Non-standard PET radionuclides: time to get ready for new clinical PET strategies

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A recent analysis of PET radiopharmaceuticals and PET imaging sales from Bio-Tech Systems Inc. [1] suggests an expanding market in oncology, cardiology and neurology. The growth of clinical PET appears to be paralleled by the growth in the scientific use of PET and PET/CT worldwide, as the number of published papers on PET appearing in PubMed is doubling every 4 years.

The volume of use of PET is likely to increase in all disease categories; in particular, there are forecasts of future growth in cancer imaging, where PET has been shown to be effective. In fact, the success of PET/CT systems has allowed radiologists to promote the advantages of multi-modality imaging to both patients and investors in PET imaging facilities, and there has been a marked shift towards highly priced multi-slice PET/CT scanners as the technology becomes more readily available and the distribution of FDG improves.

Further growth of PET procedures in oncology, cardiology and neurology will ensue as the availability of PET increases and its capabilities become more visible and more appreciated by referring physicians. New molecular tracers will overcome some of the limitations of FDG-PET scanning and will aid in the assessment, therapy planning and monitoring of cancer patients. Which tracers are currently the most likely candidates for such a role? New tracers labelled with positron-emitting isotopes of iodine, copper, technetium, bromine, yttrium, titanium, gallium or indium might be the newcomers, as suggested by the work of some research groups under the guidance of visionary leaders and the commitment of a few small companies in the US and Europe that are investing in the synthesis and distribution of these new radiopharmaceuticals labelled with non-standard radionuclides. Moreover, the use of these tracers may pave the way for new radiometabolic treatments based on the use of particle-emitting isotopes deliverable by substituting the gamma radionuclide with a beta emitter, on the same pharmaceuticals as are exploited for diagnostic, dosimetric and biodistribution studies. Only a few very recent examples of this paradigm shift are summarised below.

The commentaries in this section derive from a literature search and include summaries of articles compiled and linked to each other by extensive use of the text contained in the articles examined.

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New, optimised methods for the production of non-standard radionuclides

Nearly 10 years ago, in an interesting review, Pagani and colleagues [2] envisaged that the increasing amount of clinically relevant information obtained by PET, primarily with FDG, would generate demand for new routes for the widespread and cost-efficient use of PET radiopharmaceuticals. They examined 25 “non-standard” positron-emitting radionuclides, discussing the impact of their decay properties on image quality and reviewing methods for their production and their application in imaging techniques. However, since then, only a few radiopharmaceuticals have been labelled with positron-emitting isotopes of iodine, copper and gallium with a physical half-life that may enable the production, shipment and use of radiopharmaceuticals at distances that are affordable nowadays only when they are labelled with single-photon emitting radionuclides or fluorine. However, there is a continuous interest in optimising the production of such non-standard radionuclides with medium-energy cyclotrons, with sufficiently high energy to obtain acceptable yields and radiopharmaceuticals with the highest purity. Among the non-standard radionuclides, iodine and copper are those for which research and development are most advanced.

Optimisation of ^{124}I production via $^{124}Te(p,n)^{124}I$ reaction

Sajjad and colleagues from the Department of Nuclear Medicine, State University of New York (Buffalo, NY, USA), have recently reported in *Applied Radiation and Isotopes* the optimisation of ^{124}I production via $^{124}Te(p,n)^{124}I$ reaction [3]. ^{124}I was produced in an amount greater than 3.7 GBq (100 mCi, EOB) by bombarding $^{124}TeO_2$ targets with a current of 24 μA for about 8 h. This was achieved by keeping the target at 37° relative to the beam during irradiation, by sweeping the beam across the target and by keeping the incident energy of the proton at 14.1 MeV. The time-averaged yield of the 8-h run was 21.1 MBq/μAh (0.57 mCi/μAh), which was 90% of the theoretical yield calculated using thick target yield data obtained from the reported excitation function for the reaction. At the end of bombardment, the level of ^{125}I and ^{126}I impurities, co-produced with ^{124}I, was 0.03% and 0.007%, respectively.

