucl. Med. Biol. 2010 Oct; 37(7):727-40.

[15] Blau M, Nagler W, Bender MA. A new isotope for bone scanning. J Nucl Med 1962; 3:332–334.

[16] Lee E, Kamlet AS, Powers DC, Neumann CN, Boursalian GB, Furuya T, Choi DC, Hooker JM, Ritter TA:Fluoride-derived electrophilic late-stage fluorination reagent for PET imaging. Science 2011; 334: 639–642.

[17] Blake GM, Park-Holohan SJ, Cook GJ et al. Quantitative studies of bone with the use of 18F-fluoride and 99mTcmethylene diphosphonate. Semin Nucl Med 2001; 31:28–49.

[18] Even-Sapir E, Metser U, Mishani E et al. The detection of bone metastases in patient with high-risk prostate cancer: ^{99m}Tc-MDP planar bone scintigraphy, single- and -field-of view SPECT, 18F–fluoride PET, and 18F–fluoride PET/CT. J Nucl Med 2006 47:287–297

[19] S.K. Nandy, M.G.R. Rajan and P.S. Soni: Production Of Sterile [F-18] Naf For Skeletal PET Imaging BARC Newsletter 2007, Issue no. 281, 16-23

[20] Barthel, H., Perumal, M., Latigo, J., He, Q., Bardy, F., Luthara, S. K., Pierec, P. M. The uptake of 3'-deoxy-3'-[18F]fluorothymidine into L5178Y tumors in vivo is dependent on thymidine kinase 1 protein levels. Eur. J. Nucl. Med. Mol. Imaging 2005; 32(3), 257-263.

[21] Been, L. B., Suurmeijer, A. J. H., Cobben, D. C. P., Jager, P. L., Hoekstra, H. J., Elsinga, P. H., [^{18}F]FLT-PET in oncology: current status and opportunities. Eur. J. Nucl. Med. Mol. Imaging, 2004; 31 (12), 1659 – 1672.

[22] Chen W, Cloughesy T, Kamdar N, Satyamurthy N, Bergsneider M, Liau L, et al. Imaging proliferation in brain tumors with ^{18}F-FLTPET: comparison with ^{18}F-FDG. J Nucl Med 2005;46:945

[23] Cobben DCP, Elsinga PH, Suurmeijer AJH, Vaalburg W, Maas B, Jager PL, et al. Detection and grading of soft tissue sarcomas of the extremities with 1208 18F-3-fluoro-3-deoxy-L-thymidine. Clin Cancer Res 2004; 10:1685–90.

[24] Martina SJ, Eisenbartha JA, Wagner-Utermanna U, Mierb W, Henzeb M, Pritzkowc H, et al. A new precursor for the radiosynthesis of [18F]FLT. Nucl Med Biol 2002;29:263–73.

[25] Nandy, S. K., Rajan, M. G. R., Korde, A., Chaudhari PR. Rapid synthesis of [^{18}F]fluoro-L-thymidine with simplified purification using a combination column J Labelled Comp. Radiopharm, 2007; 50(S1), S121.

[26] Vaupel P, Schlenger K, Hoeckel M (1992) Blood flow and tissue oxygenation of human tumors: an update. AdvExp Med Biol 317:139–151

[27] Lee ST, Scott AM Hypoxia positron emission tomography imaging with 18F-fluoro-misonidazole. SeminNucl Med 2007 37:451–461

[28] Tang G, Wang M, Tang X, Gan M, Luo L. Fully automated one-pot synthesis of [^{18}F]fluoro-misonidazole. Nucl Med Biol 2005;32:553–8.

[29] S. K. Nandy, M. G. R. Rajan. Fully automated radiosynthesis of [^{18}F Fluoromisonidazole with single neutral alumina column purification: Optimization of reaction parameters. J Radioanal Nucl Chem DOI 10.1007/s10967-010-0644-z

[30] Reischl G, Ehrlichmann W, Bieg C, Solbach C, Kumar P, Wiebe LI, et al. Preparation of the hypoxia imaging PET tracer [^{18}F]FAZA: reaction parameters and automation. Appl RadiatIsot 2005;6 2: 897–901.

[31] Nandy, S.K., Rajan, M.G., Simple, column purification technique for the fully automated radiosynthesis of [^{18}F]fluoroazomycinarabinoside ([18F]FAZA), Appl. Radiat. Isot. 2010; 68: 1944-9.

[32] Jager PL, Vaalburg W, Pruim J, de Vries EG, Langen KJ, Piers DA. Radiolabeled amino acids: basic aspects and clinical applications in oncology. J Nucl Med. 2001; 42(3): 432 –445.

[33] Weber WA, Wester HJ, Grosu AL, Herz M, Dzewas B, Feldmann HJ, et al. O-(2-[^{18}F]Fluoroethyl)-L-tyrosine and L-[methyl-^{11}C]methionine uptake in brain tumours: initial results of a comparative study. Eur J Nucl Med 2000;27:542–9.

[34] Spaeth N, Wyss MT, Weber B, et al. Uptake of ^{18}F-fluorocholine, ^{18}F-fluoroethyl-L-tyrosine, and ^{18}F-FDG in acute cerebral radiation injury in the rat: implications for separation of radiation necrosis from tumor recurrence. J Nucl Med. 2004; 45:1931–1938.

[35] Heiss P, Mayer S, Herz M, Wester HJ, Schwaiger M, Senekowitsch-Schmidtke R. Investigation of transport mechanism and uptake kinetics of O-(2-[^{18}F]fluoroethyl)-L-tyrosine in vitro and in vivo. J Nucl Med. 1999; 40: 1367–1373.

[36] Wester HJ, Herz M, Weber W, et al. Synthesis and radiopharmacology of O-(2-[^{18}F]fluoroethyl)-L-tyrosine for tumor imaging. J Nucl Med. 1999; 40:205–212.

[37] Hamacher K, Coenen HH. Efficient routine production of ^{18}F-1218 labelled amino acid O-(2-[^{18}F]fluoroethyl)-L-tyrosine. ApplRadiatIsot 2002; 57:853–6.

[38] Hara T., 11C-Choline and2-deoxy-2-[^{18}F]fluoro-D-glucose in tumor imaging with positron emission tomography. Mol. Imaging Biol. (2002). 4, 267–273,

[39] DeGrado T.R., Baldwin, S.W., Wang, S., Orr, M.D., Liao R.P., Friedman, H.S., Reiman R., Price D.T., Coleman R.E., .Synthesis and evaluation of ^{18}F-labeled choline analogs as oncologic PET tracers.J.Nucl.Med. 200142,1805–1814,

[40] Beheshti Mohsen, Imamovic Larisa, Broinger Gabriele, Vali Reza, Waldenberger Peter, Stoiber Franz, Nader Michael, Gruy Bernhard, Janetschek Guenter, Langsteger Werner; 18F Choline PET/CT in the Preoperative Staging of Prostate Cancer in Patients with Intermediate or High Risk of Extracapsular Disease: A Prospective Study of 130 Patients, Radiology: 2010;254: 3-March

[41] Zuhayra M., Alfteimi A., Papp L., Lützen U., Lützen A., Von Forstner C., Meller B., Henze E.; Simplified fast and high yielding automated synthesis of [^{18}F]fluoroethylcholine for prostate cancer imaging Bioorganic & Medicinal Chemistry 2008;16: 9121–9126.

[42] Kumar P, Mercer J, Doerkson C, Tonkin K, McEwan AJ. Clinical production, stability studies and PET imaging with 16-alpha-[^{18}F]fluoroestradiol ([^{18}F]FES) in ER positive breast cancer patients. J Pharm Pharmaceut Sci 2007;10:256s–65s.

[43] Lim JL, Zheng L, Berridge MS, Tewson TJ. The use of 3-methoxymethyl-16 beta, 17 beta-epiestriol-O-cyclic sulfone as the precursor in the synthesis of F-18 16 alpha-fluoroestradiol. Nucl Med Biol 1996; 23:911–5.

[44] Garnett, E.S., Firnau, G., Nahmias, C., Dopamine visualized in the basal ganglia of living man, Nature 1983; 305: 137-138.

[45] Barrio, J.R., Huang, S.C., Phelps, M.E., Biological imaging and the molecular basis of dopaminergic diseases, Biochem. Pharmacol. 1997; 54: 341-348.

[46] Fischman, A.J., Role of [^{18}F]-dopa-PET imaging in assessing movement disorders, Radiol. Clin. North. Am. 2005; 43: 93-106.

[47] Chen, W., et al., 18F-FDOPA PET Imaging of Brain Tumors: Comparison Study with ^{18}F-FDG PET and Evaluation of Diagnostic Accuracy, J. Nucl. Med. 2006;47: 904-911.

[48] Waltern, F., et al., Impact of 3,4-Dihydroxy-6-^{18}F-Fluoro-L-Phenylalanine PET/CT on Managing Patients with Brain Tumors: The Referring Physician's Perspective, J. Nucl. Med. 2012; 53: 393-398.

[49] Hoegerle, S., et al., ^{18}F-DOPA positron emission tomography for tumor detection in patients with medullary thyroid carcinoma and elevated calcitonin levels, Eur. J. Nucl. Med. 2001:28: 64-71.

[50] Minn, H., Kauhanen, S., Seppanen, M., Nuutila, P., ^{18}F-FDOPA: A Multiple-Target Molecule, J. Nucl. Med. 50 (2009) 1915-1918.

[51] Haug A, Auernhammer CJ, Wängler B, Tiling R, Schmidt G, Göke B, et al. In traindividual comparison of 68Ga-DOTA-TATE and 18F-DOPA PET in patients with well-differentiated metastatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2009;36:765–70.

[52] Koopmans KP, Brouwers AH, De Hooge MN, Van der Horst-Schrivers AN, Kema IP, Wolffenbuttel BH. Carcinoid crisis afterinjection of 6-^{18}F-fluorodihydroxyphenylalanine in a patient withmetastatic carcinoid. J Nucl Med 2005; 46:1240–3.

[53] Adam MJ, Jivan S. Synthesis and purification of L-6-[^{18}F]fluorodopa.ApplRadiatIsot 1988;39:1203–10.

[54] Namavari M, Bishop A, Satyamurthy N, Bida G, Barrio JR. Regioselectiveradiofluoro-destannylation with [^{18}F]F2 and [^{18}F]CH_3COOF: a high yield synthesis of 6-[^{18}F]fluoro-L-dopa. ApplRadIsot 1992; 43:989–96.

[55] Choe YS, Lidstrom PJ, Chi DY, et al: Synthesis of 11 beta-[18F]fluoro-5 alpha-dihydrotestosterone and 11 beta-[^{18}F]fluoro-19-nor-5 alpha-dihydro-testosterone: preparation via halofluorination-reduction,receptor binding, and tissue distribution. J Med Chem 1995;38:816-825.

[56] Liu A, Dence CS, Welch MJ, et al: Fluorine-18-labeled androgens:radiochemical synthesis and tissue distribution studies on six fluorine-substituted androgens, potential imaging agents for prostaticcancer. J Nucl Med 1992;33:724-734.

[57] Liu A, Carlson KE, Katzenellenbogen JA: Synthesis of high affinityfluorine-substituted ligands for the androgen receptor: potentialagents for imaging prostatic cancer by positron emission tomography.J Med Chem 1992;35:2113-2129.

[58] Mori T, Kiyono Y, Asai T, et al: Automated synthesis of 16{beta}-[18F]fluoro-5{alpha}-dihydrotestosterone using a plastic cassettetypeFDG synthesizer. J Nucl Med Meeting Abstracts 2010; 51:1525.

[59] Haubner R, Wester HJ, Weber WA, et al: Noninvasive imaging ofalpha(v)beta3 integrin expression using 18F-labeled RGD-containingglycopeptide and positron emission tomography. Cancer Res 2001;61:1781-1785.

[60] Haubner R, Kuhnast B, Mang C, et al: [F-18]Galacto-RGD: synthesis,radiolabeling, metabolic stability, and radiation dose estimates. BioconjugChem 2004; 15:61-69.

[61] Beer AJ, Haubner R, Goebel M, et al: Biodistribution and pharmacokineticsof the alphavbeta3-selective tracer 18F-galacto-RGD in cancerpatients. J Nucl Med 2005; 46:1333-1341.

[62] Yu W, Williams L, Camp VM, et al: Synthesis and biological evaluation of anti-1-amino-2-[^{18}F]fluoro-cyclobutyl-1-carboxylic acid (anti-2-[^{18}F]FACBC) in rat 9L gliosarcoma. Bioorg Med Chem Lett 2010;20:2140-2143

[63] Washburn LC, Sun TT, Byrd B, et al: 1-aminocyclobutane[^{11}C]-carboxylic acid, a potential tumor-seeking agent. J Nucl Med 1979; 20:1055-1061

[64] Shoup TM, Goodman MM: Synthesis of [F-18]-1-amino-3-fluorocyclobutane-1-carboxylic acid (FACBC): a PET tracer for tumor delineation.J Labelled Comp Radiopharmaceuticals 1999; 42:215-225,

[65] Shoup TM, Olson J, Hoffman JM, et al: Synthesis and evaluation of [F-18]1-amino-3-fluorocyclobutane-1-carboxylic acid to image braintumors. J Nucl Med 1999; 40:331-338.

[66] Kilbourn MR. Fluorine-18 Labeling of Radiopharmaceuticals. Washington, DC: National Academy Press; 1990 [149 pp, NAS-NS-3203].

[67] Cai L, Lu S, Pike VW. Chemistry with [^{18}F]fluoride ion. Eur J Org Chem 2008:2853–73.

[68] Kim DW, Ahn DS, Oh YH, Lee S, Kil HS, Oh SJ, et al. New class of SN2 reactions catalyzed by protic solvents: Facile fluorination for isotopic labeling of diagnostic molecules. J Am ChemSoc 2006; 128:16394–7.

[69] Coenen HH, Moerlein SM. Regiospecific aromatic fluorodemetallation of group IVbmetallo-arenes using elemental fluorine or acetyl hypofluorite. J Fluor Chem 1987;36:63–75.

[70] Adam MJ, Jivan S. Synthesis and purification of L-6-[^{18}F]fluorodopa. ApplRadiatIsot 1988;39:1203–10.

[71] Namavari M, Bishop A, Satyamurthy N, Bida G, Barrio JR. Regioselectiveradiofluoro-destannylation with [^{18}F]F2 and [^{18}F]CH3COOF: a high yield synthesis of 6-[^{18}F]fluoro-L-dopa. Appl Rad Isot 1992;43:989–96.

[72] McBride WJ, D'Souza CA, Sharkey RM, Goldenberg DM. The radiolabeling of proteins by the [^{18}F]AlF method ApplRadiatIsot 2012; 70: 200–204.

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C-11 Based Molecular Imaging Probes: Organic Synthesis, Radiochemistry and Application in Oncology and Neuroscience

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Abstract

Radiochemistry with the short-lived positron emitter isotope ^{11}C (half-life 20.38 min) offers unique challenges in terms of radiochemistry and its applications. Currently, ^{11}C radiochemistry has steadily expanded the number of ^{11}C-labeled compounds available for vast applications in neurooncology. This article addresses selected chemical and technical aspects of ^{11}C chemistry based on the precursors [^{11}C]methyl iodide and, to a lesser extent, [^{11}C]methyl triflate that are routinely used in our radiochemistry laboratory at DRDO-INMAS to develop several compounds for research and clinical applications.

Radionuclide Production and Carbon-11 Labelling Precursors

The advancement of positron emission tomography (PET) as a powerful imaging tool in nuclear medicine and drug research and development is dependent on development of new chemical entities and convenient radiolabeling strategy especially for the short-lived positron emitters ^{11}C (half-life 20.4 min) and ^{18}F (half-life 109.8 min). The shorter half-life of ^{11}C provides the advantage to perform many synthesis in a day for PET studies as per clinical research while still allowing, to some extent, multi-step radiosynthesis sequences. Moreover, isotopic labelling through different chemical reactions of a stable carbon atom with ^{11}C makes the corresponding ^{11}C labelled radiotracers like their stable counterparts within the biological system. Several nuclear reactions can be used to produce ^{11}C, however, among all the reported processes, the $^{14}N(p,\alpha)^{11}C$ nuclear reaction on a nitrogen gas target is by far the most convenient and most commonly used method of producing ^{11}C.

The radionuclide can be produced from nitrogen in a non-carbon-containing target material, thus providing ^{11}C at high specific radioactivity. Sufficient amounts of radioactivity can be produced within reasonable irradiation times(less than 30 minutes) as the $^{14}N(p,\alpha)^{11}C$ nuclear reaction has cross-section of 250 mb using a relatively low threshold energy of 3.1MeV which allows production of ^{11}C even with a small medical cyclotron. With the addition of oxygen (up to 2%) or hydrogen (5%–10%) to the nitrogen target gas, ^{11}C is obtained in the target either as [^{11}C]-carbon dioxide or [^{11}C]-methane, respectively, as primary labeling precursor. However, [^{11}C]-carbon dioxide is the most important and most versatile primary labelling precursor. Cyclotron-produced [^{11}C]-carbon dioxide can directly be used for the ^{11}C-labeling of organic molecules. This includes the reaction of [^{11}C]-carbon dioxide with different amines and isocyanates.

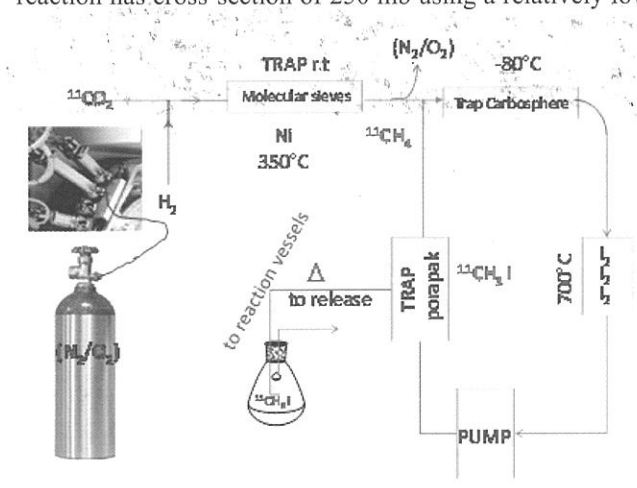

Fig. 1 Schematic for synthesis of [^{11}C]CH_3

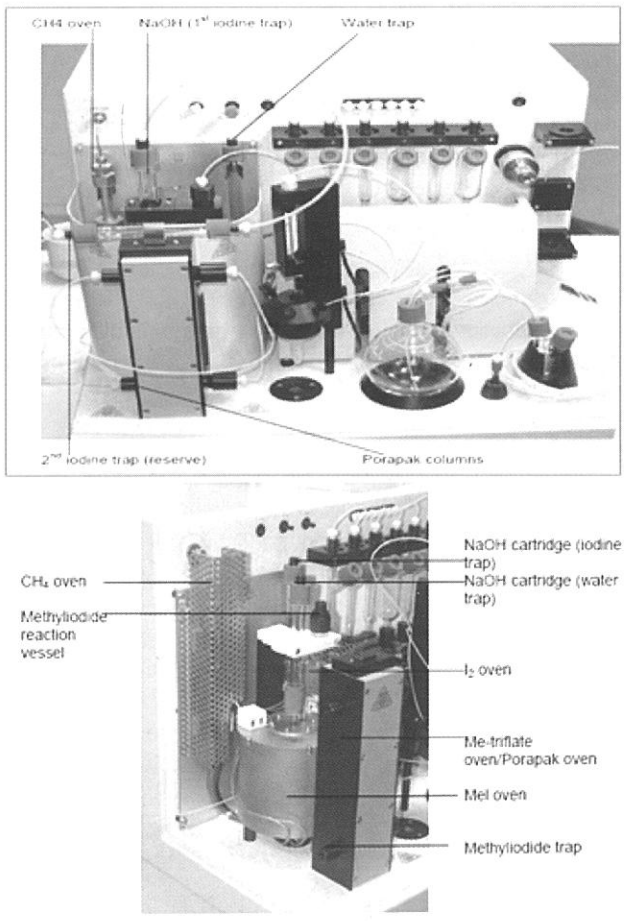

Fig. 2 Synthesis module for preparing [^{11}C]-labelled compounds

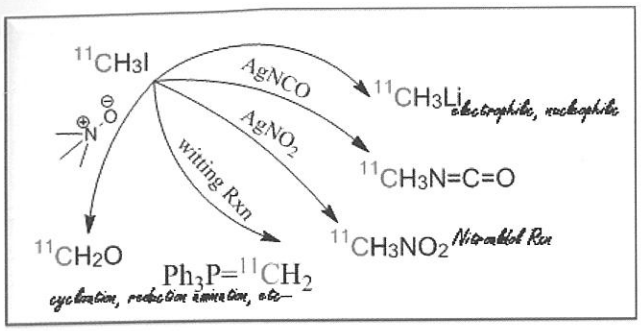

Fig. 3 Secondary labelling synthons from [^{11}C]CH_3

Starting from [^{11}C]carbon dioxide as the most important and versatile primary labeling precursor a broad spectrum of different ^{11}C-labeled synthetic

intermediates as useful secondary labeling precursors can be prepared. Scheme 1 shows a selection of ^{11}C-labeled secondary labeling precursors derived from [^{11}C]carbon dioxide precursors is [^{11}C]methyl iodide which is the most important and most frequently used. [^{11}C]Methyl iodide is being used at our centre very extensively as an alkylating agent for carbanions and heteroatom nucleophiles.

Synthesis of [^{11}C]-L-Methionine using [^{11}C]Methyl Iodide ([^{11}C]CH_3):

Synthesis of L-[S-methyl-^{11}C]methionine ([^{11}C]MET) is carried out using a C18 Sep-Pak Plus as a solid-phase support material for the [^{11}C]-methylation step. The present method, which uses [^{11}C]CH_3I produced by the gas phase route, supplies [^{11}C]MET ready for injection within 14 min from the end of bombardment (EOB) with a radiochemical yield, decay corrected at EOB, of 72% and a radiochemical purity at the end of synthesis (EOS) higher than 99%.

The required set-up is extremely simple and easy to automate and can be reset for a further synthesis within a few minutes. Moreover, due to its versatility, the method can be utilized for the production of other radiopharmaceuticals requiring a simple [^{11}C]methylation.

Quality control

Analytical HPLC was performed according to the European monograph for : stationary phase: phenosphere 10 µm ODS (1) (Phenomenex, Torrance, CA, USA); solvent: aqueous potassium dihydrogen phosphate solution 1.4 g/l; 1–4 min 1 ml/min, 4–15 min 3 ml/min.Radio-TLC: Stationary phase: SIL G/UV254 nm, mobile phase: NH_3/methanol/water (5/35/15, v/v), for detection treated with 0.2% ninhydrin in ethanol.

Application

Figure 6 shows some scans obtained with [^{11}C]-methionine developed at INMAS in patients with a history of treated primary brain tumors referred for evaluation of recurrent disease.

The time of PET studies after primary tumor diagnosis was 20.2 ± 20 months (range: 6–84 months).

