The Application of Unconventional PET Tracers in Nuclear Medicine

Amir Reza Jalilian; PharmD, PhD

Nuclear Medicine Research Group, Agricultural,
Medical and Industrial Research School (AMIRS),
Karaj, Iran

(Received 21 September 2008, Revised 9 March 2009, Accepted 19 March 2009)

ABSTRACT

The production and application of PET tracers has been a unique step in the progress of nuclear medicine in last two decades. The most important PET tracers include F-18, C-11 and N-13 radioisotopes and many nuclear medicine centers throughout the globe are using them. However some new tracers are under their way to the mass administration, currently being in the clinical trials or preliminary studies. Gallium-66 and 68 tracers such as Ga-DOTANOC and Ga-DOTANIC are currently being used in many neuroendocrine tumor studies in human in Europe and North America, and global application of these tracers remain to the cheaper and easier providence of $^{68}Ge/^{68}Ga$ generators. Copper tracers such as $^{61,62,64}Cu$-ATSM and $^{61,62,64}Cu$-PTSM are the most important unconventional tracers used in hypoxia and perfusion studies respectively using PET technology. Copper tracers can easily be produced using a medium cyclotron with simple chemistry. Many other interesting PET radioisotopes such as Tc-94m (HL. 52 min), I-124 (HL. 100h), Y-86 (HL. 14.7) and rubidium tracers are being studied in some research centers in the world. This review article would describe the properties, mechanisms, production routes and problems of unconventional PET tracers with a look to the future of some important drug candidates.

Key Words: Nuclear medicine, PET tracer, Gallium, Copper, Tc-94m

Iran J Nucl Med 2009; 17(1): 1-11

Corresponding author: Dr. Amir Reza Jalilian, Agricultural, Medical and Industrial Research School (AMIRS), Karaj, Iran. P.O.Box: 31485-498
E-mail: ajalilian@nrcam.org

INTRODUCTION

The molecular imaging revolution in medicine has opened an ultimate view in various fields of sciences, including physics, chemistry, molecular biology and medicine resulting into production and evaluation of new tools in nuclear medicine.

In mid-80s the facile production routes for the most widely used PET tracer, FDG, was introduced and in less than a decade many other ^{18}F-tracers as well as ^{13}N-NH_3, ^{15}O-H_2O and ^{11}C-simple molecules made their way to clinical trials in nuclear medicine. By the end of 1990s the four important PET radionuclides (C-11, N-13, O-15 and F-18) were known to all medical society and this trend is still ungoing. However, appart from these radioisotopes, many other PET radionuclides were prepared and some of them entered the human application phase due to the need of tracing the related elements in human diseases and conditions. Some other was used in radiolabeled form and demonstrated interesting diagnostic tools in various biological phenamena. In this review, we will focus on the physiochemical properties, production and application of theses unconventional PET radioisotopes in nuclear medicine and biology. The present paper can lead the interested readers to widen their knowledge beyoand ^{18}F, ^{11}C, ^{15}O and ^{13}N radiotracers borders. There is a great chance that some of the introduced tracers in this manuscript would be important radiopharmaceuticals in next decade especially copper tracers.

Gallium radiotracers

The positron-emitting Ga(III) radionuclides, ^{68}Ga and ^{66}Ga, have been proposed for applications in positron emission tomography imaging (PET).

Gallium-68: ^{68}Ga, a generator-produced positron-emitting isotope is an alternative radionuclide for somatostatin receptor imaging using PET (1, 2). There are better physical properties for ^{68}Ga over ^{66}Ga for imaging studies like higher ^{66}Ga positron energy and lower positron decay.

1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) is increasingly used as a versatile chelator that binds a large number of main group and transition metal ions as well as Ga with high stability constants (3). Classes of biomolecules to which DOTA may be conjugated include macromolecules such as antibodies (4) or antibody fragments, or small peptides, peptidomimetics or nonpeptide receptor ligands (5).