Cyclotron production of ^{64}Cu by deuteron irradiation of ^{64}Zn

Abbas and colleagues from the Institute for Health and Consumer Protection, Joint Research Centre, European Commission, in Ispra, Italy have recently carried out the production of ^{64}Cu by deuteron irradiation of ^{64}Zn [4]. ^{64}Cu has a 12.7-h half-life and is both a beta(+) and a beta (−) emitter. This property makes ^{64}Cu a promising candidate for novel medical applications, since it can be used simultaneously for therapeutic application of radiolabelled biomolecules and for diagnosis with PET. Following previous work on ^{64}Cu production by deuteron irradiation of natural zinc, the authors report the production of this radionuclide by deuteron irradiation of enriched ^{64}Zn. In addition, yields of other radioisotopes such as ^{61}Cu, ^{67}Cu, ^{65}Zn, ^{69m}Zn, ^{66}Ga and ^{67}Ga, which were co-produced in this process, were also measured. The evaporation code ALICE-91 and the transport code SRIM 2003 were used to determine the excitation functions and the stopping power, respectively. All the nuclear reactions yielding the above-mentioned radioisotopes were taken into account in the calculations for both the natural and the enriched Zn targets. The experimental and calculated yields were shown to be in reasonable agreement. The work was carried out with the Scanditronix MC-40 Cyclotron with 19.5-MeV deuterons, the maximum deuteron energy obtainable with the MC-40.

A simple and selective method for the separation of Cu radioisotopes from nickel

Separation of copper radioisotopes from a nickel target is normally performed using solvent extraction or anion exchange rather than using exchange. A commonly held opinion is that cationic exchangers have very similar thermodynamic complexation constants for metallic ions with identical charges, therefore making the separation very difficult or impossible. The results presented in the article of Fan and colleagues from the School of Physics and Astronomy, The University of Birmingham, UK [5] indicate that the selectivity of Chelex-100 (a cationic ion exchanger) for Cu radioisotope and Ni ions not only depends on the thermodynamic complexation constant in the resin but also markedly varies with the concentration of mobile H(+). In the method developed by the authors, separation of copper radioisotopes from a nickel target was achieved in a column filled with Chelex-100 by controlling the HNO_3 concentration of the eluent, and the separation was much more effective, simple and economical in comparison with the common method of anion exchange. For an irradiated nickel target with 650 mg Ni, after separation, the loss of Cu radioisotopes in the nickel portion was reduced from 30% to 0.33% of the total initial radioactivity and the nickel mixed into the radioactive products was reduced from 9.5 to 0.5 mg. This significant improvement will make subsequent labelling much easier and reduce the consumption of chelating agents and other chemicals during labelling. If the labelled agent is used in human medical applications, the developed method will significantly decrease the uptake of Ni and chelating agents by patients, thereby reducing both the stress on the human body associated with clearing the chemicals from blood and tissue and the risk of various acute and chronic disorders due to exposure to Ni.

Advances in the production, processing and microPET image quality of ^{94m}Tc

Heather M. Bigott and colleagues from Department of Chemistry, University of Missouri-Columbia, USA, the Division of Radiological Sciences, Washington University School of Medicine, St. Louis, MO, USA and the PET Tracer Department, Institute of Radiopharmacy, Research Centre Rossendorf, Dresden, Germany [6] have extended procedures and methods reported in the literature for the production, processing and imaging of the short-lived, rarely used PET radionuclide ^{94m}Tc. A key modification was the development of a single step that combines purification and concentration of an aqueous ^{94m}Tc-pertechnetate solution, which both reduces the processing time and increases the final concentration of the solution. Additionally, a convenient method for the direct recovery of ^{94m}Tc into an organic solvent was developed, eliminating the solvent transfer step needed for organic syntheses using ^{94m}Tc. Each of these advances potentially extends the scope of syntheses possible with this short-lived radionuclide. To explore the imaging potential of ^{94m}Tc, they carried out phantom imaging studies on small-scale high-resolution PET scanners to estimate the limitations of detection associated with ^{94m}Tc and PET. Preliminary studies demonstrate that useful images can be obtained with modern image reconstruction algorithms when using a correction for the cascade gamma ray contamination.