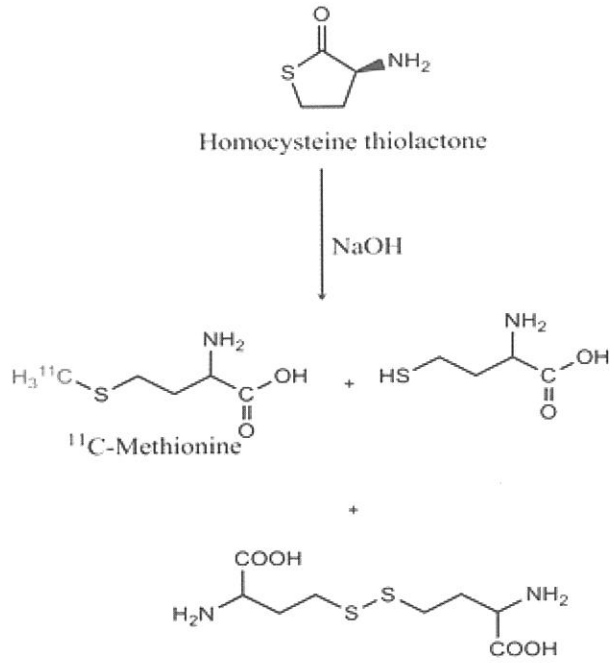

Fig. 4 Synthesis ^{11}C-Methionine using ^{11}C-methyl iodide)

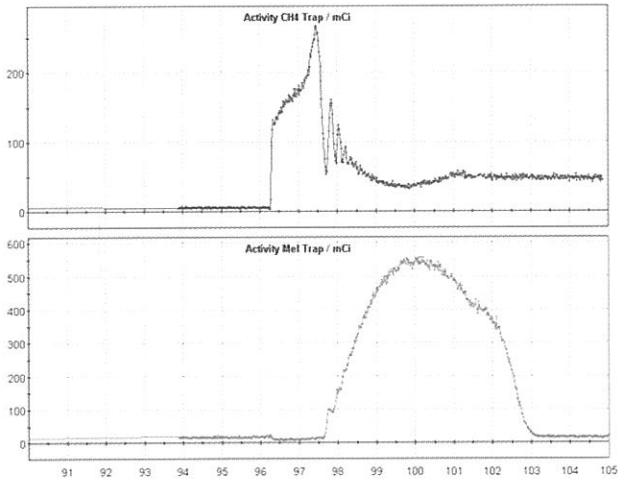

Fig. 5 HPLC of [^{11}C]CH_3 and [^{11}C]Methonine

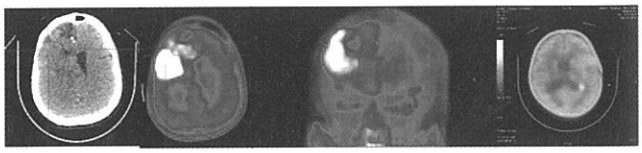

Fig. 6 PET-Brain scans with ^{11}C- Methionine

^{11}C "Click Chemistry" using [^{11}C]methyl azide: A simplified, versatile and practical alternative access to [^{11}C]-nucleosides and [^{11}C] -oligonucleotides for PET imaging

Thus, besides the direct use of [^{11}C]CO_2, labeling reagent, or its direct incorporation, optimized by Pike very recently researcher have also worked on the conversion of [^{11}C]CH_3I in order to broaden the spectrum of functionalities that may be labeled in a methylation step. Having already

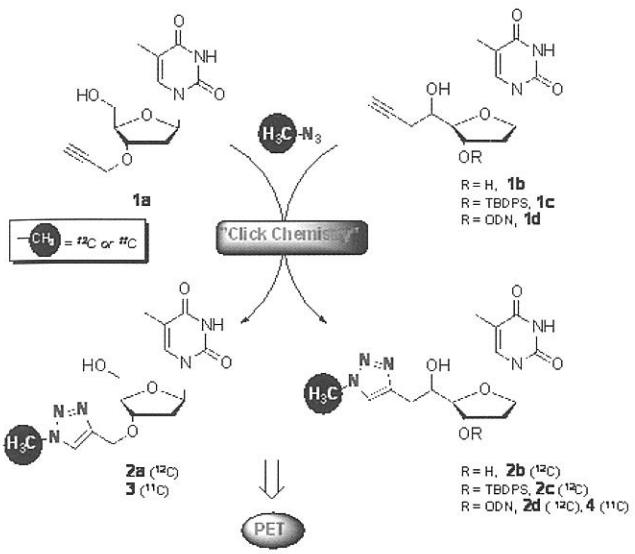

Fig. 7 Click chemistry methods to prepare [^{11}C]-compounds using [^{11}C]CH_3N

reported work on the application of 'click chemistry" in the labeling of nucleosides and oligonucleotides domain we have naturally considered with a lot of interest the possibility of using [^{11}C]methyl azide as a 'click reactant" described and applied successfully to peptide labeling, for the first time by Shirrmacher and co-workers. Indeed, the development of tracers for the study of cell proliferation is an important area of research. Thus, the labeling of thymidine in different positions is such an example. The methyl position is not optimal since it gives rise to labeled metabolites interfering with the interpretation of the PET data. Labeling in any of the carbonyl positions or [^{11}C]uracil analogue synthesis have given useful tracers, but is often laborious and /or time consuming synthesis. Among them, the Stille-type cross-coupling reaction with [^{11}C]methyl iodide, described first by Langström and coworkers for the synthesis of 1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)-[methyl-^{11}C] thymine ([^{11}C]FMAU), using 5-trimethylstannyl precursors was , until recently, described as the most direct, efficient and practical way of ^{11}C-incorporation in the structure of thymidine. However, this method has several problems to be solved from practical point of view. Suzuki and coworkers have recently proposed a revised version, and its application to the synthesis of 4'-[methyl-^{11}C]thiothymidine, replacing toxic trimethylstannyl precursor by tributylstannylanalogs, using lower temperatures and increasing, notably, the radiochemical yields, affording finally PET probes exhibiting sufficient radioactivity of 3.7-3.8 GBq and specific radioactivity of 89-200 GBq\mol^{-1}for animal and human PET studies.

However, the feasibility of the application of this methodology to the labeling of a thymidine-included artificial oligonucleotides is still to be demonstrated. Thus, we have decided to study the "click chemistry" involving [^{11}C] methyl azide, as a more practical, easier and more

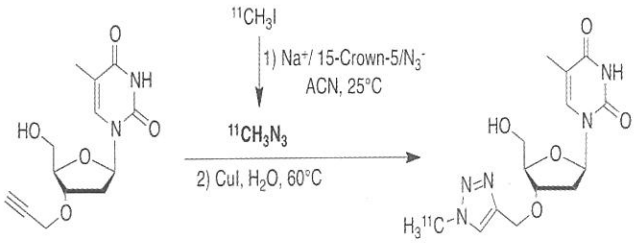

Fig. 8 Click chemistry methods to prepare [^{11}C]-compounds using [^{11}C]-Methyl azide

convenient alternative labeling strategy, as well as for thymidine than oligonucleotides, which appear to be promising as ligand for in vivo imaging. To investigate the interest of this chemistry on substrates such as nucleosides and oligonucleotides, we have studied the cyclo-addition reaction in its 'cold version" with first, the optimization of the reaction conditions using as alkyne substrate, before applying them to other nucleosides and one model oligonucleotide and finally transferring this methodology to ^{11}C chemistry.

Having in hand optimized coupling conditions for nucleosides as well as oligonucleotides, we were ready to apply it to the ^{11}C version. In this case, we decided to pass [^{11}C]CH_3I through a cartridge containing Na^+/15-Crown-5/N_3^- in acetonitrile, which is a real improvement compared to the procedure described by Shirrmacher, because itavoids the purification step of CH_3N_3 to get rid of the cryptant, potentially toxic for in vivo studies. The formed [^{11}C]CH_3N_3 was then bubbled into a vessel containing acetonitrile, and then this resulting solution was passed in the reaction vessel containing, contrary to previous procedures either of labeling of peptide by CH_3N_3 for labeling of thymidine by Stille coupling, only 1a (Fig. 6) and CuI in water heated at 60°C. Thus, 10-20 mCi of the desired ^{11}C-labeled thymidine derivative 3 (Fig. 6), in 35-60% radiochemical yield (decay corrected) was obtained.

The whole procedure, including the purification step, has taken 30 min (EOB), and the specific activity was about 20-30 mCi/μmol. So, these extremely simplified conditions, appeared to be much convenient and more suitable for in vivo purpose than those previously described, leading to the desired ^{11}C-labeling thymidine with comparable or even better yields, working with 4 to 10 times less of precursor. Although the specific radioactivity was low, due to an insufficient trapping of methylazide in reactor vessels, which can be corrected in closed loop by modifying the reactor vessels, it's still sufficiently satisfactory, at least for animal PET studies. Moreover, this procedure had allowed us to get effectively, for the first time, the ^{11}C labeled corresponding oligonucleotide starting from any precursor, even if further optimizations are still being worked out.

Palladium-assisted ^{11}C–C Bond Formations with [^{11}C]CH_3I

Many ^{11}C-labeled compounds as molecular probes for PET imaging are being developed by formation of novel

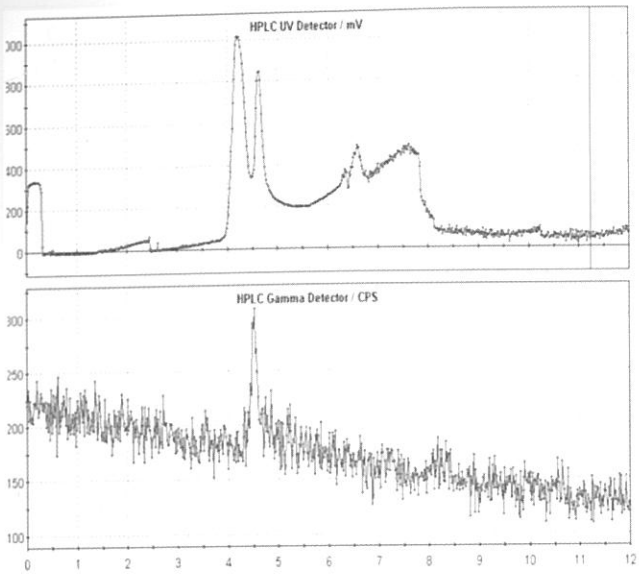

Fig. 9 HPLC profile of Labelled Clicked [^{11}C] Methyl azide

^{11}C–C bond with great interest. The genesis of these reactions originated from the possibility to place the ^{11}C label at a distinct position of a given molecule.

The easy synthesis and availability of [^{11}C] methyl iodide makes this ^{11}C labelling precursor an ideal reagent for distinct ^{11}C–C bond forming reactions. Several routes for ^{11}C–C bond formations involving [^{11}C]CH_3I have been developed by many researchers e.g. alkylation reactions of stabilized carbanions with [^{11}C]CH_3I were used to synthesise ^{11}C-labeled amino acids(Antoni and Langström 1987b) depending on the precursors. At the same time, exploiting Wittig reaction followed by a Heck coupling led to functionalized olefins (Bjorkman and Langström 2000). The synthesis of ^{11}C-labeled fatty acids was achieved by conversion of various organo-copper compounds with [^{11}C]CH_3I.

Conclusion

Among the several of ^{11}C-labeling precursors, [^{11}C]CH_3I is one of the most versatile ^{11}C-building blocks for the synthesis of a wide variety of PET radiotracers. [^{11}C]CH_3I can be easily produced in automated synthesis apparatus in high radiochemical yields and high specific radioactivity. In recent past, technical improvements and developments have made heteroatom methylation reactions with [^{11}C]CH_3I a powerful and convenient synthesis route for the preparation of ^{11}C-labeled PET radiotracers for clinical research and basic research purposes. Moreover, the scope of [^{11}C]methyl iodide as useful labeling precursor was significantly expanded through the application of transition metalmediated reactions for distinct ^{11}C–C bond formations. In this context, especially palladium-mediated ^{11}C–C bond formations have proved to be exceptionally valuable to further expand the arsenal of ^{11}C-labeled compounds. Thus, recent developments in ^{11}C radiochemistry are important to further stimulate the progress of PET as a powerful molecular imaging technique in clinical use and research, and drug research and development.

Bibliography

[1] G. Antoni, T. Kihlberg, B. Langström, Handbook of Nuclear Chemistry, Springer, 2011, vol. . 4, pp. 1983–2014

[2] P. J. Riss, S. Y. Lu, S. Telu, F. I. Aigbirhio, V. W. Pike, Angew. Chem. 2012, 124, 275

[3] R. Schirrmacher, Y. Lakhrissi, D. Jolly, J. Goodstein, P. Lucas, E. Schirrmacher, Tetrahedron Lett. 2008, 49, 4824–4827.

[4] P. W. Miller, N. J. Long, R. Vilar, A. D. Gee, Angew. Chem. 2008, 120, 9136; Angew. Chem. Int. Ed. 2008, 47, 8998–9033.

[5] G. Antoni, T. Kihlberg, B. Langström, Handbook of Nuclear Chemistry, Springer, 2011, vol. 4, pp. 1983–2014; M. Allard, E.Fouquet, D. James, M. Szlosek-Pinaud, Curr. Med. Chem. 2008, 15, 235–277.

[6] M. Pretze, P. Große-Gehling, C. Mamat, Molecules 2011, 16, 1129–1165.

[7] L. Samuelsonn, B. Langström, J. Labelled Compd. Radiopharm. 2003, 46, 263–272.

[8] P. Goethals, J. Sambre, M. Coerne, K. Casteleyn, E. Poupeye, Appl. Radiat. Isot. 1992, 43, 952–954; b) P. S. Conti, M. M. Alauddin, J. R. Fissekis, B. Schmall, K. A. Watanabe, Nucl. Med. Biol. 1995, 22, 783–789.

[9] C. J. Steel, G. D. Brown, K. Dowsett, D. R. Turton, S. K. Luthra, H. Tochon-Danguy, S. L. Waters, P. Price, Labelled Compd. Radiopharm. 1993, 32, 178–179.

[10] Thomas Bordenave, Puja Panwar Hazari, Damien James, Anil K. Mishra, Magali Szlosek-Pinaud, Eric Fouquet,11C Click Chemistry Using [^{11}C]Methyl Azide: Simplified, versatile, and practical alternative access to [^{11}C]Nucleosides and [^{11}C]Oligonucleotides for PET Imaging:, Eur. J. Org. Chem. 2013, 1214–1217:

[11] G . Antoni, B. Langström, Int J Appl Radiat Isot 1987, 655–659

[12] M. Bjorkman, B. Langström , J Chem Soc Perkin Trans 2000, 1 3031–3034

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Technical Advances in PET/CT and Hybrid Imaging Systems

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Introduction

Positron emission tomography (PET) [1] is a nuclear medicine, functional imaging technique that produces a three-dimensional image of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Three-dimensional images of tracer concentration within the body are then constructed by computer analysis. In modern PET/CT scanners, three dimensional imaging is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

X-ray computed tomography (X-ray CT) is a technology that uses computer-processed X-rays to produce tomographic images (virtual 'slices') of specific areas of the scanned object, allowing the user to see inside without cutting. Digital geometry processing is used to generate a three-dimensional image of the inside of an object from a large series of two-dimensional radiographic images taken around a single axis of rotation. Medical imaging is the most common application of X-ray CT. Its cross-sectional images are used for diagnostic and therapeutic purposes in various medical disciplines.

History

The concept of emission and transmission tomography was introduced by David E. Kuhl, Luke Chapman and Roy Edwards in the late 1950s. Their work later led to the design and construction of several tomographic instruments at the University of Pennsylvania. Tomographic imaging techniques were further developed by Michel Ter-Pogossian, Michael E. Phelps, Edward J. Hoffman and others at Washington University School of Medicine [2,3].

Work by Gordon Brownell, Charles Burnham and their associates at the Massachusetts General Hospital beginning in the 1950s contributed significantly to the development of PET technology and included the first demonstration of annihilation radiation for medical imaging [4]. Their innovations, including the use of light pipes and volumetric analysis, have been important in the deployment of PET imaging. In 1961, James Robertson and his associates at Brookhaven National Laboratory built the first single-plane PET scan nicknamed the "head-shrinker" [5].

One of the factors most responsible for the acceptance of positron imaging was the development of radiopharmaceuticals. In particular, the development of labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Prof. Alfred Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging [6]. The compound was first administered to two normal human volunteers by Dr. Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. Later, the substance was used in dedicated positron tomographic scanners, to yield the modern procedure.

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968, completed in 1969 and reported in 1972. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were reported in 1970 . It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson and Zang-Hee Cho were the first to propose a ring system that has become the prototype of the current shape of PET.

Basic Principles

The recent development of integrated PET/CT systems allows CT and PET images to be obtained in a single imaging setting and provides optimal co-registration of images. The fusion images provided by these systems allow the most accurate interpretation of both CT and PET studies. Integrated PET/CT is also a promising tool for optimising radiation therapy and guided biopsy. Due to high photon flux of X-ray beams, CT attenuation maps from these integrated PET/CT systems also allow for optimal attenuation correction of the PET images and shorter acquisition times.

With these integrated systems, a diagnostic CT scan and a PET scan can be acquired sequentially with the patient lying on the imaging table and with simple translation between two systems. Accurate calibration of the position of the imaging table and the use of common parameters in data acquisition and image reconstruction permit the fusion of images of anatomy and metabolism that are registered in space and only slightly offset in time.

Theoretically, an ideal PET tomograph should have high sensitivity and a high counting rate capability in addition to low dead-time losses and low scatter fraction, and it should provide a uniform and high spatial and energy resolution over the whole sensitive volume, allowing one to reach the highest signal - to-noise ratio (SNR) for the lowest possible injected activity. Significant progress has been achieved in the design of commercial PET instrumentation during the last decade. PET systems can now reach a spatial resolution of about 4 to 6 mm for whole-body imaging, and approximately 2.4 mm for PET cameras dedicated for brain imaging. Novel scintillation crystal-based detection

TABLE 1: Characteristics of scintillation crystals used in, or developed specifically for the design of, current generation PET imaging systems [14]

Scintillator	BGO	GSO	LSO	LYSO	LuAP	$LaBr_3$
Formula	$Bi_4Ge_3O_{12}$	Gd_2SiO_5:Ce	Lu_2SiO_5:Ce	$LuYSiO_5$:Ce	$LuAlO_3$:Ce	$LaBr_3$:Ce
Density (g/cc)	7.13	6.71	7.4	7.1	8.34	5.3
Light yield (photons/keV)	9	8	25	32	10	61
Effective Z	75	60	66	64	65	46.9
Principal decay time (ns)	300	60	42	48	18	35
Peak wavelength (nm)	480	440	420	420	365	358
Index of refraction	2.15	1.95	1.82	1.8	1.95	1.88
Photofraction (%) @511Kev	41.5	25	32.5	34.4	30.6	15
Attenuation length (cm) @511KeV	1.04	1.42	1.15	1.12	1.05	2.13
Energy resolution (%) @511KeV	12	7.9	9.1	7.1	11.4	3.3
Hygroscopic	No	No	No	No	No	Yes

technologies that materialized included the use of new cerium-doped crystals (e.g. LSO, GSO, LYSO, $LaBr_3$) as alternatives to conventional bismuth germinate (BGO) crystals, and the use of layered crystals (phoswich detectors) and other methods for depth-of-interaction determination, as well as a renewed interest in old technologies such as time-of-flight PET (TOF-PET), owing to the development of faster scintillation crystals and electronics that made this approach feasible on commercial clinical systems [10]. The scintillation crystal is one of the most critical components of a PET tomography [11]. Increased light yield, faster rise and decay times, greater stopping power and improved energy resolution, and the linearity of response with energy, in addition to their low cost, availability, mechanical strength, moisture resistance, and machinability are among the desired characteristics of scintillation crystals [12]. Most of these properties are summarised (Table 1) for selected scintillators currently in use or under development for PET applications [13]. Improvements in these characteristics enable detectors to be divided into smaller elements, achieved by designing smaller crystals, allowing the acquisition of data with finer sampling. One manufacturer (Siemens Medical Solutions, Knoxville, Tennessee) modified the block detector design by using 13 x 13 block of 4 x 4 x 20 mm^3 each crystal instead of an 8 x 8 block of 6.45 x 6.45 x 25 mm^3 crystals, allowing one to reach a transverse spatial resolution close to 4 mm (4.5 mm) at the center of the field-of-view.

Time of Flight PET

TOF-PET (Time of Flight PET) on the other hand is based on the assessment of a difference of the arrival times of the 511-keV annihilation photons to allow restricting the position of positron emission to a subsection of the coincidence line connecting the two scintillation crystals [15,16]. This technique was suggested and explored with limited success in the 1980s due to the lack of crystals combining the required timing resolution and high stopping power [17]. With the arrival of fast scintillation crystals, TOF is now viable, allowing an improvement in the SNR through incorporation of TOF information into the PET reconstruction process [18-20]. One scanner manufacturer (Philips Medical Systems, Cleveland, Ohio) recently introduced the first commercially available fully three-dimensional PET scanner (The Gemini TF) that achieves TOF capability as well as conventional imaging capabilities [10].

Commercially available, dedicated cylindrical, full-ring PET systems are still considered to provide

TABLE 2. Main performance characteristics of commercial PET/CT scanners operating in three-dimensional mode [14]

Parameter	Biograph truepoint	Gemini GXL	Gemini TF	Discovery LS	Discovery ST	Discovery STE/VCT
CT						
Number of slices	6, 16, 40, 64	6, 16	16, 64	4, 8, 16	4, 8, 16	8, 16, 64 (VCT)
Rotation speed (s)	0.33/0.42	0.4	0.4/0.5	0.5	0.5	0.4
Detector material	Ultrafast ceramic	Solid-state GOS	Solid-state GOS	Patented ceramic	Patented ceramic	Patented ceramic
Temporal resolution (ms)	~90	~100	~100/120	~120	~120	~100
Spatial resolution (line pairs/cm)	15.1/24	16/24	24	15.4	15.4	15.4
PET						
Scintillation crystal	LSO	GSO	LYSO	BGO	BGO	BGO
Number of crystals	32,448 (True V)	17,864	28,336	12,096	10,080	13,440
Detector size (mm)	4 x 4 x 20	4 x 6 x 30	4 x 4 x 22	4 x 8 x 30	6.2 x 6.2 x 30	4.7 x 6.3 x 30
Axial field of view (cm)	16.2/21.6 (True V)	18	18	15.2	15.7	15.7
Sensitivity (cps/kBq)	7.9 (True V)	8	7.2	1.3	2	2
Peak noise equivalent count rate (kcps)	165 (True V)	70	105	42	63	75
Activity concentration @ peak NEC (kBq/cc)	32	11	16	8.5	12	12
Scatter fraction (%)	<36	37	30	43	44	35
Transverse resolution @ 1 cm (mm)	4.2	5.3	4.7	4.8	6.2	5
Transverse resolution @ 10 cm (mm)	4.8	6	5.1	5.2	6.7	5.6
Axial resolution @ 1 cm (mm)	4.5	6	4.7	6.5	5.6	5.6
Axial resolution @ 10 cm (mm)	5.5	6.6	5.2	7.5	5.9	5.9

state-of-the-art performance for whole-body scanning [10,21-29], The improved performance characteristics (Table 2) of dedicated systems when compared with scintillation camera–based systems is due to their higher overall system efficiency and count rate capability, which provide the statistical realisation of the physical detector resolution and not simply a higher intrinsic physical detector resolution [30].

PET/CT

The proposal to combine PET with CT was made in the early 1990s by Townsend, Nutt and co-workers. The concept originated from an earlier low-cost PET scanner design that comprised rotating banks of bismuth germanate (BGO) block detectors that was developed by Townsend and coworkers at the University of Geneva in 1991. The gaps between the banks of BGO detectors offered the possibility to incorporate a different imaging modality within the PET scanner. A Swiss oncology surgeon, Dr Rudi Egeli, suggested adding something useful such as a CT scanner in the gaps that would provide anatomical information more familiar to surgeons at that time. Thus, the concept of PET/CT was born in 1991, in which the components of a CT scanner would be mounted in the gaps between the banks of BGO block detectors. However, it was soon evident from the inspection of a typical CT scanner that such a concept would not be feasible owing to the density of X-ray components mounted on the rotating support. Thus, it took seven more years before the first prototype combined PET/CT scanner was completed and installed in the University of Pittsburgh Medical Center. In 1993, Townsend moved to the University of Pittsburgh where, in collaboration with Dr Ron Nutt, then President of CTI PET Systems (CPS) in Knoxville, Tennessee, received NIH funding to begin the development of the first PET/CT prototype. This work followed the pioneering work of the late Bruce Hasegawa and colleagues at the University of California, San Francisco in the early

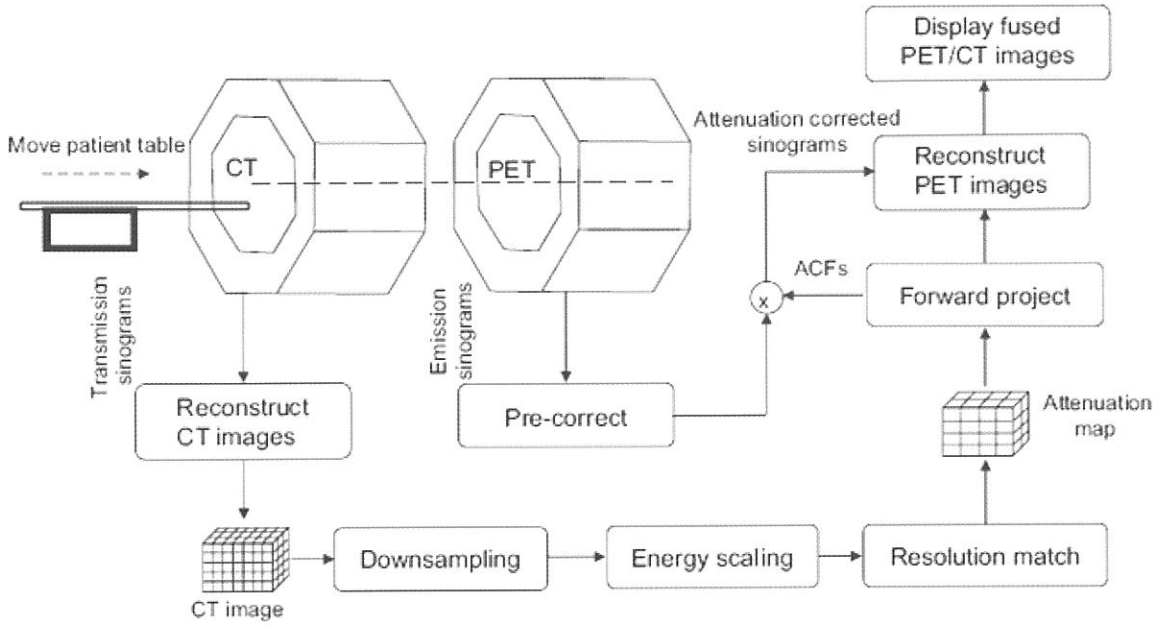

Fig. 1 Principles of operation of a combined PET/CT scanner showing the key hardware components and the main steps involved in data acquisition and processing protocols, including generation of the attenuation map required for CT-based attenuation correction of PET data, attenuation correction factors (ACFs) [14].