The most interesting DOTA-based ^{68}Ga-radiotracer i.e. ^{68}Ga-DOTATOC (Fig. 1) is clearly superior to the other DOTA-somatostatin analogs as well as Octreoscan^{TM} as indicated by its uniquely high tumor-to non-target tissue ratio (6). In particular, radiogallium isotopes labeled with somatostatin analogues may give us the opportunity for diagnosis, dosimetry and therapy of SSTR positive tumors. Other ^{68}Ga small molecules have been prepared and used for their possible diagnostic value. For instance, based on malignant suppressive effects of Ga-oxine complex (7), ^{68}Ga-labeled oxine (Fig. 1) has been prepared and used for tumor imaging as well as RBC labeling since 1977 (8).

Gallium-66: Unavailability of Ga target systems for ^{68}Ge production to prepare the ^{68}Ge/^{68}Ga generator as well as international limitations in buying the generator from external vendors, made many grouos to produce ^{66}Ga for their preliminary studies.

^{66}Ga ($T_{1/2}$ = 9.49 h, E_γ: 833.5, 1039.3 keV; β^+:56.5%, $E_{max}\beta^+$:4.153 MeV; E.C:43.5%) (9, 10) is an intermediate-lived radionuclide that is potentially suitable for positron emission tomography imaging of biological processes with intermediate to slow target tissue uptake (11, 12). Various nuclear reactions have been used for the production of this PET radionuclide such as ^{63}Cu(^{4}He,n)^{66}Ga and ^{66}Zn(p,n)^{66}Ga (13, 14).

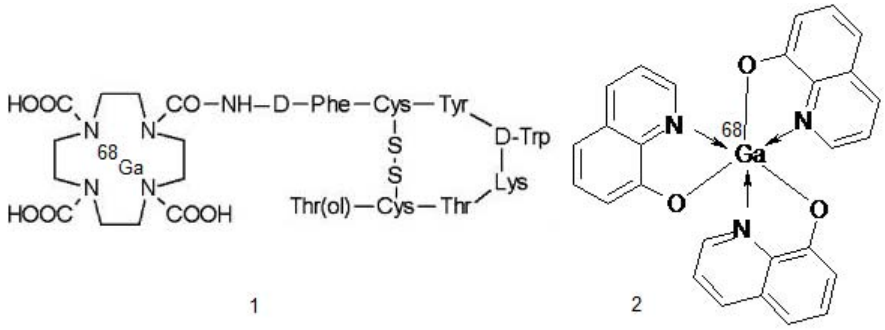

Figure 1. structure formua for ^{68}Ga-DOTATOC (left) and ^{68}Ga-Oxine (right) (7)

Table 1. Physical properties of PET copper radionuclides (9, 24)

Radionuclide	$T_{1/2}$	β^- MeV (%)	β^+ MeV (%)	E.C. (%)	γ keV(%)
Cu-64	12.7 h	0.5787 (39%)	0.65308 (17.4%)	43.6%	1345.77 (0.473%) 511 (34.79%)
Cu-62	9.7 min	----	2.927 (97.2%)	2.8%	511 (194.86%) 1173.02 (0.342%)
Cu-61	3.333 h	----	1.2164 (51%) 1.1489 (2.3%) 0.9334 (5.5%) 0.5604 (2.6%)	38.6%	656.008 (10.77%) 511 (120.87%) 373.05 (2.10%) 282.956 (12.2%) 67.412 (4.20%)
Cu-60	23.7min	----	3.7719 (5%) 2.9456 (15%) 2.4784 (2.8%) 1.9805 (49%) 1.9105 (11.6%) 1.8352 (4.59%)	12.01%	3124.1 (4.8%) 2158.90 (3.34%) 1861.6 (4.8%) 1791.6 (45.4%) 1332.501 (88%) 1035.2 (3.7%) 826.4 (21.7%) 511 (185.19%) 467.3 (3.52%)

^{66}Ga has been used as a suitable nuclide for radiolabeling of monoclonal antibodies (15) in the detection of cardial diseases, staging of neuroendocrine tumors and other lesions after dosimetric studies (16), as well as the radiolabelling of red blood cells (17).

We have recently reported the production of ^{66}Ga (18) and some of its radiolabeled compounds such as ^{66}Ga-bleomycin for possible PET oncologic applications (19) as well as ^{66}Ga-Oxinate for cell radiolabeling (20), but gallium-66 tracers remain the tools for research purposes.