Preclinical applications of alternative radionuclides

Validation of a novel CHX-A″ derivative suitable for peptide conjugation: small animal PET/CT imaging using ^{86}Y-CHX-A″-octreotide

Thomas Clifford and colleagues from the Radioimmune and Inorganic Chemistry Section, Radiation Oncology Branch, National Cancer Institute, Bethesda, Maryland, and the Mallinckrodt Institute of Radiology, Washington University School of Medicine in St. Louis, Missouri [7] have developed a versatile bifunctional chelating reagent based on a preorganised cyclohexyl derivative of DTPA (CHX-A″) for the convenient N-terminal labelling of peptides with metal ion radionuclides of Bi(III), In(III), Lu (III) or Y(III). This was achieved via the synthesis of a mono-*N*-hydroxysuccinimidyl penta-*tert*-butyl ester derivative of CHX-A″ (*trans*-cyclohexyldiethylenetriaminepenta-acetic acid) featuring a glutaric acid spacer. Commercially obtained octreotide was modified at its N terminus by this reagent in the solution phase, and its subsequent radiolabelling with ^{111}In ($T_{1/2}$=2.8 days) and ^{86}Y ($T_{1/2}$=14.7 h) demonstrated. Small animal PET/CT imaging of ^{86}Y-CHX-A″-octreotide in a somatostatin receptor-positive tumour-bearing rat model was also carried out for the validation of the novel agent. Like the previously reported DOTA-octreotide derivatives, CHX-A″-octreotide allows for the complexation of In (III), Lu(III), or Y(III). In addition, CHX-A″-octreotide provides direct access to a selection of alpha-emitting radionuclides, including ^{213}Bi, which has shown impressive results in targeted alpha-particle therapy. CHX-A″ is superior to DOTA for the complexation of ^{213}Bi ($T_{1/2}$= 45.6 min) because of more rapid complexation kinetics at ambient temperature. Future studies involving CHX-A″-peptide conjugates labelled with alpha-emitting isotopes such as ^{213}Bi may lead to the development of improved targeted radiotherapeutic agents.

Combined ^{124}I-PET/CT imaging of NIS gene expression in animal models of stably transfected and intravenously transfected tumour

Dingli and co-workers [8] from the Molecular Medicine Program, Mayo Clinic College of Medicine, Rochester, MN, USA envisage the imperative to monitor the biodistribution, expression and replication of replication-competent viruses used for cancer gene therapy in living organisms. They evaluated the potential of ^{124}I PET/CT imaging in gene therapy animal models utilising the sodium iodide symporter (NIS) and compared the findings with ^{123}I gamma camera imaging. CB17 SCID mice were implanted with myeloma cell lines expressing NIS or infected by MV-NIS given systemically. Mice were imaged by both gamma camera ^{123}I and PET/CT ^{124}I and image quality assessed. The authors found that NIS-expressing tumours concentrated 7.1% of the injected activity while tumours infected with the control virus had only 0.3% of the activity injected. They conclude that ^{124}I PET/CT in combination with NIS allows the tracking of stably transfected tumours or intravenously transfected tumours and that PET/CT allows accurate and non-invasive imaging of the distribution and gene expression of a replicating viral vector in living systems.