1990s where they developed the first combined clinical CT and SPECT prototype scanner.

Today, most of the installed PET units are combined PET/CT devices (Fig. 1). Most of the vendors, who offer stand-alone PET systems designed for dedicated clinical tasks, offer PET systems for clinical use that are combined with a CT system. The main advantages of combined PET/CT are: (i) intrinsic availability of co-registered functional and anatomical information from PET and CT, respectively, for regional (local) and whole-body examinations; (ii) ability to use available CT transmission images to replace lengthy PET transmission images using 511 keV rod sources, thus reducing overall examination time significantly and limiting noise propagation from measured attenuation correction.

Dual-modality PET/CT systems combine a whole-body PET and a standard multi-slice CT within a single gantry. Various design concepts exist (Fig. 2), all aiming at reducing footprint and bringing the PET and CT components closer together. No fully-integrated, single-detector PET/CT exists today, however, because of the challenges to manufacture a detector system that is capable of CT (40–140 keV) and PET (511 keV) imaging. By using novel patient handling systems, patients are positioned accurately and reproducibly for co-axial imaging. Reports on residual displacements between CT and PET along the co-axial imaging range in combined PET/CT indicate a maximum displacement of error of 0.5 mm. Thus, PET/CT yields the best possible alignment of extensive, complementary image volumes. With the benefits of intrinsically aligned PET and CT data, shorter overall scan times and the logistical advantages for patients and staff, the use of combined PET/CT imaging has become a prime modality-of-choice for patient management in clinical oncology.

CT-Based Attenuation Correction

While the acquisition of accurately co-registered anatomic and functional images is a major strength of the combined PET/CT scanner, an additional advantage of the hardware fusion approach is the use of CT images for attenuation correction of the PET emission data, eliminating the need for a separate, lengthy PET transmission scan. The use of the CT scan to generate PET attenuation correction factors (ACFs) not only reduces whole-body scan times by up to 40%, but also provides essentially noiseless ACFs compared with those from standard PET transmission measurements, even with singles sources. The attenuation values (μ) are energy dependent. Therefore, the correction factors derived from a CT scan at mean photon energy of 70 keV must be scaled to the PET energy of 511 keV. Since the CT attenuation value at a given energy depends on both density and relative elemental composition of the tissue, the scale factor is determined by the fractional elemental composition rather than the density, i.e. attenuation is related to electron density. Generally, a higher effective atomic number for the tissue implies a smaller scale factor because the attenuation decreases more rapidly with energy. The behavior of the scale factor calculated from the ratio of attenuation values μ (at 511 keV)/μ (at 70 keV) as a function of CT number is shown in table 3. These attenuation values are for standard reference tissues [29]. Even though lung tissue has a much lower density than water, it nevertheless has a very similar elemental composition and, therefore, a similar scale factor to other soft tissues, close to that of water. Adipose tissue has a slightly higher scale factor because of its composition. Compared with soft tissues, bone-related tissue

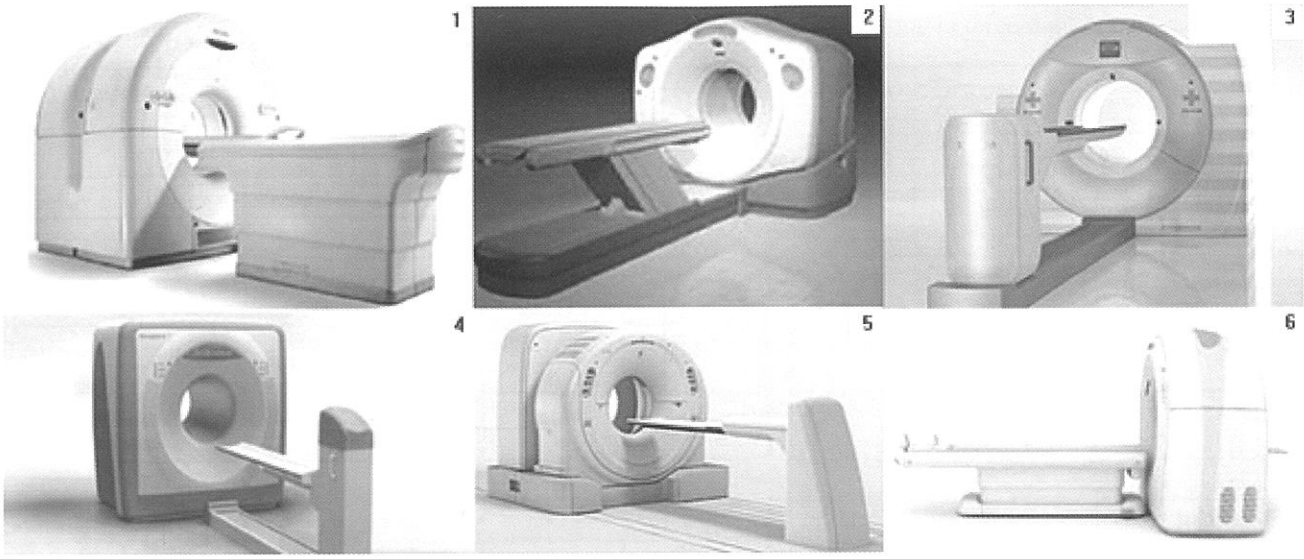

Fig. 2 Current commercial PET/CT systems: (1) Gemini series from Philips Healthcare, (2) Discovery series from General Electrics Healthcare, (3) Biograph mCT from Siemens Healthcare, (4) Sceptre series from Hitachi Medical Systems, (5) Acquiduo series from Toshiba Medical Systems, (6) Anyscan from Mediso (this device can be combined with a SPECT to form a triple-modality imaging system [14].

TABLE 3. Mass attenuation coefficients (linear attenuation coefficient/density) in cm^2/g [33]

Material	80 keV			500 keV			Ratio of totals
	Photoelec.	Compton	Total	Photoelec.	Compton	Total	80 keV:500 keV
Air	0.006	0.161	0.167	<0.001	0.087	0.087	1.92
Water	0.006	0.178	0.181	<0.001	0.097	0.097	1.90
Muscle	0.006	0.176	0.182	<0.001	0.096	0.096	1.90
Bone	0.034	0.175	0.209	<0.001	0.093	0.093	2.26
Teflon	--	--	0.168	--	--	0.087	1.93

is less uniform in composition. Bone tissues behave according to a water–bone mix with different fractional contributions from water-like and cortical bone-like tissue. Scale factors for bone are smaller than those for soft tissue, and an exact scaling procedure would account for the small differences between bone types. However, that would require a sophisticated segmentation of the different bone structures seen in a CT image. In practice, a simpler approach used in current PET/CT scanners is to transform the attenuation values above and below a given threshold with different factors [31,32]. In the approach used by Kinahan et al. [30], the threshold distinguishes regions of bone from those of non-bone. Within these two categories, no further distinction is made between the various subtypes of tissue. While a single scaling factor is a good approximation for soft tissue, a water–bone mixing model would be more appropriate for bone tissue. However, in a typical CT image, the volume of bone-related pixels is small compared with the volume of soft tissue, and the use of a single scaling factor will not introduce appreciable error. This appears to hold for the pelvic region too, where the volume of bone relative to soft tissue is somewhat larger. The original CT images acquired at a mean energy of about 70 keV are thus scaled on a pixel-by-pixel basis up to 511 keV. The scaled CT images are then interpolated from CT to PET spatial resolution, and the ACFs are generated by reprojection of the interpolated images. CT image is representation of CT numbers (Hounsfield units). Attenuation values μ are originally measured during transmission data collection using CT, which are scaled to that of water to give CT number as below:

$$\text{CT Number} = \frac{\mu_{\text{tissue}} - \mu_{\text{water}}}{\mu_{\text{water}}} \times 1000$$

Where CT number for water=0, air = -1000 and bone = 1000

Challenges and Limitations of PET/CT

There are a few challenges when designing a PET/CT imaging system and making it clinically viable. First, the axial displacement of the CT and PET components is unavoidable, as long as no single PET and CT detectors are available, thus allowing for only sequential rather than simultaneous acquisition modes. Sequential imaging holds the risk of involuntary patient motion in between the two examinations, and therefore, may increase the chance of local misalignment of the two studies. Further, residual patient motion is unavoidable in combined PET/CT imaging. Involuntary patient motion from, for example, respiration, cardiac motion, or muscle relaxation, etc. would lead to

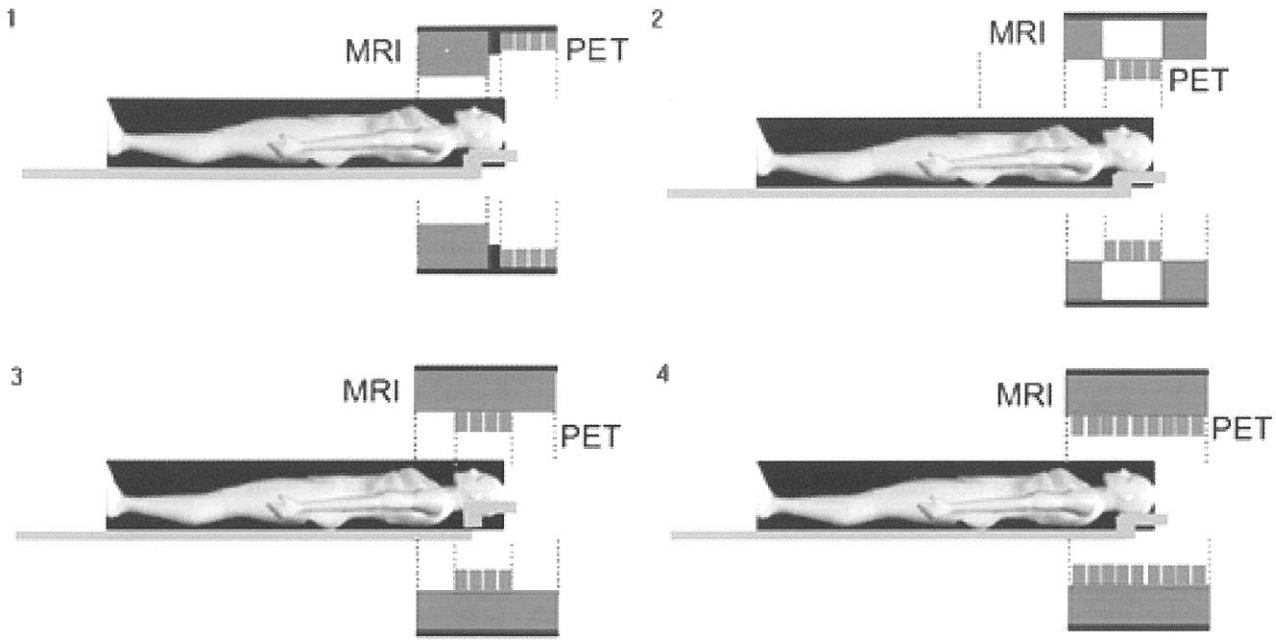

Fig. 3 Concept of PET/MRI illustrated through four potential designs that are being explored. (1) Two scanners mounted together back-to-back allow sequential rather than simultaneous acquisition like PET/CT. (2) PET scanner inserted within a gap in a superconducting magnet where the PMTs can be placed in a low magnetic field through a combination of magnet design and the use of fiberoptic bundles. (3) PET scanner inserted (between the RF-coil and gradient set of the MR system) into a standard clinical MRI system. (4) Full integration of a whole-body PET/MRI system.

PET/CT mis-registration, that may translate into artifacts on PET images following CT-based attenuation correction. Optimized imaging protocols are required to minimize these types of artifacts and image distortions.

PET/MR

A hybrid PET/MR scanner simultaneously delivers functional information plus anatomy and tissue characterisation (soft tissue contrast and blood vessel physiology), from a state-of-the-art MR scanner. At the same time, it provides metabolic imaging from PET technology. Fusing these images gives the best of both worlds, providing greatly superior information to what you'd get from either machine individually.

The idea of designing a hybrid PET/MR system goes back to the mid-1990s, even before the design of the first PET/CT prototype [34-36]. The first attempts to design MR-compatible PET units relied on simple modification of conventional PET detectors for small animal systems to keep the photomultiplier tubes (PMTs) away from the strong magnetic field of MRI [37-42]. In this approach, scintillation crystals were coupled to 3- to 5- metre long optical fibers, leading the weak scintillation light outside the fringe magnetic field to position-sensitive PMTs. One major drawback of this design is that the long fibers result in the loss of a significant fraction of the scintillation light, affecting energy and timing resolution, deteriorating crystal identification, and loosing PET signal performance. Other related approaches based on conventional PMT-based PET detectors rely on more complex magnet designs, including a split magnet [43] or a field-cycled MRI [44]. The potential of using novel readout technologies insensitive to magnetic fields, including Avalanche Photodiodes (APDs) and Silicon PMTs (SiPMs), has not yet been fully realized. APD-based technology has been successfully implemented by one small animal PET vendor [45] and in many preclinical PET/MR systems [46,47].

The conceptual design of combined PET/MR instrumentation for humans would greatly benefit from the experience gained in preclinical imaging. There are at least four evident ways to combine PET and MRI in a single gantry (Fig 3). The obvious and easiest configuration would be to combine PET/MRI as two ''standard'' scanners hardware wired to each other with a common bed and common computer console similar to PET/CT (Fig. 3.1). This configuration would be more straightforward to develop when compared with fully integrated approaches, because the PET electronics are outside the MRI scanner's field of view and high magnetic field. The main limitation of this design is that the PET and MR data will be acquired sequentially rather than simultaneously, seriously limiting the envisioned applications (e.g. the assessment of two independent functional processes with PET tracers and MRI contrast agents [functional MRI or MR spectroscopy]). Moreover, MRI has relatively long acquisition times when compared with CT, which further emphasizes the advantages of simultaneous scanning to reduce acquisition time. The full integration of PET and MRI with large and matched fields of

view in a single gantry to allow simultaneous whole-body scanning remains a long-term objective (Fig. 3.4.)

Challenges of Combined PET/MR

Traditional PET systems use PMTs to detect the scintillation light. However, PMTs are sensitive to magnetic fields and are therefore not functional inside an MRI system. To overcome this problem, various approaches to the combination of PET and MRI have been established. For example, optical fibers can be used to lead the light from the scintillation crystals outside the fringe field of the magnet to the PMTs. Alternatively, split magnets with the PET detector positioned between the two magnet halves and connected via light fibers have been proposed. In either design, long optical fibers result in loss of light, and consequently lower performance of such a PET system operated in the vicinity of an MR scanner. This loss can be overcome by the use of magnetic field compatible solid state light detectors. This approach also permits easier expansion of the axial FOV of the PET system. The mutual interference between PET and MR is a critical problem; MR can affect PET performance because of the high static magnetic field, gradient fields, and radiofrequency field. MR image quality, however, can be impaired by either radiofrequency noise introduced by the PET electronics or magnetic field non-homogeneities caused by the presence of different materials in the PET insert and eddy currents induced from the gradient system in the conducting structures of the PET housing and circuit boards. Moreover, the operating temperature needs to be stabilized to ensure reliable PET and MR performance. Finally, any combined PET/MR system must offer alternative approaches to deriving the necessary attenuation correction factors for the emission data. In PET/CT, attenuation data can be derived from transforming available CT transmission images into maps of attenuation coefficients at 511 keV, while no such transmission data are available in PET/MR. This is due to the lack of physical space in general to host a transmission source and also X-ray tube, rod or point sources would lead to grave crosstalk effects with the MR magnetic field. The available MR images represent, in essence, proton densities that cannot be transformed to maps of electron densities as obtained from CT transmission measurements. Therefore, PET/MR requires novel approaches to MR-based attenuation correction. Segmentation-based approaches have been proposed and seem to work in brain imaging. However, MR based attenuation correction in extra-cranial applications is much more demanding.

A Decade of Hybrid Imaging

A mere two years after the advent of commercial PET/CT, Johannes Czernin from UCLA commented: "PET/CT is a technical evolution that has led to a medical revolution". Today, at the dawn of PET/MR imaging, we may extend his phrase by "integrated PET/MR is a medical evolution based on a technical revolution". PET/CT appears to have replaced stand-alone PET for nearly all oncologic indications. Ongoing and future studies using first prototype and clinical systems will show how much PET/MR could supplement PET/CT imaging in the clinic. We believe that PET/MR is a required and valuable adjunct to modern healthcare, and that there will be indications for which PET/MR may become a primary or secondary diagnostic test during work-up or follow-up of a variety of patients. Nevertheless, PET/MR will not replace PET/CT as a molecular imaging modality in the near future. In India, the first PET was installed at RMC, Mumbai in 2002, while we have today nearly 90 PET/CT systems in various parts of India.

Both modalities are here to stay because both systems incorporate the diagnostic power of PET. In fact, with PET/CT being a "dual-modality imaging" platform by virtue of combining functional (PET) and anatomical (CT) imaging only, PET/MR offers true "multi-modality imaging" by virtue of combining function from PET, and anatomy *cum* function from MR. When fully developed and deployed widely, this will open new avenues in non-invasive imaging strengthening both patient management and clinical research.

The hybrid PET/MR machines currently available are the Siemens Healthcare Biograph mMR (FDA approved in June 2011), the Philips Ingenuity TF System (FDA cleared in November 2011) and the GE Healthcare SIGNA (Announced in August 2014 but FDA clearance pending) to the best of our knowledge. The first hybrid PET/MR system has arrived in India in 2013.

References

[1] Bailey, D.L; D.W. Townsend, P.E. Valk, M.N. Maisey (2005). Positron Emission Tomography: Basic Sciences Secaucus, NJ: Springer-Verlag. ISBN 1-85233-798-2.

[2] Ter-Pogossian MM, Phelps ME, Hoffman EJ, Mullani NA (1975). "A positron-emission transaxial tomograph for nuclear imaging (PET)". Radiology 114 (1): 89–98. OSTI 4251398 PMID 1208874.

[3] Phelps ME, Hoffman EJ, Mullani NA, Ter-Pogossian MM (March 1, 1975). "Application of annihihilation coincidence detection to transaxial reconstruction tomography", Journal of Nuclear Medicine 16 (3): 210–224. PMID 1113170

[4] Sweet, W.H.; G.L. Brownell (1953). "Localization of brain tumors with positron emitters". Nucleonics 11: 40–45.

[5] A Vital Legacy: Biological and Environmental Research in the Atomic Age, U.S. Department of Energy, The Office of Biological and Environmental Research, September 2010, p 25–26

[6] Ido T, Wan CN, Casella V, Fowler JS, Wolf AP, Reivich M, Kuhl DE. "Labeled 2-deoxy-D-glucose analogs. 18F-labeled 2-deoxy-2-fluoro-D-glucose, 2-deoxy-2-fluoro-D-mannose and 14C-2-deoxy-2-fluoro-D-glucose". Journal of Labelled Compounds and Radiopharmaceuticals 14 (2): 175–183. doi:10.1002/jlcr.2580140204

[7] Brownell G.L., Dave Marcum, B. Hoop JR., and D.E. Bohning, "Quantitative dynamic studies using short-lived radioisotopes and positron detection" in Proceedings of the Symposium on Dynamic Studies with Radioisotopes in Medicine, Rotterdam. August 31–September 4, 1945. IAEA. Vienna. 194824. pp. 161–172.

[8] Robertson J.S., Marr R.B., Rosenblum M., Radeka V., and Yamamoto Y.L., 32-Crystal positron transverse section

detector, in Tomographic Imaging in Nuclear Medicine, Freedman GS, Editor. 1983, The Society of Nuclear Medicine: New York. pp. 142–153.

[9] Cho, Z. H., Eriksson L., and Chan J.K., ``A circular ring transverse axial positron camera in Reconstruction Tomography in Diagnostic Radiology and Nuclear Medicine, Ed. Ter-Pogossian MM., University Park Press: Baltimore, 1975.

[10] Surti S, Kuhn A, Werner ME, et al. Performance of Philips Gemini TF PET/CT scanner with special consideration for its time-of-flight imaging capabilities. J Nucl Med 2007; 48:471–80.

[11] Marsden PK. Detector technology challenges for nuclear medicine and PET. Nucl Instr Methods A 2003; 513:1–7.

[12] Derenzo SE, Weber MJ, Bourret-Courchesne E, et al. The quest for the ideal inorganic scintillator. Nucl Instr Meth A 2003; 505:111–7.

[13] Van Eijk CWE. Inorganic scintillators in medical imaging. Phys Med Biol 2002; 47:R85–R106.

[14] Habib Zaidi, Abass Alavi et al. Current Trends in PET and Combined (PET/CT and PET/MR) Systems Design. PET Clin 2, 2007; 109-123.

[15] Lewellen TK. Time-of-flight PET. Semin Nucl Med 1998; 28:268–75.

[16] Moses WW. Time of flight in PET revisited. IEEE Trans Nucl Sci 2003; 50:1325–30.

[17] Ter-Pogossian MM, Mullani NA, Ficke DC, et al. Photon time-of-flight-assisted positron emission tomography. J Comput Assist Tomogr 1981; 5:227–39.

[18] Conti M, Bendriem B, Casey M, et al. First experimental results of time-of-flight reconstruction on an LSO PET scanner. Phys Med Biol 2005; 50:4507–26.

[19] Harrison RL, Gillispie SB, Alessio AM, et al. The effects of object size, attenuation, scatter, and random coincidences on signal to noise ratio in simulations of time-of-flight positron emission tomography. IEEE Nuclear Science Symposium Conference Record. October 23–29, 2005, Puerto Rico.

[20] Surti S, Karp JS, Popescu LM, et al. Investigation of time-of-flight benefit for fully 3-D PET. IEEE Trans Med Imaging 2006; 25:529–38.

[21] Watson CC, Casey ME, Erikksson L, et al. NEMA NU 2 performance tests for scanners with intrinsic radioactivity. J Nucl Med 2004; 45:822–6.

[22] Bettinardi V, Danna M, Savi A, et al. Performance evaluation of the new whole-body PET/CT scanner: discovery ST. Eur J Nucl Med Mol Imaging 2004; 31:867–81.

[23] Mawlawi O, Podoloff DA, Kohlmyer S, et al. Performance characteristics of a newly developed PET/CT scanner using NEMA standards in 2D and 3D modes. J Nucl Med 2004; 45: 1734–42.

[24] Erdi YE, Nehmeh SA, Mulnix T, et al. PET performance measurements for an LSO-based combined PET/CT scanner using the National Electrical Manufacturers Association NU 2-2001 standard. J Nucl Med 2004;45:813–21.

[25] Surti S, Karp JS. Imaging characteristics of a 3-dimensional GSO whole-body PET camera. J Nucl Med 2004; 45:1040–9.

[26] Brambilla M, Secco C, Dominietto M, et al. Performance characteristics obtained for a new 3-dimensional lutetium oxyorthosilicate-based whole-body PET/CT scanner with the National Electrical Manufacturers Association NU 2-2001 standard. J Nucl Med 2005; 46:2083–91.