Copper tracers

The radio-coppers have attracted considerable attention since they include isotopes which, due to their emission properties, offer themselves as agents of both diagnostic imaging (^{60}Cu, ^{61}Cu, ^{62}Cu and ^{64}Cu) and *in vivo* targeted radiation therapy (^{64}Cu and ^{67}Cu) (21, 22).

The properties and availability of these radionuclides affect the exact applications where they can be employed. The physical properties of copper radionuclides are summarized in Table 1.

In this section, the copper radiotracers and radiopharmaceuticals are categorized according to the ligands used for radiolabeling and the possible therapeutic and/or diagnostic applications are also presented.

Cu-diacetyl-bis(N^4-methylthiosemicarbazone) (Cu-ATSM):

Hypoxia is an important determinant for biological behavior of malignant solid tumors. *In vitro* and *in vivo* studies have shown that tumor hypoxia is associated with an increased likelihood of local recurrence and distant metastasis, as well as resistance to radiation therapy and certain types of chemotherapy (23).

In continuation of bis-thiosemicarbazone biological evaluation, Fujibayashi and his colleagues developed radiocopper-labeled diacetyl-bis(*N*4-methylthiosemicarbazone) (Cu-ATSM) for imaging hypoxic tissue with PET (25-29). Preclinical studies have shown that Cu-ATSM accumulates avidly in hypoxic cells, but washes out rapidly from normoxic cell. Human absorbed dose has been estimated for Cu-ATSM based on animal biodistribution data extrapolated to humans and an image-based radiation dosimetry study of ^{60}Cu-ATSM in patients with non-small-cell lung cancer (NSCLC) where organ activity concentrations were measured by longitudinal PET studies (30). Due to its multiple decay modes, ^{64}Cu can be used for the production of therapeutic radiopharmaceutical, ^{64}Cu-ATSM that has potential as a radiotherapy agent with an option of real-time PET monitoring.

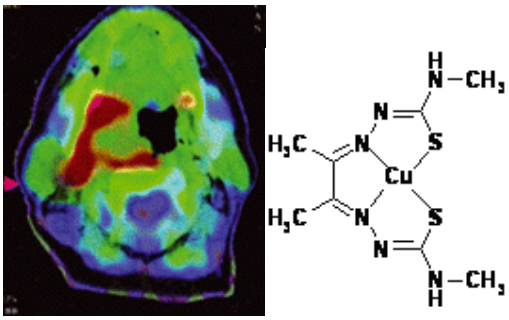

Figure 2. Heterogeneous ^{60}Cu-ATSM intensity within the gross tumour, representing the presence of tumour hypoxia (red-colored region) (31) (left) and structure formula for Cu-ATSM (right)

^{64}Cu-ATSM has been reported as a useful therapeutic agent for colorectal carcinoma using an in vivo tumor model (32). ^{64}Cu-ATSM is able to attack hypoxic tumor cells directly, as well as potentially affecting the peripheral non-hypoxic regions indirectly by the particle decay of ^{64}Cu (33). It has also shown significant increase to the survival time of hamsters bearing solid tumors without acute toxicity (32).

Cu-Pyruvaldehyde Bis(N^4-methyl)thiosemicarbazone (Cu-PTSM):

Cu-PTSM belongs to a class of neutral, lipophillic complexes that have demonstrated rapid diffusion into cells. It can be trapped in many cells as a function of blood circulation around the cells and is often categorized as a perfusion agent. When radiolabeled with PET copper radionuclides, it can be used as an important measure of perfusion. For instance, the generator-produced radiopharmaceutical, ^{62}Cu-pyruvaldehyde Bis(*N*^{4}-methyl)thiosemicarbazone (PTSM), has shown great promise as an agent for cardiac and brain perfusion studies (34, 35) using PET. The availability of this radiopharmaceutical from a generator can greatly increase the number of procedures

performed every year by removing the requirement that a cyclotron must be near the imaging facility.