Molecular imaging of EGFR kinase activity in tumours with ^{124}I-labelled small molecular tracer and PET

PET with epidermal growth factor receptor (EGFR) kinase-specific radiolabelled tracers could provide the means for non-invasive and repetitive imaging of heterogeneity of EGFR expression and signalling activity in tumours in individual patients before and during therapy with EGFR signalling inhibitors. Pal et al. from the Department of Experimental Diagnostic Imaging, MD Anderson Cancer Center, Houston, TX, USA [9] developed the synthesis morpholinand ^{124}I radiolabelling of the (*E*)-But-2-enedioic acid [4-(3-[(^{124})I]iodoanilino)-quinazolin-6-yl]-amide-morpholin(3-morpholin-4-yl-propyl)-amide (morpholino-[^{124}I] IPQA), which selectively, irreversibly and covalently binds the adenosine triphosphate binding site to the activated (phosphorylated) EGFR kinase, but not to the inactive EGFR kinase. The latter was demonstrated using in silico modelling with crystal structures of the wild type and different gain-of-function mutants of EGFR kinases. Also, this was demonstrated by selective radiolabelling of the EGFR kinase domain with morpholino-[^{131}I]IPQA in A431 human epidermoid carcinoma cells and Western blot autoradiography. In vitro radiotracer accumulation and washout studies demonstrated a rapid accumulation and progressive retention post washout of morpholino-[^{131}I] IPQA in A431 epidermoid carcinoma and in U87 human glioma cells genetically modified to express the EGFRvIII mutant receptor, but not in the wild type U87MG glioma cells under serum-starved conditions. Using morpholino-[^{124}I]IPQA, the authors obtained non-invasive PET images of EGFR activity in A431 subcutaneous tumour xenografts, but not in subcutaneous tumour xenografts grown from K562 human chronic myeloid leukaemia cells in immunocompromised rats and mice. Based on these observations, they suggest that PET imaging with morpholino-[^{124}I]IPQA should allow for identification of tumours with high EGFR kinase signalling activity, including brain tumours expressing EGFRvIII mutants and non-small-cell lung cancer expressing gain-of-function EGFR kinase mutants. Because of significant hepatobiliary clearance and intestinal reuptake of the morpholino-[^{124}I] IPQA, additional [^{124}I]IPQA derivatives with improved water solubility may be required to optimise the pharmacokinetics of this class of molecular imaging agents.

Bispecific antibody pretargeting PET (immunoPET) with an ^{124}I-labelled hapten-peptide

McBride from Immunomedics, Inc., Morris Plains, NJ, USA and colleagues from other institutions [10] have previously described a highly flexible bispecific antibody (bs-mAb) pretargeting procedure using a multivalent, recombinant anti-CEA (carcinoembryonic antigen) × anti-HSG (histamine-succinyl-glycine) fusion protein with peptides radiolabelled with ^{111}In, ^{90}Y, ^{177}Lu and ^{99m}Tc. In a new study the authors report the development of a radioiodination procedure primarily to assess PET imaging with ^{124}I. A new peptide, DOTA-D-Tyr-D-Lys (HSG)-D-Glu-D-Lys(HSG)-NH_2 (DOTA is 1,4,7,10-tetra-azacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid), was synthesised and conditions were established for radio-iodination with yields of approximately 70% for ^{131}I and 60% for ^{124}I. Pretargeting with the ^{131}I- and ^{124}I-labelled peptide was tested in nude mice bearing LS174T human colonic tumours that were first given the anti-CEA × anti-HSG bs-mAb. Imaging (including small-animal PET) and necropsy data were collected at several intervals over 24 h. Comparisons were made between animals given ^{124}I-anti-CEA Fab′, FDG, the same peptide radiolabelled with ^{111}In and pretargeted with the bs-mAb, and the radioiodinated peptide alone. The authors report that the radioiodinated peptide alone cleared quickly from the blood with no evidence of tumour targeting; however, when pretargeted with the bs-mAb, tumour uptake increased 70-fold, with efficient and rapid clearance from normal tissues, allowing clear visualisation of tumour within 1–2 h. Tumour uptake measured at necropsy was 3- to 15-fold higher and tumour-to-blood ratios were 10- to 20-fold higher than those for ^{124}I-Fab′ at 1 and 24 h, respectively. Thyroid and stomach uptake was observed with the radioiodinated peptide several hours after injection (animals were not premedicated to reduce uptake in these tissues), but gastric uptake was much more pronounced with ^{124}I-Fab′. Tumour visualisation with FDG at approximately 1.5 h was also good but showed substantially more uptake in several normal tissues, making image interpretation in the pretargeted animals less ambiguous than with FDG. The authors conclude that bispecific antibody pretargeting has a significant advantage for tumour imaging over directly radiolabelled antibodies and could provide additional enhancements for oncological imaging, particularly for improving targeting specificity as compared with FDG.