[27] Kemp BJ, Kim C, Williams JJ, et al. NEMA NU 2-2001 performance measurements of an LYSO-based PET/CT system in 2D and 3D acquisition modes. J Nucl Med 2006; 47:1960–7.

[28] Matsumoto K, Kitamura K, Mizuta T, et al. Performance characteristics of a new 3-dimensional continuous-emission and spiral-transmission high-sensitivity and high-resolution PET camera evaluated with the NEMA NU 2-2001 standard. J Nucl Med 2006; 47:83–90.

[29] Bentourkia M, Laribi M, Lakinsky E, et al. Scatter restoration in PET imaging. IEEE Nuclear Science Symposium Conference Record 1992; 2:1075–9.

[30] Phelps ME, Cherry SR. The changing design of positron imaging systems. Clin Positron Imaging 1998; 1:31–45.

[31] Kinahan PE, Townsend DW, Beyer T, Sashin D. Attenuation correction for a combined 3D PET/CT scanner. Med Phys. 1998; 25:2046–2053.

[32] Burger C, Goerres G, Schoenes S, Buck A, Lonn AHR, von Schultess GK. PET attenuation coefficients from CT images: experimental evaluation of the transformation of CT into PET 511-keV attenuation coefficients. Eur J Nucl Med. 2002; 29:922–927.

[33] Xudong (Alan) Wang et al. CT Attenuation Correction in PET/CT Image Fusion. Diagnostic Imaging 2010.

[34] Hammer BE, Christensen NL, Heil BG. Use of a magnetic field to increase the spatial resolution of positron emission tomography. Med Phys 1994; 21:1917–20.

[35] Christensen NL, Hammer BE, Heil BG, et al. Positron emission tomography within a magnetic field using photomultiplier tubes and light-guides. Phys Med Biol 1995; 40:691–7.

[36] Raylman RR, Hammer BE, Christensen NL. Combined MRI-PET scanner: a Monte-Carlo evaluation of the improvements in PET resolution due to the effects of a static homogeneous magnetic field. IEEE Trans Nucl Sci 1996; 43:2406–12.

[37] Shao Y, Cherry SR, Farahani K, et al. Simultaneous PET and MR imaging. Phys Med Biol 1997; 42:1965–70.

[38] Slates R, Farahani K, Shao Y, et al. A study of artifacts in simultaneous PET and MR imaging using a prototype MR compatible PET scanner. Phys Med Biol 1999; 44:2015–27.

[39] Mackewn JE, Strul D, Hallett WA, et al. Design and development of an MR-compatible PET scanner for imaging small animals. IEEE Trans Nucl Sci 2005; 52:1376–80.

[40] Yamamoto S, Takamatsu S, Murayama H, et al. A block detector for a multislice, depth-of-interaction MR-compatible PET. EEE Trans Nucl Sci 2005; 52:33–7.

[41] Raylman RR, Majewski S, Lemieux SK, et al. Simultaneous MRI and PET imaging of a rat brain. Phys Med Biol 2006; 51:6371–9.

[42] Raylman RR, Majewski S, Velan SS, et al. Simultaneous acquisition of magnetic resonance spectroscopy (MRS) data and positron emission tomography (PET) images with a prototype MR-compatible, small animal PET imager. J Magn Reson 2007; 186:305–10.

[43] Lucas AJ, Hawkes RC, Ansorge RE, et al. Development of a combined microPET-MR system. Technol Cancer Res Treat 2006; 5:337–41.

[44] Handler WB, Gilbert KM, Peng H, et al. Simulation of scattering and attenuation of 511 keV photons in a combined PET/field-cycled MRI system. Phys Med Biol 2006; 51:2479–91.

[45] Dumouchel T, Bergeron M, Cadorette J, et al. Initial performance assessment of the LabPET APD-based digital PET scanner. [abstract]. J Nucl Med 2007;48:39P.

[46] Catana C, Wu Y, Judenhofer MS, et al. Simultaneous acquisition of multislice PET and MR images: initial results with a MR-compatible PET scanner. J Nucl Med 2006; 47:1968–76.

[47] Pichler BJ, Judenhofer MS, Catana C, et al. Performance test of an LSO-APD detector in a 7-T MRI scanner for simultaneous PET/MRI. J Nucl Med 2006; 47:639–47.

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Application of ^{18}F-FDG and PET/CT in Oncology

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Introduction

The first PET scanner in India began performing clinical studies in October 2002 at the Radiation Medicine Centre, BARC, and then the first PET/CT scanner commenced clinical operations from December 2004 at the adjoining major cancer hospital of the Tata Memorial Centre. With ^{18}F-fluorodeoxyglucose (FDG) as the primary PET pharmaceutical used, and the acceptance of the modality across the country, today there are about 100 PET/CT units performing clinical scans on patients using ^{18}F-FDG obtained from 20-odd medical cyclotrons. No other technology has made such an impact in clinical practice, as has been realised with FDG-PET/CT in oncology practice.

Principle of FDG-based Imaging

Metabolism in a biological site is the first to change before the cell undergoes changes like dysplasia, metaplasia or cancer. This is followed by structural changes. PET scan detects the disease at metabolic level. CT and MRI detect disease at structural level. Hence, functional or biological or metabolic or molecular imaging forms a very important and sensitive method of assessing cancer. Glucose, which is the main metabolic ingredient used by almost all cells, enters a cell by the mediation of GLUT (Glucose Transporter) receptors that are present in the cell wall. Inside the cell, it gets metabolised to glucose-6-phosphate, and subsequently gets metabolised through several pathways available in the cell, for production of energy or any other cellular activity. With the introduction of afluorine atom in the glucose molecule, it becomes fluorodeoxyglucose - FDG (as for example with a radioisotope of fluorine, ^{18}F-FDG), and which can enter the cell through the same GLUT pathway and be metabolised to FDG-6-phosphate. This product is unable to get metabolised further and hence remains trapped and accumulated in the cell. The ^{18}F label provides the positron signal to be detected by thePET scanner. Most cancer cells have an over-expression of GLUT receptors, and hence FDG accumulates much more significantly in cancer cells, and thuscancer sites can be detected by the PET scanner.

The last decade of the 20th century saw several developments in the image reconstruction techniques of the PET scan. It reached maturity with the attenuation correction using germanium-68 PET sources. A combination of the emission and transmission data provided the final image and hence, transformed itself into a clinical tool from merely being a research tool. However, the PET scan acquisition could take anywhere between 40-60 minutes and hence posed logistic and economic challenges. Long acquisition time also made itunacceptable and discomforting to many patients. With the addition of a CT scanner, the system could provide attenuation correction in a few seconds, and the CT images for side-by-side viewing, and also a fusion image consisting of both PET and CT. This PET/CT modality provided excellent localisation, superior anatomical information and morphological information. Hence, PET/CT increased accuracy by decreasing false positives and by better identification of physiological uptake. The acquisition time of the PET/CT scanner came down to less than 20 minutes and hence the procedure became more patient-friendly. Furthermore, the significant increase in the number of studies that could be done with the same amount of FDG, has rendered the modality to become more viable too. There has been significant improvement in the quality and sophistication of both PET and CT components of the scanner and the latest generation scanners offer advantages of performing scans with lesser amount of FDG, lesser absorbed radiation dose to patient, and faster acquisition times.

Information provided by FDG - PET/CT Studies

The FDG-PET/CT scan provides qualitative information and semi-quantitative measurements for SUV values. A CT provides morphological dimensions and attenuation factor as measurable data. With these parameters, one can assess response to treatment in oncology using established criteria like PERSIST, RESIST 1.1 and WHO criteria. Across the world, oncology indications constitute around 90-95% of all indications of FDG-PET/CT studies.

Clinical Role in Oncology

In oncology, staging, monitoring treatment response, restaging and suspected occurrence, and in a minority of cases, diagnosis form the indications of PET/CT. In diagnosis, solitary pulmonary nodule assessment is an important indication with a high negative predictive value. If positive, there is a need for biopsy. In the clinical condition called metastasis from unknown primary, a PET/CT scan identifies a primary in 33% of cases. Breast and thyroid nodules have been characterised as possible benign or malignant using FDG-uptake. However, microscopic disease will not be identified and the resolution of the lesion is around 3-7 mm depending upon the avidity of the uptake.

In staging of a tumour, the tumour, nodal, metastatic stage form the TNM staging criteria, which decides the treatment option in an evidence based practice. Regional contrast-enhanced CT or MRI is the standard of care for T staging. However, the FDG-PET/CT protocol can be tweaked to provide CECT information. PET/CECT is the most common and popular acquisition modality for all solid tumours. Since the nodal characterisation by PET as possible malignant does not depend on morphological criteria, the

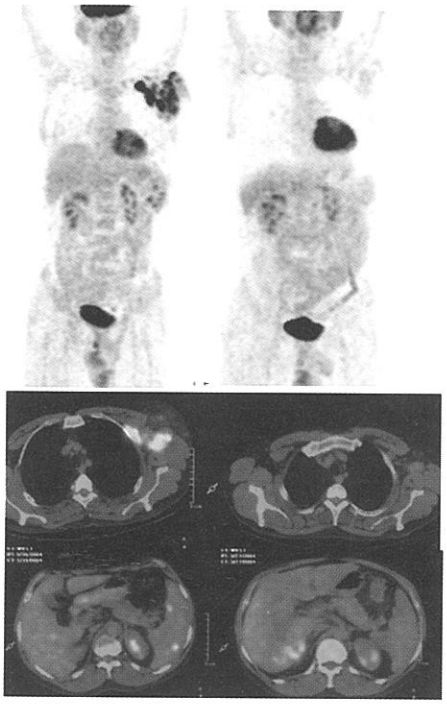

Fig. 1 A case of Non-Hodgkin's Lymphoma with disease in axilla; showing complete metabolic response, when evaluated with FDG-PET/CT after 3 cycles of chemotherapy.

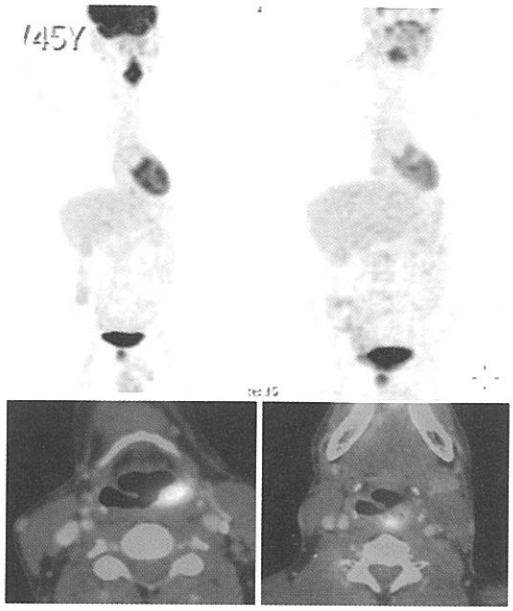

Fig. 2 Head neck cancer restricted locally. Post-chemo and radiotherapy FDG-PET/CT scan shows incomplete resolution. There is presence of residual disease.

nodal staging is more sensitive with PET. The accuracy of nodal staging with PET in most situations is better than a stand-alone CECT or MRI.

For the metastatic staging, since PET is a whole-body scan that looks at focal increased uptake of tracer in the body, the M stage accuracy is the highest with PET. In fact, it is this particular factor that causes change in treatment management in at least one third of all patients on whom PET/CT has been performed irrespective of the tumour type. As per the NOPR (National Oncological PET Registry, USA), in some situations like lung cancer, FDG-PET/CT demarcates the primary tumour from existing atelectasis and therefore significant change in the treatment volume if the patient underwent radiotherapy. It also identifies the cancer stage better and this stage migration due to the PET/CT scan has an overall impact in the treatment outcome in the patients. The whole body approach for metastatic screening has in fact identified metastasis in unusual sites and some of these patterns have helped understand the tumour better.

Treatment response evaluation imaging a patient in the middle of cancer treatment is like looking at 'half-filled glass'. It is now well-recognised in oncology that it is necessary to have complete knowledge of tumour burden and extent and staging at the beginning of the treatment, which serves as a reference for all future evaluations. As more and more tumours are being evaluated by FDG-PET, response to treatment evaluation is considered ideal when PET/CT is used. It helps to evaluate both the metabolic and morphological responses. Interim evaluation, or early response evaluation, helps to identify a responder and a non-responder. This helps in treatment planning, prognostication and tailored treatment, and avoidance of unnecessary treatment thereby reducing toxicity. This approach becomes even more important, when newer advanced therapies like targeted therapy are used, which are not only expensive, but may also be toxic. PET response evaluation hence helps in justifying such treatment approaches. The timing of investigation is important as treatment related changes due to surgery, radiotherapy or chemotherapy may cause false positives and decrease the accuracy of the scan.

To optimise and get the maximum from an investigation, the CT part of PET is fully tweeted and the patient prepared with oral and i.v. contrast. A combined approach using radiological criteria and nuclear medicine criteria gives fairly accurate result even in difficult clinical situations.

In spite of the best treatment given to a patient, by virtue of the biology of some tumours and the micro-metastatic spread, which cannot be detected by any modality, the patient may sooner or later present with a suspicious recurrence. Again, at this point of time, an entire whole body scan is required that would determine whether it is a locally-restricted disease or a disseminated disease. It has been proved by several studies that restaging using PET/CT provides the best accuracy impacting treatment and treatment-related expenses. Post-treatment, as there is a significant loss of symmetry and anatomy in areas like the head and neck, it becomes extremely difficult to recognise early recurrence using CT/MRI. FDG-PET/CT has brought about a paradigm shift in this context.

Limitation

There are several tumours which do not show adequate GLUT expression and hence do not show FDG uptake. Neuroendocrine tumours, mucinous and clear cell cancers and carcinoma of prostate are FDG-PET negative when well differentiated. However, with falling differentiation and rising undifferentiation, the tumour becomes PET positive. In these tumours, although better radiological accuracy is provided by CT or MRI, the flip-flop mechanism shows FDG-uptake as a bad prognostic indicator and suitable for certain targeted therapies.

False Positives

FDG uptake is also seen in infection and inflammation and this brings down the accuracy in certain situations. Reactive nodes and granulomatous (TB, sarcoidosis) nodes and lesions can co-exist with malignancy and metastatic sites. Although a biopsy and histopathological verification is the most accurate method, identifying differential metabolic response on FDG-PET scan to anti-infective treatment and/or anti-tumour treatment has emerged as an easy and effective tool to differentiate infection from malignancy.

Impact of Technology

FDG-PET has singularly made a huge impact in oncology. This is an evaluation of only one cellular metabolic pathway in a cancer cell, while there are several others which exist and radiopharmaceuticals specific for them have also been developed and are in clinical trial (another article in this bulletin is describing some of these products). FDG-PET/CT has proved to be an effective tool in the following cases: breast cancer-locally advanced and metastatic; all types of lymphomas; restaging treatment response and rising tumour marker in colorectal cancer; staging, restaging and treatment response in lung cancer, SCC of head and neck, melanoma.

Hybrid imaging - like PET/CT, SPECT/CT, PET/MR - isenhancing the impact in oncology. FDG-PET/CT based radiotherapy planning has been shown to significantly impact the treatment planning, in reducing treatment related complications in some cases, and in reducing inadequate treatment in some others. Metabolic biopsy or FDG-PET/CT guided biopsy significantly increases accuracy in the yield of representative tissue for biopsy.

In 2005, the Department of Nuclear Medicine of Tata Memorial Hospital (TMH) performed, on an average, 15 whole body PET scan studies in a day. By mid-2006, the references had increased exponentially so much,that there was a waiting period of 10 days for appointment,which increased further to a month in 2008. Consequently, a second PET scanner was added in 2010. The Department now performs 55 whole body scans on an average everyday. Across ourwhole country, around 1000 PET scans are being performed on a typical day. Truly ^{18}F-FDG-PET/CT has made a huge impact in oncology and delivering valuable support in the management of cancer patients.

Bibliography

[1] Purandare NC, Rangarajan V. PET-CT in oncology. J Postgrad Med. 2010, Apr-Jun;56(2):103-8. doi: 10.4103/0022-3859.65277. PubMed PMID: 20622389.

[2] Appropriate use of FDG-PET for the management of cancer patients. IAEA Human Health Series No: 9, 2010

[3] Rangarajan V, Purandare NC, Sharma AR, Shah S. PET/CT: Current status in India. Indian J Radiol Imaging. 2008 Nov;18(4):290-4. doi: 10.4103/0971-3026.43840. PubMed PMID: 19774183; PubMed Central PMCID: PMC2747449.

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PET and PET/CT: Applications beyond Oncology

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Keeping pace with PET-CT's utilization in various malignancies, the potential role of this powerful imaging modality has been explored in the investigation of a number of non-oncological disorders in various centres across the world. The applications can be enumerated under three principal domains: (A) Cardiovascular Disorders, (B) Neuropsychiatric Disorders, and the (C) Infection and Inflammatory Disorders (Table 1). Many of these have particular relevance to the developing world such as the infectious diseases and in addressing the increasing incidence of cardiovascular diseases globally due to changing lifestyle. Moreover, the recognition of immense potential of functional PET imaging in diagnosis of dementia, epileptic focus and psychiatric diseases, especially with the newer and novel PET tracers, cannot be overemphasized.

TABLE 1. Principal domains of non-oncological applications of PET with enumeration of the disorders

A.	**In Cardiovascular Diseases:**
1.	Assessing Myocardial Viability
2.	PET Perfusion Imaging: Importance of Flow Reserve
3.	Atherosclerosis Imaging
B.	**In Neuropsychiatric disorders:**
1.	Dementia
2.	Epileptic Focus Detection
3.	Parkinson's Disease
4.	Hyperkinetic Movement Disorders
5.	Psychiatric Diseases/CVA
C.	**In Infection and Inflammatory Disorders:**
	Pyrexia of unknown origin; Diabetic Foot; Periprosthetic Infection; Tuberculosis; Sarcoidosis; Vasculitic Disorders

The first two domains, namely, neuropsychiatric disorders and cardiovascular diseases, had been explored as its initial research and clinical applications, while the third domain has evolved in recent years, but had been one of the fastest and popularly growing applications of PET-CT imaging.

PET in Cardiovascular Diseases

"Hibernating myocardium" had been an important entity in the Cardiology practice, which represents that myocardium which is chronically ischemic and dysfunctional but is viable. This is thought to be an adaptive mechanism preventing irreversible myocardial damage, since myocardial and left ventricular dysfunction in hibernating myocardium improves, once the coronary blood flow is restored. Identification of hibernating myocardium can be done by several methods, but amongst the non-invasive methods, perfusion-metabolism imaging with incorporation of [^{18}F]FDG PET has been frequently considered as the gold standard for recognizing hibernating myocardium. By this method, PET (or SPECT) myocardial blood-flow, or the perfusion tracers can be utilized to identify ischemic segments at rest (popularly known as "fixed defects"), and corresponding segments are compared with the [^{18}F]FDG PET images for viable (hibernating) myocardium. [^{18}F]FDG is the most suitable metabolic tracer to study glucose metabolism in the hypo-perfused myocardial segments as these segments switch their metabolism from fatty acid to glucose, whenever there is reduction of blood flow to the myocardium. PET perfusion tracers score over SPECT perfusion tracers because of lesser attenuation problems, and also in terms of quantification of hypo-perfused segments. [^{13}N]-Ammonia ([^{13}N]NH_3) is the commonly used PET myocardial perfusion tracer at present in India. [^{99m}Tc]-MIBI is a most commonly used SPECT perfusion tracer, which can identify perfusion defects. The finding of a mismatch that is decreased perfusion on [^{13}N]NH_3-PET- or [^{99m}Tc]-MIBI SPECT, and retained metabolism on [^{18}F]FDG-PET is indicative of viable (hibernating) myocardium, while a match, that is decreased perfusion on [^{13}N]NH3-PET or [^{99m}Tc]-MIBI and decreased metabolism on a [^{13}N]NH_3-PET, is indicative of a scar. The examples are illustrated below in images Fig 1-6.

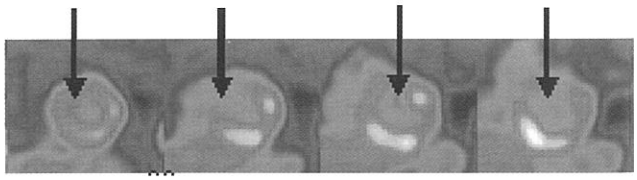

Fig. 1 ^{99m}Tc-MIBI perfusion images

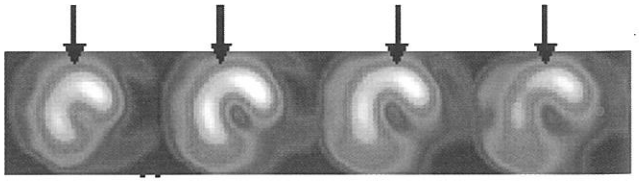

Fig. 2 ^{18}F-FDG metabolism images

Figures 1 and 2: ^{99m}Tc-MIBI images showing severe perfusion defects in the apical, mid and basal antero-septal segments of the myocardium with retained ^{18}F-FDG metabolism suggesting viable (hibernating) myocardium.

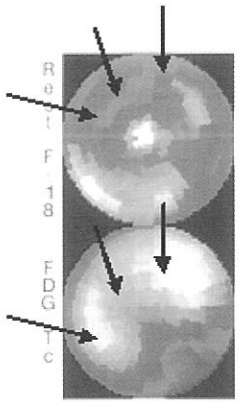

Fig. 3 Polar map showing both perfusion and metabolism images with evidence of viable myocardium

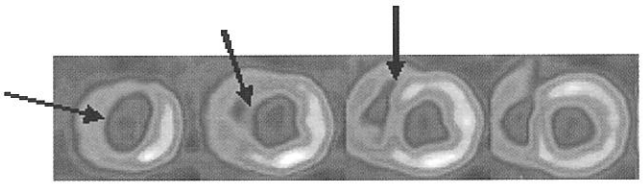

Fig. 4 ^{99m}Tc-MIBI perfusion images

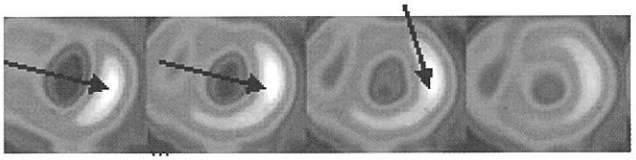

Fig. 5 ^{18}F-FDG metabolism images

Figures 4 and 5: [^{99m}]Tc-MIBI images showing severe perfusion defects in the apical, part of mid and basal antero-septal segments of the myocardium with insignificant FDG metabolism suggesting scarred myocardium

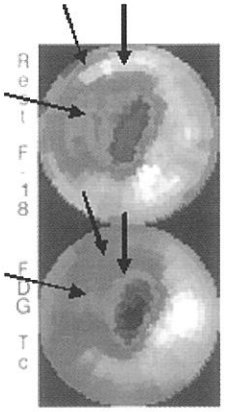

Fig. 6 Polar map showing both perfusion and metabolism images with evidence of scarred myocardium

The future potential: Coronary Blood Flow quantification and Myocardial Flow Reserve with PET Perfusion Tracers and Atherosclerosis Imaging

In the recent years, the possibility of coronary blood flow quantification with PET Perfusion Tracers ([^{13}N]-NH3 and [^{82}Rb]-RbCl) and thereby estimating myocardial flow reserve, and in turn, diagnosing micro-vascular dysfunction, and also, imaging molecular inflammation in atherosclerosis with [^{18}F]FDG-PET/CT imaging, and molecular calcification with [^{18}F]-fluoride (ahead of CT calcification), have generated significant interest in the Nuclear Medicine community. Absolute myocardial blood flow is altered in patients with micro-vascular dysfunction as well as in patients with diffuse and severe CAD. Both these approaches have the potential for early detection, but have not been yet utilized widely in the clinical domain.

PET in Neuropsychiatric Disorders

The potentially important areas of PET applications in the domain of neuropsychiatry include: differential diagnosis and evaluation of (i) dementia and its subtypes, (ii) detection of epileptic focus, (iii) Parkinson's disease (PD), and (iv) other hyperkinetic movement disorders.