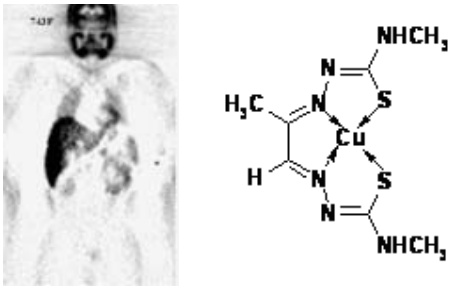

Figure 3. Whole body PET images illustrate the biodistribution of Cu-PTSM (left) (36) and molecular formula of Cu-PTSM

The amount of tracer accumulation in the cells is a function of cell thiol containing compounds such as glutathione and sulfur-containing proteins, due to the reduction capacity of the cell media.

Therefore, in some cases Cu-PTSM can be trapped into tumor cells. In experiments using cultured single-cell suspensions of EMT6 mammary carcinoma cells, 80% of ^{64}Cu-PTSM added was retained within the cells after only 1 min (28). The therapeutic potential of ^{64}Cu-PTSM in inhibiting cancer cell implantation and growth at doses well below the maximum tolerable dose, with no signs of toxicity to hamsters has been reported (37). In another study at our group, ^{64}Cu-PTSM showed significant bioaccumulation in fibrosarcoma tumors in animal models, showing the potential of therapeutic effects of this tracer (38).

Technetium-94m

Recent progress in both Tc radiopharmaceutical chemistry and the single photon emission computed tomography (SPECT) imaging technique has broadened its applications. However, to quantitate the biodistribution of those radiopharmaceuticals in humans, it would be meaningful to use positron emission tomography (PET) and a positron-emitting Tc isotope. Among Tc positron emitter radioisotopes, ^{94m}Tc [T1/2 52.5 min], with its relatively high positron branching (72%), medium positron end-point energy (2.47 MeV), and suitable half-life, appears to be most interesting. The bridging of ^{99m}Tc SPECT and ^{94m}Tc PET seems to be very relevant for the new generation of ^{99m}Tc tracers. In an interesting study, an octreotide analog was developed for Tc-94m labeling and used in tumor imaging in animal models (39).

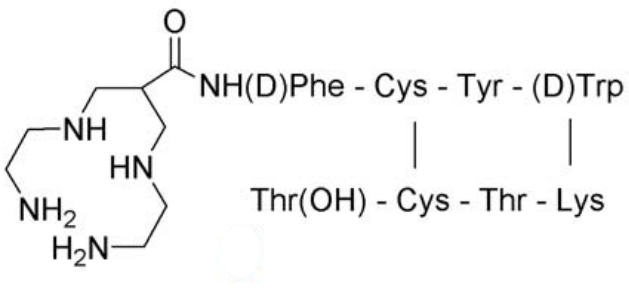

Figure 4. An octreotide analog for ^{94m}Tc-labeling (left) and a PET scan in tumor-bearing rat (38)

Many other previous ^{99m}Tc labeled tracers especially cardial agents were also labeled with ^{94m}Tc and used in the biological evaluation and animal studies such as methoxyisobutyl isonitrile (MIBI) (40) and teboroxime (41). In a separate study ^{94m}Tc-MIBI was employed in multidrug resistance P-glycoprotein transport evaluation (42). The application of ^{94m}Tc-immunoPET for the study of however there are various breakpoints in the cyclotron production and application of this radionuclide, such as;

short half life, molibdenum targetry difficulties and recovery of enriched material.

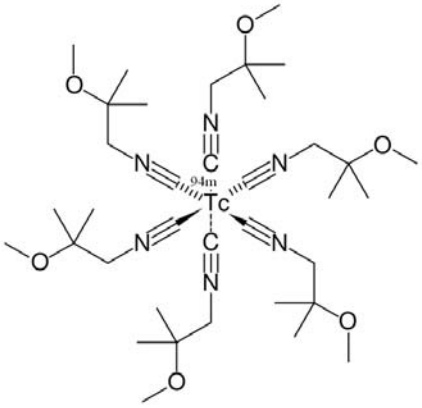

Figure 5. ^{94m}Tc-MIBI formula (43)

Iodine-124

An interesting PET radionuclide is I-124 (t1/2=100.3 h), which based on its natural accumulation in tyroid gland, its most important application would be tyroid related malignancies using PET scan after administration of ^{124}I-NaI. Figure 5. (left) demonstrates a PET scan of differentiated thyroid cancer in a human subject (43).