MicroPET imaging of breast cancer using radiolabelled bombesin analogues targeting the gastrin-releasing peptide receptor

Mammography is a well-established method for detecting primary breast cancer; however, it has some limitations that may be overcome using nuclear imaging methods. Current radiopharmaceuticals have limited sensitivity for detecting small primary lesions, and it has been suggested that novel radiopharmaceuticals are necessary for the detection of primary breast cancer, as well as for the detection of metastases and recurrence and for monitoring therapy. The gastrin-releasing peptide receptor (GRPR) is a seven-transmembrane G protein-coupled receptor that is over-expressed on primary breast cancer and lymph node metastases. Bombesin (BN) is a tetradecapeptide that binds with high affinity to GRPR and can be radiolabelled with the positron emitter, ^{64}Cu for imaging with PET. Parry et al. from the Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO, USA [11] evaluated BN analogues that could be radiolabelled with ^{64}Cu for PET imaging of breast cancer. A series of BN analogues containing 4-, 5-, 6-, 8- and 12-carbon linkers were evaluated with regard to their binding and internalisation into T-47D human breast cancer cells. The ^{64}Cu-labelled analogues were then evaluated in mice bearing morpholinT-47D xenografts by tissue biodistribution and microPET imaging. These studies showed that all of the analogues had IC_{50} values <100 n*M* and were all internalised into T-47D cells. Biodistribution studies showed that the BN analogue with the 8-carbon linker not only had the highest tumour uptake but also had high normal tissue uptake in the liver. The analogues containing the 6- or 8-carbon linkers demonstrated good tumour uptake as determined by microPET imaging. Overall, this study shows the feasibility of using positron-labelled BN analogues for PET detection of GRPR-expressing breast cancer.

PET of human prostate cancer xenografts in mice with increased uptake of $^{64}CuCl_2$

Peng and colleagues from the Department of Pediatrics, School of Medicine, Wayne State University, Detroit, MI, USA [12] aimed to determine whether human prostate cancer xenografts in mice can be localised by PET using $^{64}CuCl_2$ as a probe (^{64}Cu PET). Athymic mice bearing human prostate cancer xenografts were subjected to ^{64}Cu PET, followed by quantitative analysis of the tracer concentrations and immunohistochemistry study of human copper transporter 1 expression in the tumour tissues. The authors found that human prostate cancer xenografts expressing high levels of human copper transporter 1 were well visualised on the PET images obtained 24 h after injection but not on the images obtained 1 h after injection. PET quantitative analysis demonstrated a high concentration of $^{64}CuCl_2$ in the tumours in comparison to that in the left shoulder region (percentage injected dose per gram of tissue: 3.6±1.3 and 0.6±0.3, respectively; p=0.004), at 24 h after injection. The conclusion of the authors was that the data from their study suggest that locally recurrent prostate cancer might be localised with ^{64}Cu PET using $^{64}CuCl_2$ as a probe.