Interictal PET, MRI and ictal SPECT all play important role in the pre-surgical localization of the epileptic focus in patients with refractory epilepsy. PET is likely to be the most useful in situations, where MRI is equivocal or normal, and PET abnormalities can be detected in upto 40% of patients with normal MRI. The best results have been obtained in temporal lobe epilepsy, for which metabolic abnormalities may be evident in as many as 90% of surgical candidates. Among the various seizure subtypes, complex partial seizures in a significant proportion of patients remain uncontrolled despite optimal medical therapy. Surgical removal of epileptogenic foci in intractable temporal lobe epilepsy results in significant improvement in control of the seizures and the quality of life. As much as 20–30% of potential surgical candidates with focal epilepsy have normal MRI. The main clinical uses of PET in epilepsy are localisation of epileptogenic foci in potential surgical candidates with partial seizures and corroborating findings from other investigational modalities such as electroencephalography (EEG). Interictal [^{18}F]FDG-PET typically shows decreased glucose metabolism and blood flow in the epileptogenic focus. Incorporation of [^{18}F]FDG-PET into the evaluation of children with infantile spasms has resulted in identification of a substantial number of children who could benefit from cortical resection. [^{18}F]FDG-PET has revealed marked focal cortical glucose hypo-metabolism associated with malformative or dysplastic lesions that are not evident on anatomic imaging.

[^{18}F]FDG-PET has a sensitivity of 93% and specificity of 76% in identifying dementias, while evaluating patients with cognitive impairment. For Alzheimer's disease (AD), the sensitivity is 94% and specificity is 73%, respectively, with typical metabolic pattern. The characteristic temporo-parietal glucose hypometabolism in early stage of AD can aid in the preclinical diagnosis and hence, can be useful in screening of AD in high risk groups of asymptomatic patients, such as asymptomatic carriers of the apolipoprotein E type 4 allele, who are at increased risk for familial AD. A negative [^{18}F]FDG-PET potentially rules out a pathologic progression of cognitive impairment. On the

other hand, vascular dementia is characterized by scattered areas with reduction in regional cerebral glucose metabolism extending over cortical and subcortical structures. In dementia with Lewy bodies (DLB), [^{18}F]FDG-PET reveals changes similar to those seen in AD, plus additional hypometabolism in the visual primary and associative cortices.

[^{18}F]-6-Fluorodopa ([^{18}F]-DOPA) is one of the most promising and effective tracers for studying the dopaminergic system in movement disorders. In the early stage, there is reduced putamen dopaminergic terminal function (particularly the posterior putamen contralateral to the affected limbs). There is relative preservation of the head of caudate and ventral striatal function. The [^{18}F]-DOPA uptake in the putamen correlates inversely with bradykinesia and rigidity of PD patients. [^{18}F]-DOPA uptake features, though can be used with high sensitivity for detecting atypical Parkinsonian syndromes, they demonstrate limited specificity for discriminating them from typical PD. The typical pattern of loss of dopaminergic function in PD is less evident in progressive supranuclear palsy and corticobasal degeneration; among these, progressive supranuclear palsy shows more symmetrical pattern of nigrostriatal dysfunction than in other Parkinsonian syndromes. Measurements of resting glucose metabolism with [^{18}F]FDG-PET can be of value: typical idiopathic PD demonstrates preservation of lentiform nucleus glucose metabolism, unlike most atypical parkinsonian syndrome patients, where it is reduced.

Similarly, multiple studies have found reduced striatal D_2 binding and glucose metabolism in the Huntington's disease carriers, which could be useful in identifying carriers nearing the onset of disease. Intervention at the early stage of the disease (neuro-protective agents) may be of greater benefit than treatment in later stages.

PET in Drug Abuse, Depression and Schizophrenia

PET has been proposed to be very useful for studying cocaine abuse (DAT blockade by inhibitors has been postulated as an important step for drug development), depression (through quantification of 5-HT_{2A} receptors selective 5-HT_{2A} antagonists such as [^{18}F]-altanserin, and [^{18}F]-setoperone), and in schizophrenia (reduced benzodiazepine receptor binding in limbic cortical regions and psychotic symptoms).

Research Endeavours of PET in Neuropsychiatric Disorders

Receptor Based PET Imaging in Epilepsy

γ-Aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the brain, acting at up to 40% of synapses. A decreased number of GABAergic inhibitory interneurones was found in epileptogenic cortex. Flumazenil (FMZ) is a specific reversible antagonist that binds to the benzodiazepine binding site of the $GABA_A$– central benzodiazepine receptor complex. [^{11}C]-FMZ PET therefore provides an in vivo marker of $GABA_A$ receptor binding. [^{11}C]-FMZ binding is reduced by 30% in epileptogenic foci. Relative increases in uptake of [^{11}C]-carfentanil, a selective mu opiate receptor agonist, and [^{11}C]-deuteriumdeprenyl, an irreversible inhibitor of monoamine oxidase type B (MAO-B), have also been described.

Receptor Based PET Imaging in Stroke

PET imaging has been utilized in identification of viable penumbra in acute ischemic stroke, to differentiate irreversible tissue damage from viable penumbra tissue, as irreversibly damaged areas cannot benefit from reperfusion therapy (thrombolysis). Central benzodiazepine receptor ligands such as ^{11}C-flumazenil (FMZ) are markers of neuronal integrity and therefore have been found to be useful in differentiation of functionally and morphologically damaged tissue early in ischemic stroke.

Monitoring Treatment Effect in AD

[^{18}F]FDG-PET before and after treatment with donepezil or rivastigmine has been proposed to be helpful in assessing the treatment benefits.

Newer PET Tracers and approaches in AD imaging

In vivo imaging of β-amyloid plaques in AD: Specific ligand for β-amyloid plaques may further enhance the sensitivity of PET for early diagnosis of AD and provide a biological marker of disease progression. Three ^{18}F radiolabeled heterocycles have been explored as PET tracers for imaging β-amyloid plaques in Alzheimer's disease: [^{18}F]3'-F-PIB (flutemetamol), ^{18}F]AV-1 (florbetaben) and [^{18}F]AV-45 (florbetapir).

In-vivo imaging of Activated Microglia in AD

It has been proposed that activated microglia plays an important role in the pathogenesis of neurodegenerative diseases such as AD by mediating neuro-inflammation. [^{11}C](R)-PK11195 is a selective ligand for the peripheral benzodiazepine binding sites (PBBS). PBBS are present in the normal brain at very low levels, but they are selectively expressed and upregulated by activated microglia. [^{11}C](R)-PK11195 PET in AD patients showed increased binding in the entorhinal, temporoparietal and cingulate cortices, corresponding to postmortem distribution of AD pathology. This approach has been proposed to be deployed to monitor disease activity in the many proposed and ongoing neuro-protective studies in AD using anti-inflammatory agents.

PET-CT in Infectious and Inflammatory Disorders

Over the past 5-10 years, [^{18}F]FDG-PET/CT has fast evolved as a promising diagnostic modality for assessing several inflammatory and infectious diseases. This has direct and important relevance in the day-to-day clinical practice, especially in developing countries including the Indian scenario. Recent studies have shown that [^{18}F]FDG-PET has

high diagnostic sensitivity in detecting active inflammation and has been investigated in the following infectious and non-infectious inflammatory disorders:

1. Pyrexia of unknown origin (PUO),
2. Chronic osteomyelitis,
3. Complicated diabetic foot,
4. Complicated lower limb prostheses,
5. Acquired immunodeficiency syndrome (AIDS),
6. Vascular graft infection and fistula and
7. Granulomatous infectious conditions (e.g. sarcoidosis, tuberculosis).

Among these, the strongest application appears to be evaluation of fever of unknown origin (FUO), which forms now a Cochrane B indication for application of [^{18}F]FDG-PET/CT. Amongst the non-infectious inflammatory conditions, the areas where promise has been demonstrated include: (a) large-vessel vasculitis, (b) inflammatory bowel disease, (c) sarcoidosis, and (d) inflammatory arthritis. Promising results have been obtained in Rheumatoid arthritis for assessing response to disease-modifying antirheumatic drugs, DMARDs. A number of advantages exist with [^{18}F]FDG-PET/CT, compared to the conventional radiolabeled leucocyte imaging. These include: Securing results within a short period of time (1.5-2 h); Superior-resolution tomographic images; High target-to-background ratio; Sensitive in chronic infections; Technically less demanding and less labour-intensive, all-in-one technique, no requirement of additional scans; High inter-observer agreement; Useful in detecting uptake in the axial skeleton, an area where WBC scanning is of limited value.

In addition to detection and diagnosis, a major area of interest and advantage of functional imaging is early assessment of treatment response. This is extremely important in a number of these disorders, where diagnosis of drug resistance is of pivotal importance. In addition to analysis, with regular semi-quantitative SUV values, global metabolic burden are frequently available in the current generation PET-CT scanners. The PET-CT response forms a valuable adjunct to the other clinical response parameters in multiple conditions and correlates well with the change in clinical response after treatment. It is imperative from the preliminary results that, the impact of [^{18}F]FDG-PET/CT results on decision making of treatment and long-term outcomes in this group of patients holds substantial promise to be incorporated in the management algorithm of these diseases.

RMC's PET Service to Patients

During the past several years, RMC has handled over 25,000 PET and PET-CT studies, of which at least 7,000 belonged to cases of patients with one or more of the disorders described in this article. RMC has rendered valuable support to the referral physicians in their management planning and/or monitoring strategies. Similarly, other leading NM Centres, as for example, AIIMS, have been providing services to such patients. In the current times of emphasis on 'evidence-based-medicine' and 'personalized treatment' of patient, PET-CT role will only continue to grow and play increasingly crucial roles in future.

Bibliography

[1] McArdle B, Dowsley TF, Cocker MS, Ohira H, deKemp RA, DaSilva J, Ruddy TD, Chow BJ, Beanlands RS. Cardiac PET: metabolic and functional imaging of the myocardium. Semin Nucl Med. 2013 Nov;43(6):434-48.

[2] Danad I, Raijmakers PG, Knaapen P. Diagnosing coronary artery disease with hybrid PET/CT: it takes two to tango. J Nucl Cardiol. 2013 Oct;20(5):874-90.

[3] Tatsch K, Ell PJ. PET and SPECT in common neuropsychiatric disease. Clin Med. 2006 May-Jun; 6(3):259-62.

[4] Basu S, Chryssikos T, Moghadam-Kia S, Zhuang H, Torigian DA, Alavi A. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. Semin Nucl Med. 2009 Jan;39(1):36-51.

[5] Basu S, Asopa RV, Baghel NS. Early documentation of therapeutic response at 6 weeks following corticosteroid therapy in extensive sarcoidosis: promise of FDG-PET. Clin Nucl Med. 2009 Oct; 34(10):689-90.

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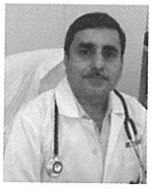

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Production of ^{64}Cu and ^{124}I and their Applications in Nuclear Medicine

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Introduction

Positron Emission Tomograpy (PET)has revolutionized the field of Nuclear Medicine in the past two decades with a large number of medical cyclotrons installed and advances in the imaging technology. PET has become an invaluable tool in diagnostic nuclear medicine, especially in cancer management, owing to the excellent high resolution images,especially in combination with the CT. PET tracers prepared from the traditional positron emitters, mainly ^{18}F and at times ^{11}C, have witnessed a steady steep growth. While the use of these tracers of short half-lives continues to remain vital, they are not suitable for certain investigations of slow biochemical pathways, or assess patient suitability for treatment with molecules such as expensive antibodies.A suitable positron emitting radioisotope with a longer half-life would allow PET evaluation of biochemical path ways too slow to be analysed using short-lived positron emitting radionuclides. In addition, the longer half-life is compatible with the time scales required for the optimal bio-distribution of slower clearing agents, such as monoclonal antibodies (mAbs), nanoparticles, and higher molecular weight polypeptides that require longer imaging times. The adequately long half-life also allows the user hospitals to avail more facile access from a production facility that may be located at some farther distance. This has led to a re-look at the longer-lived positron emitters, and in this pursuit, ^{64}Cu, ^{124}I and ^{89}Zrhave drawn considerable attention [1-4]. Of these, the first two have been investigated more extensively, while the potential of ^{89}Zr for wider use is yet to be proven.

^{64}Cu and ^{124}I are quite different in their chemistry, while they have similar multiple-decay mode, which would help widen the scope of their use beyond PET imaging. Multiple radioisotopes of these two elements are used or usable in nuclear medicine -^{131}I, ^{125}I and ^{123}I for iodine; ^{67}Cu, ^{62}Cu and ^{61}Cu for copper.Owing to the emission of beta particles/Auger electrons along with positrons, both ^{64}Cu and ^{124}I have potential for therapeutic application in addition to PET imaging. Moreover,these two positron emitters can be produced in small medical cyclotrons (MC) used for production of traditional PET radioisotopes, making them attractive for exploring their use as 'theranostic' (useful in both diagnosis and therapy) radioisotopes. This article briefly describes the salient aspects in the production of these two positron emitters, their chemistry and the current status of applications of PET tracers derived from them.

^{64}Cu

^{64}Cu ($t_{½}$ = 12.7 h) is one of the rare radioisotopes, where all the three beta decay modes, namely, EC (45%), β^+ emission (17.9%), and β^-emission(37.1%) coexist. As a result of this, ^{64}Cu has potential use in both PET diagnostic imaging, as well as in therapy, the latter being enabled by Auger electrons (more efficient in cell killing) associated with electron capture decay of ^{64}Cu. Above all, the advantageous chelating chemistry of copper makes ^{64}Cu useful for labeling biomolecules through formation of stable complexes with bifunctionalchelatorslike cyclic polyamines (cyclam) and cyclic polyaminocarboxylates (denoted as DOTA,TETA, NOTA).

Production of ^{64}Cu

^{64}Cu can be produced in a nuclear reactor or in a cyclotron. Table-1summarises different routes of practical production of ^{64}Cu. It is evident that ^{64}Cu produced through $^{63}Cu(n,\gamma)^{64}Cu$reaction in a nuclear reactor results in very low specific activity,unsuitable for labeling antigen or receptor-based ligands as targeting compounds.The production route through $^{64}Zn(n,p)$ ^{64}Cu reaction using fast neutrons gives ^{64}Cu of high specific activity (>100 mCi/μg Cu), but access to fast neutron irradiation is limited in most reactors. A look at the excitation function curve for the reaction $^{64}Zn(n,p)^{64}Cu$ indicates the threshold for the reaction to be around 2 MeV, while the maximum cross-section is obtained with 10 MeV neutron. Thus the yield of $^{64}Cu$with fast neutrons (e.g. from aspallation source) would be appreciably higher than that from the present day fission reactors [5].

At present, the most common production method for ^{64}Cu (Table 1) is$^{64}Ni(p,n)^{64}Cu$ reaction in medical cyclotron, using enriched ^{64}Ni target, electroplated onto a gold disk[6]. This method is especially attractive as many medical cyclotrons (11-18 MeV proton machines) are operational throughout the world, including in India. The use of minimal amount of enriched target material not only makes the production more cost-effective, but also yields a product of higher specificactivity.Bombardment for 3–4 h at 30 μA resultsin300-500 mCi of ^{64}Cu with a specific activity of 94-310 mCi/μg Cu.Chemical separation of ^{64}Cu is relatively simple. Irradiated ^{64}Ni is dissolved in 6M HCl and loaded on ananion exchange resin column. While ^{64}Ni is not retained in the column, ^{64}Cu is eluted from the column with water. The ^{64}Ni containing fraction in the void volume is preserved for recovery of enriched ^{64}Ni, which has been reportedly recovered to the extent of 85-95%.

^{64}Cu Radiopharmaceuticals

Copper,a transition metal,exhibits oxidation states I, II and III, and its coordination chemistry has been well established. Copper predominantly exists in I and II valence states and forms coordinated complexes with a variety of

TABLE 1. ^{64}Cu production routes

Route	Target	Projectile energy	Yield	Reference
^{64}Ni(p,n)^{64}Cu	95% Enriched ^{64}Ni	11-18 MeV	2.3-5 mCi/μAh	6
^{63}Cu(n,ã)^{64}Cu	Enriched ^{63}Cu	Thermal neutron	85 mCi/mg of ^{63}Cu in 1d irradiation at 10^{14} n.s^{-1}.cm^{-2}	7
^{64}Zn(n,p)^{64}Cu	Enriched ^{64}Zn	Fast neutron in fission reactor	few hundred mCi per batch 50 μCi/mg of ^{64}Zn in 1d irradiation at 10^{14} n.s^{-1}.cm^{-2}	8 7

molecules that could be of relevance to radiopharmaceuticals science [9]. While Cu(I) complexes are labile and lack kinetic stability, Cu(III) complexes are formed only with the use of strong π-donating ligands. On the other hand Cu(II) complexes are less labile than Cu(I) and are found to be kinetically stable in vivo. Consequently, development of ^{64}Cu(II) complexes for radiopharmaceutical applications has been an active area of research. Molecules having moieties such as amines, imines, and bidentate ligands such as bipyridine form complexes of square planar, distorted square planar, trigonal pyramidal, square pyramidal, as well as distorted octahedral geometries.Copper chelates with acyclic polyaminocarboxylates lack in vivo stability and hence are unsuitable for preparing ^{64}Cu-radiopharmaceuticals [10].However, several cyclic bifunctional chelating agents have been found to form stable complexes with Cu(II). The most widely studied and successful bifunctional chelating agents include different derivatives of cyclic polyamines (cyclam) and cyclic polyaminocarboxylates (DOTA,TETA etc.) (Fig. 1). Suitable derivatisation of these ligands enables one to conjugate them tobiological targeting molecules,such as antibodies, proteins, and peptides to make ^{64}Cu radiopharmaceuticals.It has been reported that among the various cyclic polyaminocarboxylate complexes with ^{64}Cu, TETA forms complexes with higher in vivo stability than the others [11,12]. It has been further observed [13] that cross-bridged derivatives of DOTA and TETA (abbreviated as H_2CBDO2A and H_2CBTE2A, Fig. 1) form complexes with Cu(II), which are kinetically more stable in solution, compared to DOTA or TETA respectively, making these moieties better suited for use in radiopharmaceuticals.

^{64}Cu has also biological specificity in its different chemical forms, even without being linked to a separate biological carrier molecule, such as an antibody or a peptide. The biological behaviour of such radiopharmaceuticals depends on the chemical form of copper itself. For example, bis-thiosemicarbazones, are known to possess anti-tumour activity,which is markedly enhanced by co-administration with copper (with which stable square-planar copper-II is formed) complexes. Both the ligand and the complex being

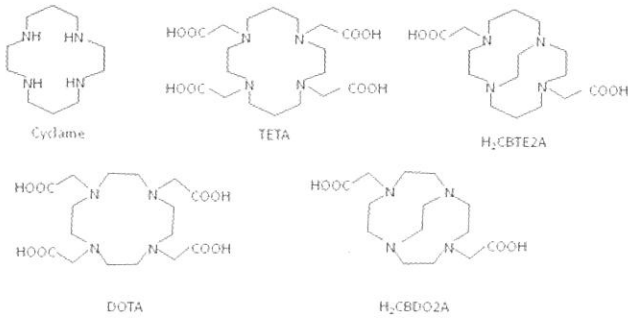

Fig. 1 Structure of few cyclic bifunctionalchelating agent with which C(II) forms stable complex.

lipophilic freely diffuse across the cell membrane and dissociate when inside the cell. As a result, 95% of ^{64}Cu dissociated from the complex remains cell-bound without specificity for subcellular compartments. Among various bis-(N^4-methylthiosemicarbazone) derivatives, the ^{64}Cu complex with pyruvaldehydebis-(N^4-methylthiosemicarbazone) (PTSM) (Fig. 2) has been shown toexhibit this property to the maximum extent. This makes [^{64}Cu]PTSM, a PET radiopharmaceutical, suitable for quantification of myocardial, cerebral, renal, and tumor blood flow [14].

Another Cu-64-labeled thiosemicarbazone, diacetyl-bis(N4-methylthiosemicarabazone) (Cu-64-ATSM) (Fig. 2) has been used widely for imaging hypoxia in tumours/other lesions [15,16]. It is known that tumour hypoxia indicates poor prognosis for treatment and contributes strongly to poor response to radiotherapy. Therefore,hypoxia imaging in cancer helps to predict response to radiotherapy, identify hypoxic regions within tumours requiring higher radiation doses, and to locate tumours that may otherwise be not visible using conventional radiopharmaceuticals. Non-invasive identification of hypoxic regions could improve the outcome by use of intensity modulated radiotherapy (IMRT). Targeting hypoxiais also considered a new modality for targeted radionuclide therapy. In non-cancer applications,hypoxia imaging is useful in neurological and cardiovascular disorders.It may be noted that the studies began with ATSM, and in the course of time,several analogs

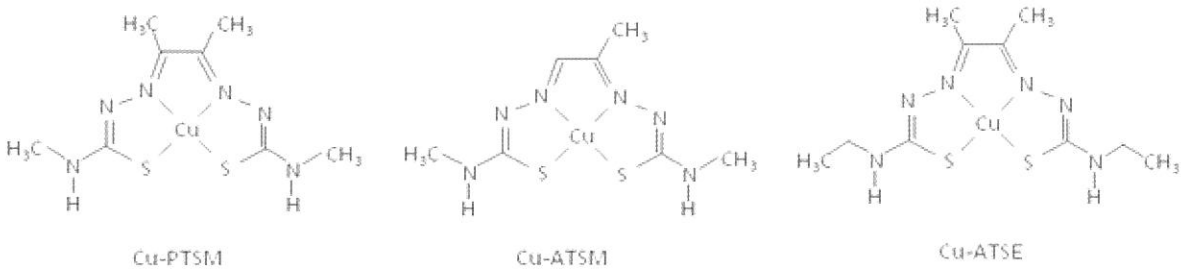

Fig. 2 Structure of few complexes of Cu(II) with bis-thiosemicarbazones

TABLE 2. Applications of a few ^{64}Cu radiopharmaceuticals

Radiopharmaceuticals	Application	Clinical Use references
[^{64}Cu]ATSM ([^{64}Cu]-diacetyl-bis(N4-methylthiosemicarbazone))	Hypoxia imaging	15, 16
[^{64}Cu]PTSM ([^{64}Cu]-pyruvaldehyde bis-(N^4-methylthiosemicarbazone))	Quantification of myocardial, cerebral, renal, and tumor blood flow	14
[^{64}Cu]Octreotide	imaging & therapy of tumours over-expressing somatostatin receptor on cell surface	22
[^{64}Cu]RGD peptide	imaging & therapy of tumours with upregulated $\alpha_\upsilon\beta_3{}^\circ$ integrin	21
[^{64}Cu] chloride	imaging & therapy of tumors; glioblastomas, prostate cancers	17,18 ,19 ,20

of ATSM have been studied in vitro with many of them exhibiting hypoxia selectivity. It has been found that, in comparison with [^{64}Cu]ATSM, [^{64}Cu] ATSE (Fig. 2) fared better with higher uptake in tumour,and lower accumulation in liver and kidney.

An interesting development in the recent years is the use of ^{64}Cu in the form of simple inorganic form Cu(II)chloride to image and treat cancerous tissues. A recent paper discusses [17] the possible role of Cu(II) in tumour accumulation. Impressive images and therapy efficacy results have been reported [18-20], making this an attractive molecule to pursue further.Currently five clinics in Italy are carrying out investigational clinical studies with Cu-64 chloride and have treated patients with prostate cancer, breast cancer and melanoma. Thus far, 150 patients have been treated (50 under each type) successfully.

An example of a biomolecule that could have potential for labelling with ^{64}Cu is $\alpha_\upsilon\beta_3{}^\circ$ integrin, which is upregulated in endothelial cells involved in active angiogenesis but not in quiescent endothelial cells, which makes it an ideal biomarker for angiogenesis and tumor imaging. Glioblastomas, breast and prostate tumors, malignant melanomas, and ovarian carcinomas are found to overexpress $\alpha_\upsilon\beta_3{}^\circ$ integrin and have been targeted with ^{64}Cu labeled RGD peptide (peptides having the three-amimo-acid sequence, arginine-glycine-aspartic acid) [21].

^{64}Cu radiopharmaceuticals are gaining a worthy role in the PET imaging and targeted therapy. Currently, there are few applications in medicine, but numerous ongoing studies will most likely result in novel use in the future. A list of potential ^{64}Cu radiopharmaceuticals and their applications is given in Table 2.