One of the candidate positron emitters for PET with tumour-seeking MAbs (immuno-PET) is ^{124}I, as its physical half-life is compatible with the time needed for MAbs to achieve optimal tumour-to-non-tumour ratios (2–4 days for intact MAbs).

Thus far, no definite preclinical or clinical proof has been provided that ^{124}I-immuno-PET can be used in the above-mentioned scouting approach, taking into account that such an approach demands fully congruent uptake of the radioiodinated MAbs in tumour and normal organs (44).

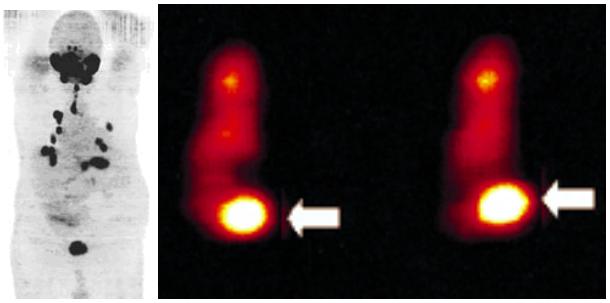

Figure 6. ^{124}I PET scan in poorly differentiated thyroid cancer patient (42) (left) and Immuno-PET images of ^{124}I-huA33 in BALB/c nude mice bearing SW1222 colorectal cancer xenografts (45) (right)

An interesting application of I-124 in radiolabeling of polypeptides is the use of ^{124}I-annexin for the detection of apopthosis in various human diseases involving cell death (46).

The use of this nuclide is still limited due to the low number of production methods and centers however based on the suitable half-life and the existing radioiodination experiences around the globe, we should be expecting progress in the application of I-124.

Yttrium-86

Yttrium-90 (t1/2=64.1 h, β^+=100%, E β^+=1.3 MeV) is one of the most widely used radionuclides for therapy with radiolabeled antibodies. However, because Y-90 emits only beta- particles, accurate dosimetry is difficult.

Therefore, the positron-emitting ^{86}Y (t1/2=14.7 h, β^+=33%, E β^+=1.2 MeV) has been proposed for use as a quantitative PET imaging agent for in vivo determination of biodistribution and dosimetry of therapeutic

^{90}Y pharmaceuticals for individual patients (47, 48).

Rubidium radionuclides

Among Group IA elements in periodic table any radioisotope can more or less mimick potassium cation in Na^+/K^+ ATPase pump especially in myocardial cell surface. Rubidium is an interesting element due to the existence of various medically applicable radionuclides. These radioisotopes have been used in nuclear cardiology. Rubidium-81 has been used in diagnosis of ischaemic heart disease (49), coronary stenosis (50) and noninvasive myocardial imaging (51).

Since 1980, Lambrecht and colleagues showed that Rb-82m can be a useful radionuclide for cardiac imaging, while the other rubidium radionuclide (52), *i.e.* Rb-82, used as a radiotracer for nuclear cardiology (53), has a very short half life (1.27 min) (54), and its use has not been reported widely.

Rb-82m can be a good substitute for cardio-PET clinical studies due to its suitable physical properties (Table 2). This radionuclide decays to the stable kryptom-82 isotope and as mentioned above is potassium analog for like other Rb isotopes (55). With respect to the increasing importance of positron emitters in clinical studies, use of PET rubidium nuclides have come to a great importance (56, 57).

In one study, Rb-82m was produced, purified and formulated as a PET radiopharmaceutical in our group in the country. Preliminary imaging studies were carried out using a dual head SPECT system, equipped with a co-incidence camera (58).