Intertumoural differences in hypoxia selectivity of the PET imaging agent ^{64}Cu(II)-diacetyl-bis(N_4-methylthiosemicarbazone)

Cu-Diacetyl-bis(N_4-methylthiosemicarbazone) (Cu-ATSM) is a recently developed PET imaging agent for tumour hypoxia. However, its accuracy and reliability for measuring hypoxia have not been fully characterised in vivo. Yuan and co-workers from the Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA [13] aimed to evaluate ^{64}Cu-ATSM as a hypoxia PET marker by comparing autoradiographic distributions of ^{64}Cu-ATSM with a well-established hypoxia marker drug, EF5. R3230 mammary adenocarcinomas (R3230Ac), fibrosarcomas (FSA), and 9L gliomas (9L) were used in the study. EF5 and Hoechst 33342, a vascular perfusion marker, were administered to the animal for immunohistochemical analysis. ^{64}Cu-ATSM microPET and autoradiography were performed on the same animal. The tumour-to-muscle ratio (T/M ratio) and standardised uptake values (SUVs) were characterised for these three different types of tumours. Five types of images—microPET, autoradiography, EF5 immunostaining, Hoechst fluorescence vascular imaging and haematoxylin and eosin histology—were superimposed, evaluated and compared. A significantly higher T/M ratio and SUV were seen for FSA compared with R3230Ac and 9L. Spatial correlation analysis between ^{64}Cu-ATSM autoradiography and EF5 immunostained images varied between the three tumour types. There was close correlation of ^{64}Cu-ATSM uptake and hypoxia in R3230Ac and 9L tumours but not in FSA tumours. Interestingly, elevated ^{64}Cu-ATSM uptake was observed in well-perfused areas in FSA, indicating a correlation between ^{64}Cu-ATSM uptake and vascular perfusion as opposed to hypoxia. The same relationship was observed with two other hypoxia markers, pimonidazole and carbonic anhydrase IX, in FSA tumours. Breathing carbogen gas significantly decreased the hypoxia level measured by EF5 staining in FSA-bearing rats but not the uptake of ^{64}Cu-ATSM. These results indicate that some other ^{64}Cu-ATSM retention mechanisms, as opposed to hypoxia, are involved in this type of tumour. This study is the first comparison between ^{64}Cu-ATSM uptake and immunohistochemistry in these three tumours. Although the authors have shown that ^{64}Cu-ATSM is a valid PET hypoxia marker in some tumour types, but not in all, this tumour type-dependent hypoxia selectivity of ^{64}Cu-ATSM challenges the use of ^{64}Cu-ATSM as a universal PET hypoxia marker. Further studies are needed to define retention mechanisms for this PET marker. However, independent of the full understanding of its uptake mechanism, Cu-labelled ATSM has been demonstrated to be very effective for the assessment of hypoxia. Using this tracer, Dehdashti and colleagues have demonstrated that ^{60}Cu-ATSM PET in patients with cervical and lung cancer allows the acquisition of clinically relevant information about tumour oxygenation that is predictive of tumour behaviour and response to therapy [14, 15].

Use of non-standard radionuclides in human PET studies

Acquisition settings for PET of ^{124}I administered simultaneously with therapeutic amounts of ^{131}I

Lubberink and colleagues from the Department of Nuclear Medicine and PET Research, VU University Medical Centre, Amsterdam, The Netherlands [16] assessed the influence of large amounts of ^{131}I on ^{124}I PET image quality and accuracy with various acquisition settings, as radiation dosimetry of thyroid cancer therapy with ^{131}I can be performed by co-administration of ^{124}I followed by longitudinal PET scans over several days. Noise equivalent count (NEC) rates of ^{124}I only were measured with a standard clinical PET scanner. Apart from the standard 350- to 650-keV energy window, 425- to 650-keV and 460- to 562-keV windows were used and data were acquired both with (two-dimensional) and without (two-dimensional [3D]) septa. A phantom containing six hot spheres, filled with a combination of ^{131}I and ^{124}I and with a sphere-to-background ratio of 18:1, was scanned repeatedly with energy window settings as indicated and emission and transmission scan durations of 7 and 3 min, respectively. NEC rates were calculated and compared with those measured with the phantom filled with only ^{124}I. Sphere-to-background ratios in the reconstructed images were determined. One patient with known metastatic thyroid cancer was scanned using energy window settings and scan times as indicated 3 and 6 days after administration of 5.5 GBq of ^{131}I and 75 MBq of ^{124}I. The results of the study demonstrate that the highest ^{124}I-only NEC rates were obtained using a 425- to 650-keV energy window in 3D mode. In the presence of ^{131}I, the settings giving the highest NEC rate and contrast were 425–650 keV and 460–562 keV in 3D mode, with the clinical scans giving the highest quality images with the same settings. The authors conclude that acquisition in 3D mode with a 425- to 650-keV or 460- to 562-keV window leads to the highest image quality and contrast when imaging ^{124}I in the presence of large amounts of ^{131}I using a standard clinical PET scanner.