^{124}I

^{124}I decays with a half-life of 4.2 days, both by positron emission (23%) and electron capture (77%), followed by the emission of a large number of high-energy gamma photons 603 keV(61%), 723 keV(10%), and 1691keV(10.5%), in addition to 511 keV annihilation photons. The high energy gamma rays (comparable to that of ^{131}I),as well as the copious Auger electrons resulting from the electron capture decay,permit its use as a therapeutic nuclide, in addition to its

TABLE 3. Major routes of ^{124}I production methods

Route	Target	Projectile energy, MeV	Thick target yield mCi/μAh	Reference
$^{124}Te(p, n)$	Enriched $^{124}TeO_2$ with 5% Al_2O_3	11-14	0.157-0.57	23, 24, 25, 26
$^{124}Te(d, 2n)^{124}I$	Enriched $^{124}TeO_2$	14-16	0.47	27, 28
$^{121}Sb(\alpha, n)^{124}I$	Enriched ^{121}Sb	22→13	0.057*	29

*Based on experimental cross section data

role as diagnostic radionuclide. There latively low percentage of β^+ emission and high energy gamma ray emission, are somewhat less attractive for use in PET imaging. This, taken along with the cost and logistics concerns in using extremely high purity target for production, has invariably led to lack of commercial availability and regular use of ^{124}I radiopharmaceuticals, although many products have been studied since several decades. In recent times, interest in ^{124}I has been revived, due to increasing use of PET/CT and availability of a large number of medical cyclotrons for production of PET tracers and the scope for utilizing the relatively long-lived PET radionuclides. More importantly, the use of radioiodine compounds and their labeling chemistry are so well-established that a variety of compounds are available with potential for PET imaging studies. These advantageous attributes make ^{124}I a suitable radioisotope for PET applications, despite some limitations of its nuclear properties.

Production of ^{124}I

^{124}I is produced in cyclotron by irradiation of enriched tellurium-124target with proton beam, while it can also be produced with deuterons, or using antimony target and $^3He/\alpha$ beam. Use of highly enriched target is an imperative need to obtain ^{124}Iproduct of acceptable radionuclidic purity. Presence of co-produced $^{123}I/^{125}I/^{126}I$ impurity impacts the radionuclidic purity of the product and its useful shelf-life. Major routes of production, which would yield the required purity of ^{124}I are outlined in Table 3.Production through the antimony target results in lower yield of ^{124}I. $^{124}Te(p,n)^{124}I$ route offers the highest level of ^{124}I purity at the envisaged time of administration, though higher yield of ^{124}I can be obtained through $^{124}Te(d,2n)$ reaction. $^{124}Te(p,n)^{124}I$ reaction has gained popularity, as this route offers the option of ^{124}Iproduction in a large number of available medical cyclotrons deployed for producing mostly ^{18}F, and at times ^{11}C.

TeO_2 with 5% Al_2O_3 is used as target for irradiation to increase the uniformity of the target material, giving a glassy solid structure and enhanced adherence of the target layer with the target plate, usually made from platinum. ^{124}I is most often separated from the irradiated target by dry distillation. In this method the irradiated target is heated to about 750°C in a flow of a gas (mostly O_2). Volatile ^{124}I is swept away by the carrier gas and finally trapped in a small volume of dilute NaOH solution. An advantage of this method is that there is generally no need for additional step for the recovery of the enriched ^{124}Te from the irradiated target;the same target may be irradiated repeatedly for production of ^{124}I [23].

^{124}I Radiopharmaceuticals

One of the earliest radioisotopes used in nuclear medicine is of the element iodine, namely, ^{131}I. Chemistry of iodine and radioiodination reactions has thus been extensively studied for over half a century and reviewed thoroughly [30]. Nucleophilic and electrophilic substitution reactions are generally used in synthesis of radioiodine labeled radiopharmaceuticals.The low stability of the carbon-iodine bond may result in substantialdeiodination in vivo, which in turn,would lead to accumulation of radioiodidein thyroid and stomach. Aromatic carbon-iodine bond is more stable than aliphatic carbon-iodine bond, and for this reason, aromatic or vinyl carbon is usually preferred for radioiodination and preparation of the corresponding radiopharmaceuticals.

In nucleophilic substitution,halogen exchange reactions are most commonly used for introduction of radioiodine into organic molecules. However, this exchange reaction proceeds slowly with aromatic compounds. To accelerate the exchange reactions in aromatic compounds, various metal-assisted reactions have proved to be quite successful. For example, copper(I) salt is added in the preparation of [^{124}I]m-Iodobenzylguanidine (MIBG).

The ease of oxidizing iodide into an electrophilic form of iodine makes electrophilic labeling the most frequently employed radioiodination method. In this method radioiodide is oxidized in situ to a positively charged iodine (I^+) species by means of anoxidizing agentsuch asICl, chloramines T, N-chlorosuccinimide or enzymes (e.g. lactoperoxidase).Electrophilic radioiodination on an aromatic system can be performed directly or by means of various demetallation techniques.Radioiodination of

TABLE 4. Few ^{124}I radiopharmaceuticals and their applications

Radiopharmaceuticals	Application	Clinical use references
[^{124}I]-mIBG (^{124}I-metaiodobenzylguanidine)	Cardiovascular imaging, diagnosis& dosimetry of neuroblastoma, paraganglioma, pheochromocytoma, carcinoids	31, 32
[^{124}I]-cG250 (^{124}I labelled antibody chimericG250	To identify renal cell cancer	33
[^{124}I]IAZG (^{124}I-iodine azomycin galactoside)	Imaging of hypoxia in tissue	34
[^{124}I]IUdR (5-[^{124}I]Iodo-2 -deoxyuridine)	Functional imaging of cell proliferation	35
[^{124}I]Annexin V	Apoptosis imaging	37
[^{124}I]βCIT ([^{124}I]-β-carbomethoxy-3β(4-iodophenyl) tropane)	Early diagnosis of Parkinson's disease	38
[^{124}I]NaI	PET imaging of thyroid and thyroid diseases; for evaluating spread of metastatic thyroid carcinoma	
[^{124}I]fatty acid	PET imaging of myocardial metabolism, marker of viability	-

peptides and proteins proceeds through the incorporation of radioiodine in the tyrosine (or histidine) residues.

A list of some the promising ^{124}I radiopharmaceuticals is given in Table 4.[^{124}I]NaI, the simplest radiopharmaceutical of ^{124}I, is potentially useful for diagnosis of thyroid-related disorders. [^{124}I]-m-iodobenzylguanidine ([^{124}I]-MIBG) has potential for use in cardiovascular imaging[31,32], as well as indiagnosis and dosimetry for management of malignancies such as neuroblastoma, paraganglioma, pheochromocytoma, and carcinoids, for subsequent treatment using the established product ^{131}I-MIBG or the potential of ^{124}I-MIBG.

When the radioiodinated pharmaceuticals, prepared from monoclonal antibodies, receptors or other molecules are intended for quantitative imaging of tissue,which may require several days of imaging protocol, ^{124}I is the most suited candidate. Thus various [^{124}I]mAbs are being used in immuno-PET imaging of specific tumours in oncology.

[^{124}I]Iodo-azomycin-galactopyranoside([^{124}I]IAZG) has been reported as a potential hypoxia imaging agent [34]. However, considerable deiodination of the tracer followed by uptake in the thyroid was noted, which could be avoided by suitably blocking the thyroid.

Imaging of tumor proliferation helps to evaluate the tumor growth and to estimate its malignancy grade.For imaging of tumor proliferation, the approach is to incorporate suitable radiolbelled DNA analogs in the replicated DNA strand in the proliferating tissue. Such an agent should have adequately long half-life and resistance to in-vivo degradation. 5-[^{124}I]Iodo-2-deoxyuridine ([^{124}I]IUdR) is one such analog developed [35] that is under investigation for imaging of tumor proliferation. However, the main limitation in this approach is the in-vivo deiodination of the radiotracer.

Apoptosis can be observed in a wide variety of malignant tumors, particularly in hypoxic zones adjoining areas of necrosis. Imaging of apoptotic cells would be of great help in cancer therapy management. It has been reported [36] that phosphotidylserine, a phospho-lipid is translocated to the external leaflet in the apoptotic cells. Phosphatidylserine is therefore targeted for imaging apoptosis. ^{124}I labeled AnnexinV has been studied for imaging apoptosis [37].

Monoclonal antibodies(mAbs), which allow targeting of cancer tissues with great specificity are being increasingly used for radiolabelling, including with ^{124}I, for preparation of radiopharmaceuticals. I-124-labelled antibody chimericG250, [^{124}I]-cG250, a potential immuno-PET

imaging agent, can identify accurately renal cellcarcinoma, the most common and aggressive renal tumor.

Conclusion

A large volume of research is currently being carried out all over the world in the quest for ideal radiopharmaceuticals for use in nuclear medicine to manage various diseases/disorders, especially cancers and neurological disorders, wherein PET radiopharmaceuticals occupy a prominent place. The advantages of ^{64}Cu and ^{124}I described in this article, such as amenable/versatile chemistry and scope for wide availability and usage across the world, have led to revived interest in the development of promising radiopharmaceuticals using these radionuclides. Among the explored products of ^{64}Cu and ^{124}I, and of other similar radionuclides, some have already entered the clinics for evaluation and/or regular use. However, all of them may not find their way into clinics. It is yet expected that many more of the products under investigation would make their mark in nuclear medicine practice in foreseeable future.

References

[1] Koehler, L., Gagnon, K., McQuarrine, S., Wuest, F., (2010). Iodine-124: a promising positron emitter for organic PET chemistry. Molecules Apr 13,15(4), 2686-718.

[2] Rice, S.L., Roney, C.A., Daumar, P., Lewis, J.S. (2011). The next generation of positron emission tomography radiopharmaceuticals in oncology. Semin. Nucl. Med. Jul, 41(4), 265-82.

[3] Artor Niccoli Asabelia, Giuseppe Lucio Cascini,Corinna Altini, Domenico Paparella, Antonio Notaristefano, and Giuseppe Rubini. (2014). The Copper Radioisotopes: A Systematic Review withSpecial Interest to ^{64}Cu. Bio. Med. Research International; Volume 2014, Article ID 786463,

[4] Williams, H. A., Robinson, S., Julyan, P., Zweit, J., Hastings, D. (2005). A comparison of PET imaging characteristics of various copper radioisotopes. Eur J. Nucl. Med. Mol. Imaging 32:1473–1480.

[5] Al-Abyada, M.,Spahn, I., Sudaà, S., Morsy, M.,Comsan,M.N. H.,Csikai, J., Qaim, S.M., Coenen,H.H. (2006). Nuclear data for production of the therapeutic radionuclides ^{32}P, ^{64}Cu, ^{67}Cu, ^{89}Sr, ^{90}Y and ^{153}Sm via the (n,p) reaction: Evaluation of excitation function and its validation via integral cross-section measurement using a 14MeV d(Be) neutron source. Applied Radiation and Isotopes 64, 717–724.

[6] McCarthy, D.W., Shefer, R.E., Klinkowstein, R.E., Bass, L.A., Margeneau, W.H., Cutler, C.S., Anderson, C.J. , Welch, M.J.(1997). Efficient production of high specific activity ^{64}Cu using a biomedical cyclotron. Nucl. Med. Biol.24 (1),35–43.

[7] IAEA-TECDOC-1340. (2003). Manual for reactor produced radioisotopes, IAEA, Vienna, page 52.-53

[8] Zinn, K. R., Chaudhuri T. R., Cheng T. P., Meyer W. A. and Morris, J. S. (1993). Production and purification of high specific activity Cu-64for PET imaging. J. Nucl. Med. 34, 238P.

[9] Wadas, T.J., et al. (2010). Coordinating radiometals of copper, gallium, indium, yttrium, and zirconium for PET and SPECT imaging of disease. Chem Rev, 110(5): p. 2858-902.

[10] Blower, P.J., Lewis, J.S., Zweit, J., (1996). Copper radionuclides and radiopharmaceuticals in nuclear medicine. Nucl. Med. Biol. 23, 957–980.

[11] Meares, C.F. (1986). Chelating agents for the binding of metal ions to antibodies. Int. J. Rad. Appl. Instrum B, 13(4): p. 311.

[12] Sun, X. and Anderson, C. J. (2004). Production and applications of copper-64 radiopharmaceuticals. Methods Enzymol. 386: p. 237-61.

[13] Boswell, C.A., McQuade, P., Weisman, G.R., Wong, E.H., Anderson C.J. (2005). Optimization of labeling and metabolite analysis of copper-64-labelled azomacrocyclicchelators by radio-LC-MS. Nuclear Medicine and Biology 32, 29–38.

[14] Jalilian, A. R., Rowshanfarzad, P., Kamrani, Y. Y., Shafaii, K., Mirzaii, M.(2007). Production and tumour uptake of [64Cu]Pyruvaldehyde-bis (N4-methylthiosemicarbazone) for PET and/or therapeutic purposes. Nuclear Medicine Review, 10, pp. 6–11.

[15] Bourgeois, M., Rajerison, H., Guerard, F. et al. (2011).Contribution of [^{64}Cu]-ATSM PET in molecular imaging of tumour hypoxia compared to classical [^{18}F]-MISO—a selected review," Nuclear Medicine Review, 14, no. 2, pp. 90–95.

[16] Chao, K. S. C., Bosch, W. R., Mutic, S. et al., (2001). A novel approach to overcome hypoxic tumor resistance: Cu-ATSM-guided intensity-modulated radiation therapy,International Journal of Radiation Oncology Biology Physics, 49, no. 4, pp. 1171–1182.

[17] Donita Brady et al. (2014). Copper is required for oncogenic BRAF signalling and tumorigenesis.Nature. May 22;509(7501), 492-6.

[18] Peng, F., et.al. PET of Human Prostate Cancer Xenografts in Mice with Increased uptake of ^{64}Cu chloride(2006).Journal of Nuclear Medicine, V 47, 1649-1652.

[19] Valentini, G., Panichelli, P., Villano, C., Pigotti, G., Martini, D. (2014). $^{64}CuCl_2$: A new theranostic agent. Eur. J. Nucl. Med. Mol. Imaging, 41 (Suppl 2), S42029.

[20] Qin, C., Liu, H., Chen, K., Hu, X., Ma, X., Lan, X., Zhang, Y. and Cheng., Z.(2014). Theranostics of Malignant Melanoma with $^{64}CuCl_2$.; J Nucl Med 55:812-817.

[21] Lee, JW., Park, J. A., Lee, Y. J., Shin, U. C. Parket. H.et. al. (2013). Synthesis and biological evaluation of dimeric RGD peptide conjugated Cu-64 and glucosamine for tumor imagingJ Nucl Med.; 54 (Supplement 2), 1086.

[22] Pfeifer, A., Knigge, U., Mortensen, J. et al. (2012). Clinical PET of neuroendocrine tumors using ^{64}Cu-DOTATATE: First-in-Humans study. J. Nucl. Med., 53, pp. 1207–1215.

[23] Qaim, S. M., Hohn, A., Bastian, Th., El-Azoney, K. M., Blessing, G., Spellerberg, S.; Scholten, B., Coenen, H.H. (2003). Some optimization studies relevant to the production of high-purity ^{124}I and ^{120g}I at a small- sized cyclotron. Appl. Radiat. Isot.,58, 69–78.

[24] Scholten, B., Kovács, Z., Tárkányi, F., Qaim, S.M. (1995). Excitation functions of ^{124}Te(p, xn)^{124}, ^{123}I reactions from 6 to 31 MeV with special reference to the production of 124I at a small cyclotron. Appl. Radiat. Isot., 46, 255–259.

[25] Glaser, M., Mackay, D. B., Ranicar, A. S. O., Waters, S.L., Brady, F., Luthra, S.K. (2004). Improved targetry and production of iodine-124 for PET studies. Radiochim. Acta., 92, 951–956.

[26] Nye, J.A., Avila-Rodriguez, M.A.; Nickles, R.J. (2006). Production of [124I]-iodine on an 11 MeV cyclotron. Radiochim. Acta, 94, 213–216.

[27] Lambrecht, R.M., Sajjad, M., Qureshi, M.A.; Al-Yanbawi, S.J. Production of iodine-124. (1988). J. Radioanal. Nucl. Chem. Lett., 127, 143–150.

[28] Knust E. J., Weinreich, R. Yields and impurities in several production reactions for ^{124}I. (1997). In Proc. 7th Workshop on Targetry and Target Chemistry, Heidelberg, Germany, June 8–11, pp. 253–262.

[29] Hassan, K. F., Qaim, S. M.; Saleh, Z. A. Coenen, H.H. (2006). Alpha-particle-induced reactions on natsb and ^{121}Sb with particular reference to the production of the medically interesting radionuclide ^{124}I.Appl. Radiat. Isot.,64, 101–109.

[30] Lever, J.R. Radioiodinated Compounds in Principles of Nuclear Medicine, Edited by Wagner, H.N., Szabo, Z., Buchanan, J.W., 2nd Edition, W.B. Saunders Company, Page199-213.

[31] Moroz, M.A., Serganova, I., Zanzonico, P., Ageyeva, L., Beresten, T., Dyomina, E., Burnazi, E., Finn, R.D., Doubrovin, M., Blasberg, R.G. (2007). Imaging hNET reporter gene expression with ^{124}I-MIBG. J. Nucl. Med., 48, 827–836.

[32] Lee, C.L.,Wahnishe,H.,Sayre,G.A.,Cho,H.M.,Kim,H.J., Hernandez-Pampaloni, M., et al. (2010).Radiation dose estimation using preclinical imaging with I-124-metaiodobenzylguanidine (MIBG) PET. Med.Phys. 37, 4861–4867.

[33] Divgi, C.R., Pandit-Taskar, N., Jungbluth, A.A., Reuter,V.E., Gonen, M., Ruan, S.,etal., (2007). Preoperative characterisation of clear-cell renalcarcinomausing iodine-124- labelled antibody chimericG250 (I-124-cG250) and PET in patients with renal masses:a phase I trial. Lancet Oncol.8, 304–310.

[34] Zanzonico, P., O'Donoghue, J., Chapman, J.D., Schneider, R., Cai, S., Larson, S.D., Wen, B.X., Chen, Y. C., Finn, R., Ruan, S. T., Gerweck, L.; Humm, J., Ling, C. (2004).Iodine-124-labeled iodoazomycin-galactoside imaging of tumor hypoxia in mice with serial micro PET scanning.Eur. J. Nucl. Med, 31, 117–128.

[35] Blasberg, R. G.; Roelcke, U., Weinreich, R., Beattie, B., von Ammon, K., Yonekawa, Y., Landolt, H., Guenther, I., Crompton, N.E.A.; Vontobel, P., Missimer, J., Maguire, R.P.; Koziorowski, J., Knust, E.J., Finn, R.D.; Leenders, K.L. (2000) Imaging brain tumor proliferative activity with I-124 iododeoxyuridine. Cancer Res., 60, 624–635.

[36] Glaser, M., Collingridge, D.R., Aboagye, E.O., Bouchier-Hayes, L., Hutchinson, O. C., Martin, S. J., etal.(2003). Iodine-124 labelled Annex in-Vasapotential-radiotracer to study apoptosis using positron emission tomography.Appl.Radiat. Isot. 58,55–62.

[37] Keen, H.G., Dekker, B.A., Disley, L., Hastings, D., Lyons, S., Reader, A.J., Ottewell, P., Watson, A., Zweit, J. (2005). Imaging apoptosis in vivo using I-124-annexin V and PET. Nucl. Med. Biol., 32, 395–402

[38] Giuseppe Lucio Cascini, Artor Niccoli Asabella, Antonio Notaristefano, Antonino Restuccia, Cristina Ferrari, Domenico Rubini, Corinna Altini, and Giuseppe Rubini. (2014).^{124}Iodine: A Longer-Life Positron Emitter Isotope—New Opportunities in Molecular Imaging. Bio.Med. Research InternationalVolume 2014, Article ID 672094, 7 pages.

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Generator-Based PET Tracers: ^{68}Ga and ^{82}Rb

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Introduction

The impact made by positron emission tomography (PET), in conjunction with hybrid imaging device PET/CT, in the clinical management of patients of cancer and several other diseases/disorders, has given a phenomenal boost to nuclear medicine (NM) [1] . Currently, ^{18}F products are the most commonly used PET tracers, and among these, ^{18}F - fluoro-2-deoxy-D-glucose (FDG) has proven to be the work-horse of PET in NM clinics [2]. The prospect of accessing other PET tracers through a radionuclide generator is another important approach to not only enable PET examinations at remote hospitals, but also expand the PET tracer arsenal at NM centers, with or without on-site cyclotrons. A number of radionuclide generators yielding PET tracers have been known or studied, and some developed to a good extent through continuous evolution (Table 1).Two of them are valuable for wider use in daily NM procedures and they are: ^{68}Ge-^{68}Ga and ^{82}Sr-^{82}Rb generators. The surge of clinical interest in the use of the two PET tracers, ^{68}Ga and ^{82}Rb, obtained from the respective radionuclide generator, is the motivation to provide an overview of the status, prospects and limitations in this article.

^{68}Ge-^{68}Ga Generator

^{68}Ge-^{68}Ga generator is one of the earliest recognized systems of potential interest in NM, and it thus got a boost as soon as there was a surge in the installation of PET and subsequently PET-CT systems. The ^{68}Ge-^{68}Ga generator has many attractive features and one main limitation. The nuclear characteristics of ^{68}Ga - $t_{½}$=68 min, 89% β^+ and 11% EC, E_{max} = 1.92 MeV and the versatile chemistry of Ga(III) make it eminently suited for radiopharmaceutical development, with both chemical and biochemical targeting moieties. The long half-life of ^{68}Ge (271 d) has a dual impact, namely, potentially long shelf-life generator, and difficult logistics for production (long irradiations; targetry etc.).

The ^{68}Ge-^{68}Ga generator has been a subject of investigation for almost 50 years. However, only in more recent years, generators meeting the needs of modern requirements of radio-metal labelling chemistry have been developed and deployed, thanks to innovative separation strategies using various column matrices, including TiO_2, SnO_2, or organic adsorbents, with a view to obtain $^{68}Ga^{3+}$ in dilute acid eluent, amenable for subsequent radio-metal labeling [3]. ^{68}Ge-^{68}Ga generator development during the last few decades is briefly summarised in Table 2. ^{68}Ge is produced mainly by the reactions ^{69}Ga(p,2n) and (nat)Zn (α,xn) or ^{66}Zn (α,2n), while the number of production centres and availability are limited. Consequently, its commercial availability is restricted among certain producers of the raw material and generator producers. There is a need for a breakthrough, if ^{68}Ge-^{68}Ga generator has to become a widely useful product.

The efforts have come to fruition and commercial availability of a range of ^{68}Ge-^{68}Ga generators exists (though at a relatively high cost) for use in NM centres (Fig-1).

Table 1: Key Examples of Radionuclide Generator Systems for PET imaging

Generator	Half life		β^+ branch (%)	Status	Comments
	Parent	Daughter			
^{44}Ti/^{44}Sc	60.3 y	3.927 h	94.0	^{44}Sc-DOTA-conjugated tumor targeting vectors under investigation.	^{44}Ti sourcing issues; ^{44}Sc labeling to be refined.
^{62}Zn/^{62}Cu	9.26 h	9.74 min	97.0	Hypoxia and perfusion with ^{62}Cu-ATSM & ^{62}Cu-PTSM, respectively; Limited use.	9.3-h half-life of ^{62}Zn; 1-day shelf-life generator; daily production of ^{62}Zn required.
^{68}Ge/^{68}Ga	270.8 d	1.14 h	89.0	Widely used generator	^{68}Ge sourcing issues
^{72}Se/^{72}As	8.4 d	1.083 d	88.0	Organoarsenic precursors and subsequent labeling procedure being studied.	^{72}Se sourcing issues; nd-user labeling techniques yet to be established.
^{82}Sr/^{82}Rb	25.6 d	1.27 min	95.0	Used for myocardial perfusion studies	^{82}Sr sourcing issues.
^{118}Te/^{118}Sb	6.00 d	3.6 min	74.0	myocardial perfusion study interest	
^{140}Nd/^{140}Pr	3.37 d	3.39 min	51.0	myocardial perfusion study interest	The short half-life of parent radionuclide emerged as the major impediment that limits the shelf life of the generator to few (2-3) days.

Table-2: Types of ^{68}Ge-^{68}Ga generators

Years	Generator type	Remarks
1960-1970	liquid-liquid extraction,	Tedious time consuming separation; not amenable for hospital radiopharmacy
1970-2004	Column chromatography system based on Al_2O_3 and EDTA as eluent	This system served as a convenient and economical source of ^{68}Ga-EDTA; clinical use was limited to measure increased blood flow of brain tumors, in particular.
After 2004	Column chromatography system based on TiO_2, ZrO_2, CeO_2, SnO_2 or an organic resin	^{68}Ga is availed in an ionic form, with elution yields 70% to 80%; ^{68}Ge breakthrough still in the range, 0.01-0.001%.