Table 2. Physical characteristics of Rubidium radionuclides

Radioisotope	Nuclear Reaction	Half-life	Decay Mode (%)	Maximum β^+ energy	Gamma Energies(keV)
Rb-81	$^{82}Kr(p,2n)^{81}Rb$	4.576 h	β^+ (27.2), E.C.(72.8)	2.1 MeV	190.38 (64.0%) 456.76 (3.02%) 446.15 (23.2%) 510.31 (5.3%) 537.60 (2.23%)
Rb-82	$^{82}Kr(p,n)^{82}Rb$	1.273 m	β^+ (95.5), E.C.(4.5)	3.38 MeV	776.517 (13%)
Rb-82m	$^{82}Kr(p,n)^{82m}Rb$	6.472 h	β^+ (26), E.C.(74)	0.8 MeV	776.517 (84%) 554 (64%) 619 (38%) 698.374 (26.3%) 1474.88 (15.53%) 1044.002 (32.00%) 619.106 (37.975%) 1317.473 (23.7%) 554.348 (62.4%) 827.828 (21.0%) 1007.59 (7.17%)

Selenium-73

The nuclear properties of ^{73}Se ($t_{1/2}$=7.1 h; β^+=65%; EC=35%; E_{β^+}=1.32 MeV) suggest that it may be a more useful radioselenium label for *in vivo* medical applications using positron emission tomography (PET). For

instance, a comparison of the calculated radiation doses to the liver from ^{73}Se and ^{75}Se in the case of seleno-methionine shows an approximate ratio of 1:50 (59, 60).

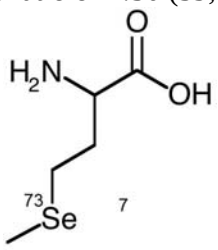

Figure 7. The structure of ^{73}Se-selenomethinine (60)

Cobalt-55

Cobalt offers a selection of radionuclides suitable for imaging as well as tracing techniques (9). The most commonly used cobalt PET radionuclide, ^{55}Co, (t1/2: 17.53 h) provide suitable physical properties for diagnostic purposes using PET imaging. A couple of studies using ^{55}Co-$CoCl_2$ compounds have been reported in the detection of caratid artery disease (61), vascular dementia (62), renographic studies (63) and stroke (64).

Zinc-62

^{62}Zn (HL=6.9 h, EC: 3 %, β+: 97%) is a rather long-half life PET radioisotope mostly used in preparation of ^{62}Zn/^{62}Cu generators (65), but its direct use has not been reported in labeling or imaging studies. [^{62}Zn] labeled bleomycin preparation had been once reported without further biological studies (66).

Bromine-86

One possible long-lived positron-emitting label for mAbs and their fragments is ^{76}Br. This nuclide has a half-life of 16.2 h and decays by emitting positrons (54%). The use of the ^{76}Se(p,n)^{76}Br nuclear reaction and enriched Cu_2Se targets enables the production of useful quantities of ^{76}Br using 16-MeV cyclotrons, which are available at many PETcenters (67). Alternatively, this nuclide could be used in a satellite PET center in combination with regional production (68). The imaging and quantification properties of ^{76}Br have been carefully studied (69); it has been demonstrated that despite its relatively high positron energy (Eh+max=3.9 MeV), resolution degradation is minor compared to that of ^{18}F. There are reports regarding the use of simple ^{76}Bromide for malignancy scans in brain tumors (70) however the most important future use of this radionuclide would be in radioimmunoscintigraphy.

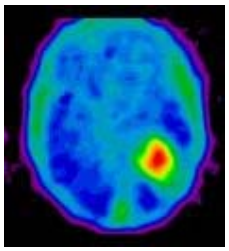

Figure 8. A PET scan of ^{76}Br-bromide in a brain tumor (70)

CONCLUSION

Gallium-68 tracers are the most important unconventional PET tracers but for most of countries production and/or application of the ^{68}Ge/^{68}Ga generator is bothersome. ^{68}Ga-DOTANOC and ^{68}Ga-DOTANOC are widely used in PET scan of neuroendocrine tumors with high quality and many human studies are under progress. PET copper radionuclides, *i.e.* copper 60, 61, 62 and 64 are more or less used in the production of two important tracers; Cu-PTSM, a perfusion agent and Cu-ATSM a hypoxia imaging agents and many studies are being performed in some coutries. Bromine-76 and iodine-124 are 2 radiohalogen that can be used in immunoPET studies and considerable works are focused on I-124. other tracers including Co-55, Se-73, Rb-82,… are at the research level and are considered at the study level in many academic research centers.

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