Feasibility of central cannabinoid CB1 receptor imaging with ^{124}I-AM281 PET demonstrated in a schizophrenic patient

Berding and colleagues from the Department of Nuclear Medicine, University School of Medicine, Hannover, Germany [17] studied central cannabinoid CB1 receptors in a schizophrenic patient using the pyrazole derivative AM281 labelled with the positron-emitting nuclide ^{124}I. A dynamic PET acquisition with simultaneous blood sampling was performed up to 1.5 h post injection. The classical Logan plot analysis was applied to generate a three-dimensional map of distribution volume (DV). The map was spatially normalised into the Montreal Neurological

Institute stereotactic space. Using a volume of interest template, mean values of DV were extracted from multiple grey matter regions and white matter (as a reference). As a measure of regional receptor availability, ratios of DV in grey matter to DV in white matter minus one (DVR-1) were calculated. The highest receptor binding was observed in the striatum and the pallidum (DVR-1 0.35–0.37). Binding in basal ganglia regions was lower on the left than on the right side. Moderately high binding was seen in the frontal cortex (0.22), the temporal cortex (0.18) and the cerebellum (0.15). In conclusion, ^{124}I-AM281 PET can be used to reveal areas with prominent CB1 receptor binding. Nevertheless, limited image contrast and relatively high radiation exposure (physical half-life of ^{124}I: 4 days) have to be taken into account. Asymmetrical receptor binding may possibly reflect pathological changes in schizophrenia.

Conclusions

Over the years, a number of studies have been performed in human subjects with ^{124}I as well as with positron-emitting radioisotopes of copper, though their use has been rather discontinuous. Most have been proof of principle studies and have not been followed up by large series of patient studies. This is probably due to a time lag between consolidation of PET as a clinical tool, currently based almost exclusively on the use of FDG, and the growth of the industrial production and distribution of PET radiopharmaceuticals. Now that PET is widely accepted in clinical practice, cyclotrons are in place and distribution networks are being developed worldwide, the sole production of FDG, often with in-house small cyclotrons, appears a somewhat limited goal given the opportunity to produce and distribute to peripheral users a broad variety of other PET tracers that offer an overall beneficial return for patients and investors in this area of medical imaging. This is therefore both a challenge and an opportunity for molecular imaging. The nuclear medicine community appreciates that beyond FDG there are other radiopharmaceuticals which promise to be of value, and that the power of PET resides in their potential, regardless of the number of CT slices a PET/CT scanner can provide. Radiochemists are also well aware of these opportunities and are working to exploit them, focussing on the production, yields, use and dissemination of the following "non-standard" PET nuclides: ^{45}Ti, ^{60}Cu, ^{61}Cu, ^{64}Cu, ^{66}Ga, ^{72}As, ^{74}As, ^{76}Br, ^{86}Y, ^{89}Zr, ^{94m}Tc and ^{124}I.

It is obvious that only a few centres worldwide will be able to offer the variety of production that will be needed to thoroughly exploit PET, and that small-scale in-house production will be clearly inadequate to satisfy the growing diversity of requests. Therefore the future of PET rests with the growth of industrial production and the development of distribution networks for radiopharmaceuticals. The opportunities that can derive from rethinking the applications of non-standard radionuclides lie primarily in the hands of the molecular imaging community; patients will benefit from these endeavours as long as we remain loyal to the goal of advancing functional and biochemical diagnosis, through imaging, in the quest for individualised treatment as required by the standards of molecular medicine.

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