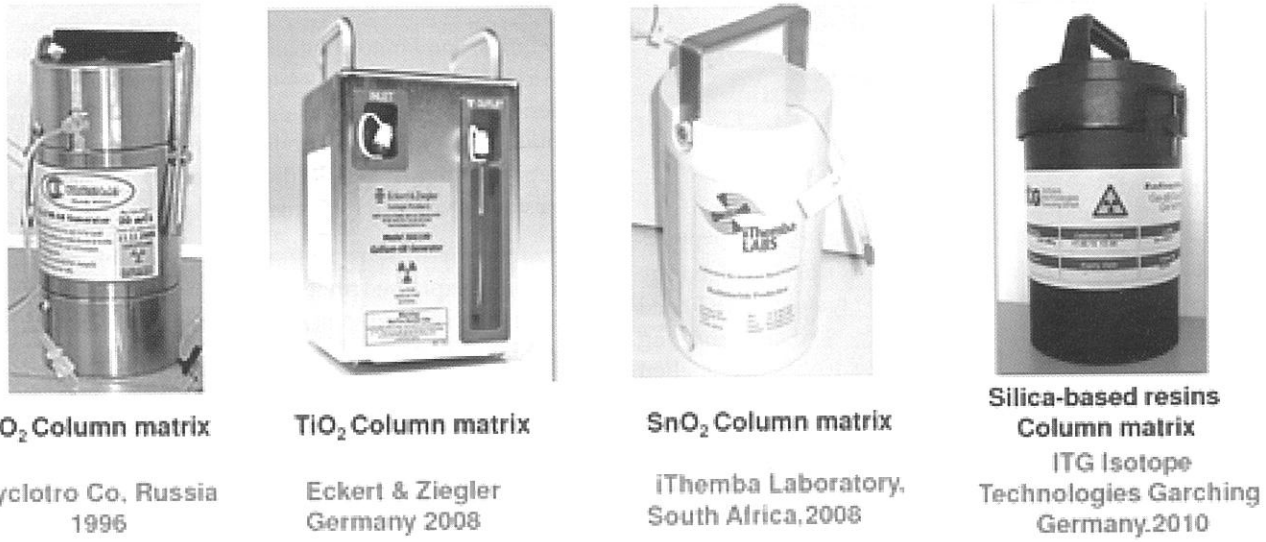

Fig. 1 Commercially available ^{68}Ge-^{68}Ga generators, showing the column matrix used, manufacturer and the year of introduction

The low radioactive concentration, highly acidic eluate, relatively high ^{68}Ge breakthrough and the presence of potential metal ion impurities in the generator eluates are deterrents for the desired direct use of ^{68}Ga generator eluate for radiolabeling of lignads, especially of biomolecules [4]. To circumvent these limitations, several post- elution processing strategies, along with automated systems, have been tried and some made available commercially for safe, effective and reproducible use in the radiopharmacy. Commercial availability of ^{68}Ge-^{68}Ga generator yielding ionic form of ^{68}Ga, along with post elution processing system, has led to exploring a broad spectrum of ^{68}Ga-labeled products for use as radiopharmaceuticals, mainly for targeted imaging of specific protein expression products and pre-targeted imaging [5].

The availability of ^{68}Ge-^{68}Ga generators providing $^{68}Ga^{3+}$ of requisite quality amenable for direct radiolabeling is a much more desirable option. In this regard, the potential of BARC-developed ^{68}Ge-^{68}Ga Generator, based on the nanoceria-polyacrylonitrile composite [6] (CeO_2-PAN) sorbent, is capable of yielding ^{68}Ga of requisite quality (free from metal ion impurities such as Al, Fe, Cu, Zn, Ti or Sn ions and very low ^{68}Ge breakthrough) and without the need for any post-elution processing, and is deemed very significant to expand the scope of ^{68}Ga products handling in radiopharmacy. Schematic diagram of BARC's $^{68}Ge/^{68}Ga$ Generator is shown in Fig. 2.

Over the years, BARC ^{68}Ge-^{68}Ga Generator has been effectively developed and refined for use in the preparation of ^{68}Ga tracers, for both research and limited clinical use. A comprehensive quality assurance system is necessary to ensure that the quality of ^{68}Ga availed form the generator meets the standards for clinical use.

^{68}Ga Radiopharmaceuticals

Several promising ^{68}Ga tracers, targeting biologic activities, such as proliferation, angiogenesis, and apoptosis, are currently under preclinical and clinical investigation. One of the most rapidly expanding areas is the development

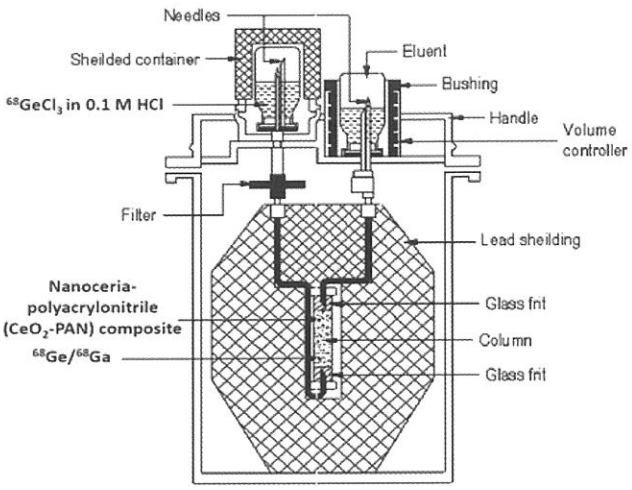

Fig. 2 BARC's ^{68}Ge-^{68}Ga Generator based on nanoceria-polyacrylonitrile composite

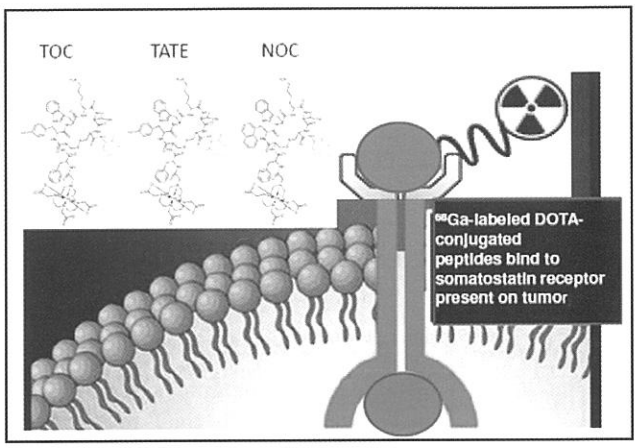

Fig. 3 Principle of ^{68}Ga-labeled peptides targeting peptide receptor for molecular imaging [5]

of ^{68}Ga labeled peptide-based agents for targeted imaging, of tumours in particular. Schematic representation of ^{68}Ga-labeled peptides targeting peptide receptor for molecular imaging is shown in Fig.3.

The use of ^{68}Ga labeled small tumour-affine peptides targeting somatostatin receptors (SSTR) has changed the diagnostic approach to neuroendocrine tumours (NET) and has led to a search for other products for molecular imaging applications. Among the SSTR agonists, ^{68}Ga-labelled DOTA-conjugated somatostatin analogues have emerged as the breakthrough vector molecules owing to in vivo stability, favourable pharmacokinetics, high and specific receptor-mediated tumor uptake. They have proven to be increasingly useful due to their fast clearance, rapid tissue penetration and low antigenicity, as well as a shorter procedure and scope for whole body imaging. The scope of using ^{68}Ga-labelled DOTA-conjugated somatostatin analogues (e.g. DOTATATE, DOTANOC) for diagnosis has further merits, as the same compound labeled with the chemically analogous therapeutic radionuclides like ^{90}Y or ^{177}Lu and used for therapy. Thus diagnosis-tailored to the subsequent therapy can be availed, the so called 'theranostic' approach, and also the prospect for better planning of therapy and evaluating therapeutic outcome. Recently, ^{68}Ga-DOTATOC has been officially designated as 'an orphan drug' by the U.S. Food and Drug Administration, which is likely to accelerate and facilitate its availability to NET patients.

The use of a kit-based labeling procedure in conjunction with a ^{68}Ge-^{68}Ga generator for the synthesis of ^{68}Ga labeled peptides (akin to the case of ^{99m}Tc kits) would be highly desirable. Towards this end, a single vial freeze-dried kit formulation strategy for DOTA-TOC, DOTA-NOC and DOTA-TATE has been developed by our group at BARC for use in clinical setting [7].

The currently available data for potential use of other ^{68}Ga-labeled peptide analogues as PET tracers are mainly preclinical and limited human studies have been carried out. ^{68}Ga-labeled DOTA-4-amino-1-carboxymethyl-piperidine-D-Phe-Gln-Trp-Ala-Val-Gly-His-Sta-Leu-NH2 peptide (BAY86-7548) having high affinity to bombesin receptor subtype II for the detection of primary and metastatic prostate carcinoma merits attention.

Integrin $\alpha_v\beta_3$ is an important member of receptor family and expressed preferentially on regenerative vascular endothelial cells and some tumour cells. Preliminary clinical studies indicate that it is effective for detecting intra-prostatic prostate cancer. ^{68}Ga-labeled $\alpha_v\beta_3$ integrin-targeting ^{68}Ga-c[Lys-(NOTA)-Arg- Gly-Asp-D-Phe] is one of the RGD peptides for which initial clinical data are available. Clinical trial on ^{68}Ga-BNOTA- PRGD2[^{68}Ga-p-SCN-Bn-NOTA-PEG3-RGD2] is in progress to investigate post-myocardial infarction and post-stroke repair [8].

Prostate-specific membrane antigen (PSMA) is a cell surface protein, which is expressed at higher levels in prostate cancer compared to other tissues and constitutes a promising target for specific imaging. ^{68}Ga-Glu-NH-CO-NH-Lys-(Ahx) [^{68}Ga- DKFZ-PSMA-11] has emerged as an attractive agent currently used in clinical studies for the detection of recurrent prostate cancer and metastatic spread [9]. The combination of DOTA with the PSMA targeting inhibitors offers the prospect of using the same vector molecule for imaging (with ^{68}Ga) and therapy (with ^{90}Y, ^{177}Lu).

There has been research also on potential ^{68}Ga labeled radiopharmaceuticals, proposed in place of certain ^{18}F, ^{11}C products, mainly with the aim to support PET centres without on-site cyclotrons, or access to cyclotrons (Table 3) [7].

With expanding areas of applications and growing interest in the use of ^{68}Ga labeled radiopharmaceuticals, it may be a matter of time, when the routine imaging load of NM clinics (e.g. sentinel lymph node scanning) may also be partly shared by ^{68}Ga products and PET/CT.

Table-3. ^{68}Ga labeled products for possibly substituting ^{18}F, ^{11}C products in regular use

Diagnostic modality	Established products of ^{11}C and ^{18}F in use	Proposed products of ^{68}Ga
Angiogenesis	^{18}F-galacto-RGD	^{68}Ga-DOTA-RGD, ^{68}Ga -VEGF
General cancer imaging	^{18}FDG	^{68}Ga -CXCR4 biomarker, ^{68}Ga -uPAR biomarker, ^{68}Ga -SCN-NOTA-BZA
Hypoxia	^{18}F-nitroimidazloes (FAZA, FMISO, FETNIM)	^{68}Ga -DOTA-imidazoles
Proliferation	^{18}FLT	^{68}Ga -DO3A-thymidine
Glioma	^{18}FET, ^{11}C-methionine	^{68}Ga -glutamine, ^{68}Ga -DO3A-alanine, ^{68}Ga -DO2A-tyrosine
Prostate cancer	^{18}FDG, ^{11}C-acetate, ^{18}F-choline, ^{11}C-choline	^{68}Ga -DOTA-PSMA

RGD, arginylglycylaspartic acid; FAZA, [^{18}F]-1- _-d-(2-deoxy-2-fluoroarabinofuranosyl)-2-nitroimidazole; FMISO, [^{18}F]- fluoromisonidazole; FETNIM, [^{18}F]-fluoroerythronitroimidazole; FLT, [^{18}F]-fluorothymidine; FET, [^{18}F]-fluoroethyl-l-tyrosine; VEGF, vascular endothelial growth factor; CXCR4, chemokine receptor; BZA, benzamide; PSMA, prostate specific membrane antigen; UPAR, urokinase-type plasminogen activator

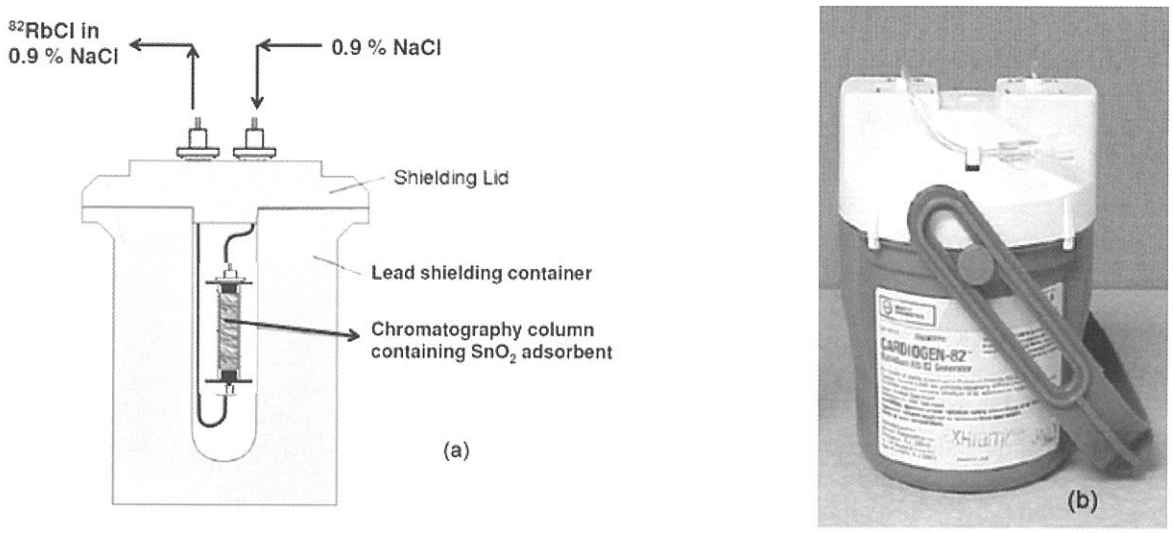

Fig. 4 ^{82}Sr-^{82}Rb generator system: (a) Schematic diagram with shielding; (b) commercial generator with shielding

^{82}Sr-^{82}Rb Generator

There is a great deal of interest on the use of ^{82}Sr-^{82}Rb generators to avail ^{82}Rb for myocardial perfusion PET imaging. Rubidium-82 is the first generator-produced positron emitters that made its entry into clinical nuclear medicine to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease. Rubidium-82, with a half life of 76 seconds, decays by positron emission into stable Krypton (^{82}Kr), a noble element. Rb^+ being an ionic mimic of K^+, with similar chemical and biological properties, accumulates in myocardium as a function of blood flow in a manner similar to that of potassium [10,11].

Cardiac PET using ^{82}Rb has several advantages over traditional SPECT (with ^{99m}Tc complex of MIBI or Tetrofosmin) in terms of images of much superior resolution, better quantification, and also scope for repeated studies, where required, including in the case of pharmacological interventional studies. In 1989, the US FDA approved the use of ^{82}RbCl availed from a commercial ^{82}Sr-^{82}Rb generator system trade name CardioGen-82, that has been available from Bracco Diagnostics Inc. for some years. This generator is composed of a small chromatography column (4 cm x 0.5 cm) containing hydrous SnO_2 and housed in a lead shielding container. Schematic diagram of the ^{82}Sr-^{82}Rb generator system is depicted in Fig.4. When the column is flushed with a solution, such as normal saline, $^{82}Rb^+$ gets eluted. Quality control of generator eluate includes ^{82}Sr breakthrough measurement using a dose calibrator.

As the secular equilibrium status of ^{82}Rb activity ($T_{1/2}$76 s) from the decay of ^{82}Sr ($T_{1/2}$ 25 d) is very rapidly attained, 90% activity of ^{82}Rb is replenished within 5 to 10 minutes after the previous elution; serial clinical studies can hence be planned in quick succession, maximising patient throughput. There was an interest on the use of an automated infusion system to administer the ^{82}Rb eluted from the ^{82}Sr-^{82}Rb generator directly to patients, in view of the short

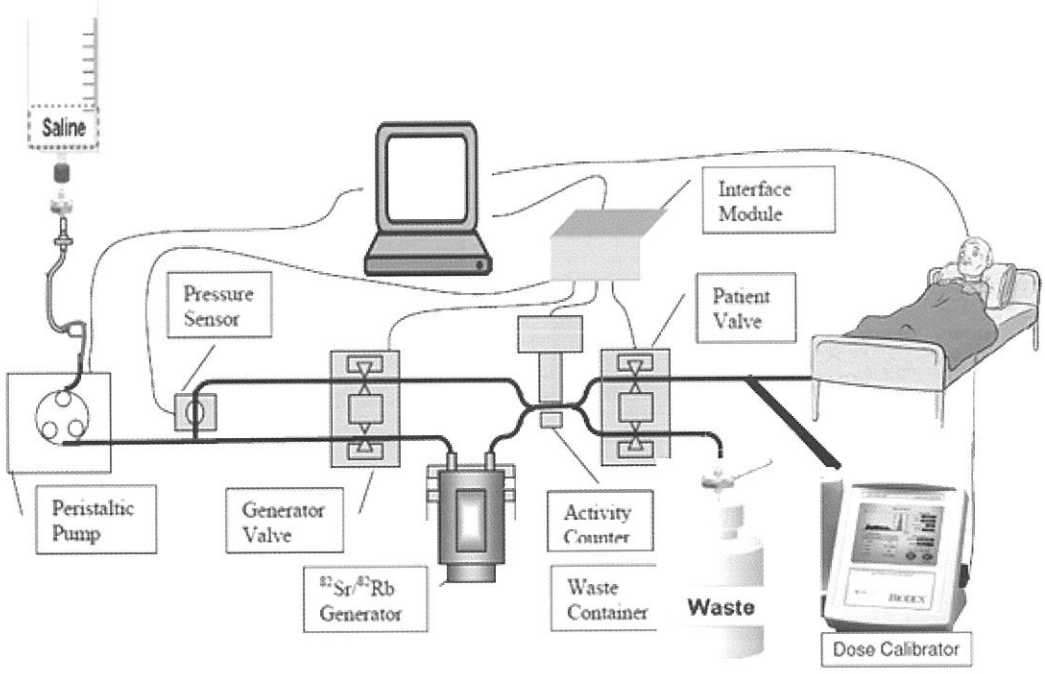

Fig. 5 Schematic representation of ^{82}Rb infusion system, that can control concentration of ^{82}Rb activity administered to the patient, perform quality assessment, and flush the activity from the patient line at the end of the infusion.

half-life of ^{82}Rb and also the decreasing amount of available ^{82}Rb as the generator is used over a few weeks [12]. To avail accurate and reproducible constant-activity of ^{82}Rb activity form the ^{82}Sr-^{82}Rb generator, Klein et al. developed an automatic infusion system. The schematic representation of such a concept of ^{82}Rb infusion system is shown in Fig. 5.

Automated ^{82}Rb infusion systems capable of accurate measurement and delivery of adequate doses of ^{82}RbCl from a ^{82}Sr-^{82}Rb generator have been developed by Bracco Diagnostics, NJ, USA (CardioGen-82 Infusion System) and Jubilant DraxImage Inc, Canada (Ruby-Fill™ Infusion System). Rubidium-82 is eluted from the generator by a computer-regulated elution pump and infused directly into patients using commercially available i.v. infusion system. Use of these systems substantially reduces the radiation dose, ensures optimum performance of the ^{82}Sr-^{82}Rb generator, and provides a log of ^{82}Rb activity infused to the patients. Photograph of the CardioGen-82 Infusion System along with various part of the system is shown in Fig.6.

In addition to regular myocardial PET imaging use of ^{82}Rb, new approaches to kinetic modeling and software tools for analysis of clinical ^{82}Rb studies are being developed and evaluated, enabling quantification of absolute myocardial blood flow and flow reserve, which would further enhance the valuable utility of PET findings by the cardiologists.

The primary impediment for the widespread clinical use of ^{82}Rb is the logistics difficulties and costs associated with ^{82}Sr production, as well as the need for generator replacement at monthly intervals. A number of studies have reported the value of ^{82}Rb PET for myocardial perfusion

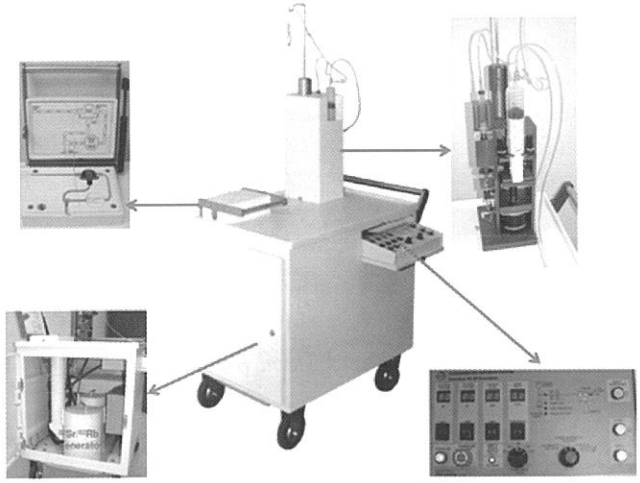

Fig. 6 Photograph of the CardioGen-82 Infusion System along with various parts of the system

imaging, at a cost similar to that for ^{99m}Tc agents with SPECT [13]. With the advent of hybrid PET/CT and growing number of centres, cardiac PET with ^{82}Rb [14] has seen increasing acceptance in clinical practice. This trend is expected to continue in the future.

Conclusion

The expanding use of clinical PET and PET/CT portends an eminent status for the future of radionuclide generators capable of providing PET tracers on demand. It is surmised that generator-derived PET tracers for molecular imaging would offer scope for promising developments. This field is likely to grow as an important tool for

translational research and spur new approaches in molecular imaging. The clinical drivers and acceptance of such new PET tracers will depend much on the success in the use of existing generators and products derived from them.

Acknowledgements

Figures of commercial generators were taken from the product brochure of respective manufacturers. Figures of ^{82}Rb infusion system have been derived from the product brochures of Bracco Diagnostics Inc. U.S. The author gratefully acknowledges the manufacturers while reproducing the figures and information in this article. The author expresses his deep sense of gratitude to Dr. N. Ramamoorthy, Associate Director, International Collaboration and Technical Coordination, BARC for his encouragement, helpful suggestions, scientific discussions and patiently editing the manuscript.

References

[1] Hicks RJ. Should positron emission tomography/computed tomography be the first rather than the last test performed in the assessment of cancer? Cancer Imaging. 2012; 12: 315-23.

[2] Zaidi H , Prasad R. Advances in multimodality molecular imaging. J Med Phys. 2009 ; 34(3): 122–128.

[3] RÖesch F, Riss PJ. The renaissance of the ^{68}Ge/^{68}Ga radionuclide generator initiates new developments in ^{68}Ga radiopharmaceutical chemistry. Curr Top Med Chem 2010;10: 1633-1668

[4] Zhernosekov KP, Filosofov DV, Baum RP, Aschoff P, Bihl H, Razbash AA, Jahn M, Jennewein M, RÖsch F. Processing of generator-produced ^{68}Ga for medical application. J Nucl Med 2007;48:1741-1748.

[5] Velikyan I. Prospective of ^{68}Ga-Radiopharmaceutical Development, Theranostics, 2014; 4(1):47-80.

[6] Chakravarty R, Shukla R, Ram R, Venkatesh M, Dash A, Tyagi AK. Nano-ceria-PAN composite based advanced sorbent material: A major step forward in the field of clinical grade ^{68}Ge/^{68}Ga generator. ACS Appl Mater Interfaces 2010; 2: 2069.

[7] Mukherjee A, Pandey U, Chakravarty R, Sarma HD, Dash A.Development of single vial kits for preparation of (68)Ga-labelled peptides for PET imaging of neuroendocrine tumours. Mol Imaging Biol. 2014;16(4):550-557.

[8] Sun Y, Zeng Y, Zhu Y, Feng F, Xu W, Wu C, Xing B, Zhang W, Wu P, Cui L, et al,.Application of (^{68})Ga-PRGD2 PET/CT for $\alpha_v\beta_3$-integrin imaging of myocardial infarction and stroke.Theranostics. 2014; 4(8):778-86.

[9] Afshar-Oromieh A, Zechmann CM, Malcher A, et al Comparison of PET imaging with a (^{68})Ga-labelled PSMA ligand and (^{18})F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014; 41(1):11-20.

[10] Yoshinaga K, Klein R, Tamaki N. Generator Produced Rubidium-82 Positron Emission Tomography Myocardial Perfusion Imaging From Basic Aspects to Clinical Applications. J Cardiol. 2010; 55(2):163-173.

[11] Alvarez-Diez TM, deKemp R, Beanlands R, Vincent J.Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography. J Appl Radiat Isot. 1999; 50(6):1015-23.

[12] J Epstein N, Benelfassi A, Beanlands RSB, DeKemp RA. An ^{82}Rb infusion system for quantitative perfusion imaging with 3D PET. Appl Radiat Isot. 2004;60:921-927.

[13] Merhige ME, Breen WJ, Shelton V, Houston T, D'Arcy BJ, Perna AF. Impact of myocardial perfusion imaging with PET and (^{82})Rb on downstream invasive procedure utilization, costs, and outcomes in coronary disease management. J Nucl Med. 2007;48:1069-1076.

[14] Groves AM, Speechly-Dick ME, Dickson JC, Kayani I, Endozo R, Blanchard P, Shastry M, Prvulovich E, Waddington WA, Ben-Haim S, Bomanji JB, McEwan JR, Ell PJ, Cardiac ^{82}Rubidium PET/CT: Initial European experience. Eur J Nucl Med Mol Imaging. 2007; 34(12):1965-1972.

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Impressions and Perspectives on PET/CT: Contributions from alumni of BARC, DAE, representing a national institute and entrepreneurship

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- **Dr. A. Velumani, CEO & Director, Nueclear Healthcare Ltd., Navi Mumbai.**
- **Dr. Shrikant V. Solav, Director, Spect Lab Nuclear Medicine and PET-CT Services, Pune.**

Integrated PET/CT and Medical Cyclotron Facility at AIIMS

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Positron Emission (computed) Tomography (PET) provides a non-invasive, accurate diagnostic method of detecting possible diseases at cellular, molecular and tissue level. The initial handicap of PET alone vanished with the introduction of hybrid imaging (PET and CT) in 2001 by Davis Townsend. The second major driving force is the proven utility of the versatile tracer, ^{18}F-FDG, and introduction of newer and more specific radiopharmaceuticals, both of which have changed the rules of the game in the management algorithm of oncology. To fully exploit this new technology, two government organisations, namely, Radiation Medicine Centre (RMC) of BARC, Mumbai, and AIIMS, New Delhi started initial ground work. RMC placed the order for the first PET-alone scanner with a dedicated 16.4 MeV Medical Cyclotron. At AIIMS, we were slightly reluctant to go for PET-alone scanner. We waited for 2 more years and got the better equipment, at that point of time, a dual-slice PET/CT scanner, along with a dedicated 11 MeV Medical Cyclotron and automated synthetic modules for radiopharmaceuticals production. These systems were finally installed in July 2005 (Fig 1).

Interestingly, the new technology was quickly adopted by our clinicians and demand for the PET/CT scanner was overwhelming. In view of the heavy demand for PET scanning, our Institute quickly decided to install a second PET/CT scanner, and that was done in 2010 (Fig. 2). The radiologist is not part of the PET/CT reporting team at AIIMS. Till date, we have conducted 34,868 patient studies, with the two state-of-art PET/CT machines at the Department of Nuclear Medicine. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG), a glucose analogue, is the most commonly used biomarker for functional characterization of cancers. The inexpensive precursor by-product of ^{18}FDG synthesis is sodium fluoride - ^{18}F, a PET/CT bone-seeking tracer, that is used to detect skeletal metastasis with high target to background ratio, compared to the conventional bone imaging agent, ^{99m}Tc-MDP. Unlike ^{99m}Tc-MDP commonly used for bone scan (with typically 10-15 mCi doses), ^{18}F-NaF bone scan can be done with just 2-3 mCi of PET tracer, and also, scanning done with 30-45 minutes waiting only. Again, AIIMS was the first to introduce the regular clinical use ^{18}F-NaF - PET/CT in our country.

We have been looking for amino acid tracer for oncology and neurological applications. Finally, we decided to use ^{18}F-DOPA, which is taken up into cancer cells by amino acid transporters, which are over-expressed in cancer. FDOPA in particular undergoes decarboxylation; increased activity of L-DOPA decarboxylase is a hallmark of (benign and malignant) neuroendocrine tumours. Likewise, for neurological purposes, ^{18}F-DOPA crosses the blood-brain barrier, where it is converted to ^{18}F-Fluorodopamine by the enzyme amino acid decarboxylase (AADC) in the striatum. ^{18}F-Fluorodopamine is stored in presynaptic vesicles, until the neuron activation triggers its release and subsequent binding to the dopamine receptors. The problem we later realised was that a gas target is difficult to handle, and as electrophilic substitution reaction was required for ^{18}F-DOPA synthesis, the production uncertainty was huge.

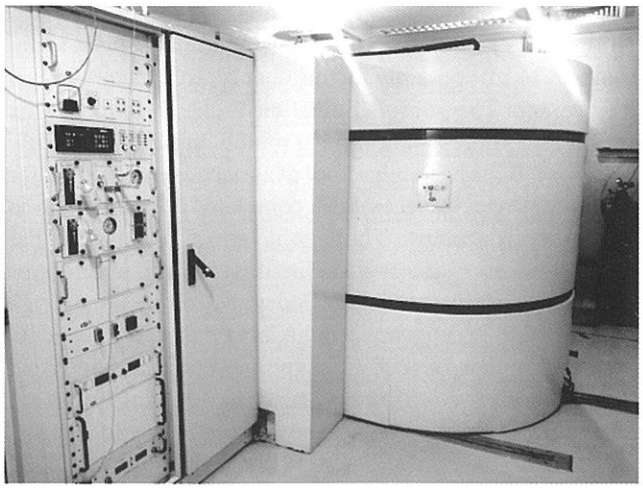

Fig. 1 11 MeV Cyclotron with 8 Target System installed at AIIMS in 2005

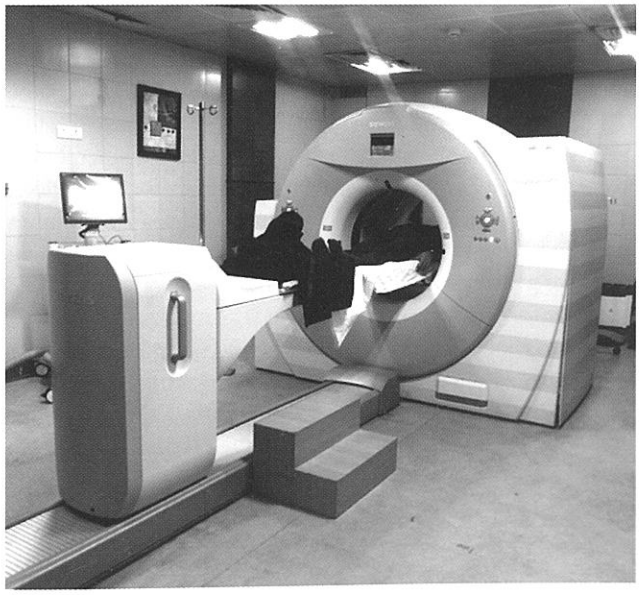

Fig. 2 64-Slice PET/CT Scanner at AIIMS (Biograph mCT, Siemens)

In spite of initial difficulties, we could manage with this agent 156 patients' study. Recently, we have shifted to nucleophilic substitution method of ^{18}F-DOPA synthesis, which is based on reagents-in-cartridge unit.

We are interested in quality, and exploring possible use of newer tracers in specific disease conditions. Our motto at AIIMS is 'Beyond ^{18}FDG Imaging'. We are lucky to have a dedicated Cyclotron available on-site to explore all possible new tracer products (Fig. 1).

Non-^{18}FDG newer radiotracers for PET imaging

As AIIMS always plays a leadership role in medical science in India, we quickly added ^{68}Ge-^{68}Ga generator-based products for use with PET/CT imaging in 2007 with the help of a noted radiochemist collaborator from Germany. The ^{68}Ga radioisotope has favourable physical properties and is also significantly lower in cost than cyclotron-produced radioisotopes. [(^{68}Ga)-DOTA,1-Nal(3)]-octreotide] (^{68}Ga-DOTA-NOC) is the second most widely tracer used in our Department after ^{18}FDG. It is known for its diagnosis and response evaluation of neuroendocrine tumours (NET). Gastro-enteropancreatic neuroendocrine tumours (GEP-NETs) are a heterogeneous group of tumours, originating from the diffuse neuroendocrine system of the gastrointestinal tract or bronchopulmonary system. They are characterized by the over-expression of somatostatin receptors. A total of 2178 scans with ^{68}Ga-DOTA-NOC have been performed. We have also adopted Theranostic principle, from 2008 onwards, and treated these inoperable metastatic NET patients with ^{177}Lu-DOTATATE, for the first time in India. For this Herculean task, we received generous support from our collaborators at BARC and friends and well-wishers in India and abroad and (CRP) funding from the IAEA,.

Another new agent, which has drawn lot of attention recently, is for managing castrate-registant prostate cancer patients with low to borderline raised PSA. In this scenario, conventional imaging with CECT/MRI/US is not much helpful. Here is a scientifically sound opportunity to explore, whether fuctional PET/CT with specific bio-marker, can be of greater help to urologists in managing such cases. Prostate specific membrane antigen (PSMA) is a transmembrane protein, which is more avidly expressed in prostate cancer, compared to other sites such as kidneys, proximal tubules and salivary glands. This protein thus provides a promising target for prostate cancer imaging, and possibly therapy. The substrate for this membrane protein is a simple "urea-based" pharmacophore called "Glu-NH-CO-NH-Lys". The highly efficient, acyclic Ga(III) chelator N,N'-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N'- diacetic acid (HBED-CC), also known as PSMA-11, was introduced as a lipophilic side chain into the hydrophilic pharmacophore Glu-NH-CO-NH-Lys, which was found favourable to interact with the PSMA "active binding site". ^{68}Ga-PSMA for prostate cancer imaging was started in 2013 at AIIMS, and we have successfully completed 50 cases. ^{68}Ga-PSMA has proved to be a promising agent in assessing primary staging of the tumour, lymph nodal involvement, and distant metastasis of prostate cancer.

Yet another novel DOTA-based bisphosphonate, (4-{[bis-(phosphonomethyl) carbamoyl]methyl} -7,10-bis(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl) acetic acid (BPAMD), was labelled using the ^{68}Ga resulting in the PET tracer ^{68}Ga-BPAMD. The very high target to background ratio, fast clearance, and being a generator-based tracer, all together give ^{68}Ga-BPAMD many advantages over the conventional ^{99m}Tc-MDP tracer based bone imaging. Unlike ^{18}F-fluoride, which is adsorbed on the bone surface and is related to blood flow, ^{68}Ga-BPAMD is additionally taken up also by osteoclasts, reflecting the farnesyl diphosphate synthase enzyme dynamics in the HMG-CoA reductase pathway, thus becoming an ideal tracer in diagnosing several disorders relating to osteoclastic bone destruction also. It can also be used to monitor radionuclide therapy for palliation of bone pain. So far, we have evaluated 29 cases of breast cancer for skeletal metastasis using this tracer. Results have been comparable to that of ^{18}F-fluoride.

For nuclear cardiology applications, ^{13}N-ammonia is routinely used at our Centre along with ^{18}FDG for viability study. Till date, 231 cardiac cases have been successfully imaged during the past 6 years.

We have recently added two more tracers ^{18}F-MISO and ^{18}F-FLT. Five new ^{11}C-carbon chemistry-based biomarkers, namely, ^{11}C-methionine, ^{11}C-Fallypride, ^{11}C-Choline, etc. are just being introduced at AIIMS. The studies are at the preliminary stage and their role in oncology is yet to be evaluated in a larger number of patients.

I am proud to announce that AIIMS is at the advanced stage of procuring the PET/MR system, and this feat will probably be achieved in the current financial year.

The only limitation that we have experienced in our decade-long journey in PET/CT imaging is the lack of a good/innovative PET radiochemist within AIIMS team. That may be true possibly for the other PET/CT centres too in the country. The second limitation is the dependence on imported synthesis modules, which are prohibitively expensive. India has a huge pool of a vast range of talents; for example, we have successfully completed Mars Mission in our maiden attempt. Then, why can't we master the micro-fluidics - automation in developing indigenous synthetic chemistry modules? Today, we are spending huge resources for buying such synthetic modules from vendors abroad. It is time to do serious introspection, and set good examples of development targets for our younger generation. If we can have innovative PET radiochemists and support them well, "sky shall be the limit" in PET imaging.

PET-CT Accessibility and Affordability: Personal Experience and Impressions

A. Velumani

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Preamble

I was working at the Radiation Medicine Centre (RMC), a unit of Bhabha Atomic Research Centre, for several years. It was at this premier Nuclear Medicine institute, that I got an opportunity to learn, work and use the Nobel Prize winning technology "Radioimmunoassay (RIA)". I was extensively involved in doing laboratory-based in vitro thyroid hormone investigations using RIA. This experience enabled me to establish the in vitro Nuclear Medicine (RIA) brand "Thyrocare"[i]. Having been associated with Nuclear Medicine field at RMC-BARC, I had basic understanding and clarity on applications of radioisotopes and radiopharmaceuticals, especially in the field of Oncology, and that subsequently led me to launching another initiative, Nueclear[ii].

Cancer - PET-CT, ^{18}F-FDG & Medical Cyclotron - Cost Factor

Amongst all the state-of-the-art high-end imaging systems, Positron Emission Tomography (PET) combined with Computed Tomography (CT) is the latest, most powerful 3-Dimensional, high resolution fusion imaging technology. Since its prototype introduction in the early 2000's, numerous cancer patients have been scanned on PET-CT systems globally. It has proven to be the functional imaging modality of choice not only in aiding diagnosis, but also in staging, monitoring of treatment efficacy and evaluation of disease recurrence. Despite the potential of PET-CT imaging technology in cancer management, the growth of this modality in India has been very slow and still remains elusive for medical specialists and patients. The reasons primarily are considered to be three-fold. Firstly, the PET-CT technology requires huge initial investment (Rupees 7 to 9 Crores); added to it are the cost towards space, infrastructure, consumables and human resources, and this has deterred many nuclear medicine professionals, practitioners, diagnostic centres and hospitals, from installing and operating this imaging modality on their own. Secondly, the tracer ^{18}F-FDG used in PET-CT requires the availability, operation and maintenance of a "Medical Cyclotron" and an attached radiochemistry facility. The huge investment (Rupees 18 to 24 Crores), and the associated operational and maintenance costs (Rupees 3 Crores per annum) of the Medical Cyclotron, has rendered the technology prohibitively expensive. Thirdly, a cancer patient in India today spends on an average Rs. 25,000/- for a PET-CT study in a private diagnostic centre or a hospital. The cost of the scan being high and unaffordable by the large segment of cancer patients, most of the referring oncologists and physicians therefore hesitate and avoid recommending PET-CT investigations.

PET-CT - Where we stand?

We hugely lag behind countries like United States, Europe and Japan in the wide-spread adoption of PET-CT and Medical Cyclotron technologies. World Health Organization recommends two PET scanners for every million people. The first PET scanner was commissioned in our country (at RMC) in the year 2002. Almost a decade later, today there are around 100 PET-CT systems, available for a population of over 1.2 billion. In the United States, there are roughly 2,000 PET scanners, that is, an availability ratio of about 6.5 per million Americans; in India the ratio is only 0.08 per million Indians. The shortfall in the PET-CT diagnostic infrastructure for cancer care obviously is very large and of concern as well.

PET-CT & Medical Cyclotron Technology - How to make it available?

The government health care system alone cannot meet this disproportionate demand and supply gap. It necessitates urgent participation from private entities, entrepreneurs and investors to reduce this technology gap.

Nueclear – PETCT & Medical Cyclotron – Journey Begins

"Thyrocare" as a brand having done successfully well in mid-volume - mid-value in vitro testing, I was tempted to venture into low-volume - high-value in vivo diagnostics, with a primary focus on PET Nuclear Medicine and started another brand "Nueclear". Dilution of 25% of equity in Thyrocare gave me the cash resources, and the single tracer product, ^{18}FDG, tempted me to enter the arena. I did study the concerns of half-life, manufacturing, logistics, business aspects of ^{18}FDG and concluded that 10 cyclotrons and 100 PET-CT would be able to take care of the needs of Oncology in next 10 years.

Indian population is in need of health care solutions at affordable costs. As a social responsibility, "Nueclear" has a vision and focus, namely, to reach and provide affordable and accessible PET-CT imaging services to patients throughout the country.

In its first phase, we ordered one Cyclotron and 5 PET-CT machines (2 in Delhi, 2 in Mumbai and 1 in

i Started in 1995; Single laboratory for the billion; 600 Employees, 1000 Franchisees, 30,000 specimen and 150,000 tests a night, Rs 180 crore turnover. Brought down the Thyroid hormone testing rates from Rs. 1000 to Rs. 250.

ii Started in 2010; One cyclotron, 5 PET-CT, 3 cities; Dream to bring down cancer diagnosis from Rs 25,000 to Rs 10,000.

Hyderabad). Our interest was to study the effective utilization and application of these from real and practical operations, rather than only listening from others about its potential. After doing 8000 scans, after reaching 1000 scans a month, and having produced 1500 curies of ^{18}FDG, I wish to share my experience - salient findings and inferences - as under.

1. Machines are capable, both Cyclotron and PET-CT, in terms of revenue generation, as long as workloads are there.
2. Vendors appear to be competing with one another, but they work with a fair understanding and hence PET-CT scanners continue to remain costly.
3. India has got the best rates for scanners, according to vendors, while for India, these rates are yet too high for many to dream it.
4. At Rs.10000/- per scan, if we do 10 scans per scanner per day, it is viable, and if we do 20 scans a day, it is great business.
5. In Mumbai, we have 30 Curie ^{18}FDG production capacity per day, while the demand, as of now, is only 3 Curie per day.
6. Delhi has more scanners, and performs more scans per scanner, as compared to Mumbai.
7. There are regulatory concerns and some of them often does stress the operators, since at times, weeks to months may be lost waiting for action from the representative(s) of the national regulatory body (AERB).
8. Getting even a fresh NM doctor for serving appears to be a major challenge, and also, cost of the NM doctor is steadily increasing due to growth in the NM industry.
9. India has 100 PET-CT scanners and the present national average is 5 scans per machine per day, i.e. 500 scans in a day.
10. In a cancer focused hospital, it just takes 12 months to reach viability while in others, it takes 36 months.
11. Cost of ^{18}FDG is a big pain to those who do not have a cyclotron in their own city.
12. Only 10% of oncologists know how useful PET-CT is and only half of them regularly use them for patient management.
13. In 18 months, we have some patients who have got monitored more than 5 times, because it is useful in disease management and also affordable.
14. Cost of electricity accounts for more than the cost of ^{18}FDG in low volume centres.
15. Almost 95% of the usage of ^{18}FDG is in oncology, and hence this modality is for Oncologists.

It would take a few more years for the Nuclear Medicine industry to realign the economics of PET-CT and Medical Cyclotron, and I am confident that the days of affordable PET imaging of cancer patients in our country is going to come soon.

PET-CT in Real World: Personal Experience and Impressions

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I belong to the DRM Graduate Fraternity of RMC, BARC. I quit a faculty position at RMC (1995) to join a corporate hospital, and within years, decided to start a dedicated private Nuclear Medicine services center in Pune (2001).

Over the past 14 years, the focus of this initiative has been on providing nuclear medicine services with the motto of 3 C: "Care- Compassion-Conviction" - care of equipment cum people associated with the lab; compassion towards patients; conviction in results.

Unlike many other branches of medicine, nuclear medicine (NM) is invariably referral-based; this means that the referring physician must be convinced that the services offered by NM Clinic come with certain dependability and assured value-addition. Publication of work performed and results demonstrated (typical ones are listed at the end) is an authentic means to build confidence among the consultants, who use our services from time to time.

Between 2001 and 2006, our Clinic had invested in three gamma cameras (SPECT systems). Introducing newer test procedures with superior outcome and keeping them economically viable are unending challenges, although this is not exclusive to nuclear medicine alone. Over a period of time, our Clinic has also published several papers in peer reviewed journals (typical ones are listed at the end).

The first PET facility was introduced by BARC at RMC in 2002. Corporate hospitals in Mumbai (receiving PET tracer supplies from the BARC-BRIT facility at Parel) initially invested in co-incidence imaging systems, and within years, graduated to full-ring PET-CT system. When I expressed my desire to introduce PET at our clinic, there was resistance (as always in the past).

Finance was a big challenge for the PET project. As the financial risk was high, I did not want to involve a private bank - that shows my confidence in our government banking system - no matter how they are deficient at times, in terms of lengthy procedures, lack of adequate/valid reasoning at times, etc.; yet there is ONE fact, that I cannot deny - that they are transparent (at least all those whom I dealt with). One nationalized bank agreed to finance our PET project. We had to locate it at about 5 km away from our original Clinic. This resulted in division of work force and duplication of many factors. We performed well yet over the past seven years, and have rendered PET imaging services to hundreds of patients. We have availed PET tracer supplies, mostly ^{18}F-FDG, from cyclotron - radiopharmacy facilities located at Mumbai (RMC-BRIT at the beginning; Thyrocare currently), Bangalore (FDI), Hyderabad (Indo-American), and Chennai (Kamakshi). I have a dedicated team of three physicians and six technologists, apart from many supporting agencies and their staff.

Finally, in 2012, we decided to build a new facility that could host all our equipment and services under one roof (Fig. 1). We have now 2000 sq m space that houses two gamma cameras, PET/CT as well as therapy wards. We use currently about 100 to 500 mCi doses of ^{18}FDG every day. Our clinic has also procured Gallium-68 generator recently for using with the lesion-specific bio-ligands, PSMA for prostate cancer, and DOTA-NOC (somatostatin receptor binder) for neuro-endocrine tumour imaging.This is all done over and above the regular NM services rendered involving the use of ^{99m}Tc and ^{131}I and other products.

Unlike other industries, medical-care always comes with sentiments/emotions attached to it. Patients, their relatives and friends are invariably very anxious to get the best and as quick as possible. Raising issues related to cost may bring in arguments - irritability etc. It takes huge efforts to address these issues and my wife Dr. Pallavi must get all the credit for effectively handling these matters.

Medical equipment-care comes at huge cost, especially when you decide (or need) to buy comprehensive maintenance services. People-care is always difficult, because of various factors, and more so is the staff-care; here one of the aims of our Clinic has been to provide medical insurance coverage to the family of all those, who have worked at the Clinic for more than 2 years.

I am thankful to all the staff members of our Clinic - present and past - who worked hard to bring it to its present stature. One of my accounts consultants used to tell the staff

Fig. 1 The new facility at Pune "Dr Solav's Spect-lab"

of our Clinic that, "anyone who has an experience of working in this Clinic, can stand all adversities in life". I dedicate this write-up of my Impressions to my colleague, Late Shree KC Jain, a humble, methodic, honest gentleman, whom we lost a few years ago.

I thank Dr. N. Ramamoorthy, who is my very long time associate; initially as teacher in Radiopharmacy, followed by professional association as Chief Executive of BRIT, and later as a friend, for giving me the opportunity to share some thoughts and impressions through this article for IANCAS Bulletin.

Publications

[1] ATLAS ARTICLE: FDG PET/CT in Evaluation of Pyrexia of Unknown Origin, Clinical Nuclear Medicine • Volume 36, Number 8, August 2011

[2] Correlative Imaging in Skeletal Tuberculosis with Special emphasis on Radionuclide Bone Scintigraphy: A Pictorial Essay, World Journal of Nuclear Medicine, Volume 6, Number 1, January 2007

[3] Lack of hyper-vascularity on three phase bone scan : Osteoid osteoma revisited, World Journal of Nuclear Medicine, Volume 5, Number 1, January 2006

[4] Bone scinti-scanning in osteolytic lesions, Clinical Nuclear Medicine • Volume 29, Number 1, January 2004

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