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Review

# Present and future of PET-radiopharmaceuticals

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## Abstract

The use of Positron Emission Tomography (PET) is increasing dramatically worldwide. To further apply the unique properties of PET, more clinically validated PET-radiopharmaceuticals are required. To increase the availability of more PET-radiopharmaceuticals on one hand new and better radiochemical preparation methods are being developed and on the other hand legislation with respect to the production of PET-radiopharmaceuticals should be appropriate.

With respect to radiochemistry development, most efforts have been made on the use of $^{11}$C and $^{18}$F as radionuclides. $^{11}$C-radiochemistry mainly relies on $^{11}$C-methylation reactions, but recently simple and reliable $^{11}$C-radiochemistry based on $^{11}$C-carbon monoxide has become available.

Recent developments in the production of $^{18}$F-radiopharmaceuticals are focused on synthesis methods that are simple to perform and therefore enabling easy dissemination. Click chemistry, chelation of $^{18}$F and new catalytic systems are being developed.

Also developments in labeling methods with $^{68}$Ga, $^{89}$Zr and $^{64}$Cu will stimulate the use of these radiometals for clinical use.

Application of PET-radiopharmaceuticals for use in patients is subject to strict legislation. The guidelines with respect to Good Manufacturing Practice (GMP) however pose severe constraints to small scale radiopharmacies in hospitals. Currently there is a debate to adapt GMP-regulations for specific production of PET-radiopharmaceuticals intending to maintain the required quality aspects but not to hamper innovation and further development of PET.

**Key words: PET, radiophamaceutical, radiochemistry, GMP, legislation**

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It has been generally accepted that Positron Emission Tomography (PET) has a positive impact on human health, especially in the case of treatment of cancer, cardiovascular diseases and brain disorders. PET is more and more being used in medical decision making and the management of patients. Therefore evidence is growing that PET is cost-effective. As a result PET is being increasingly applied worldwide. Also in developing countries with rapidly growing economies the number of cyclotrons and PET-CT cameras is rapidly increasing.

PET is a cost-effective tool in therapy evaluation and can largely contribute to the growing need for personalized medicine. Examples where PET is a unique tool are: 1. detection and characterization of metabolic activity of tumors; 2. measurement of cell proliferation; 3. measurement of tumor hypoxia; 4. detection and characterization of beta-amyloid plaque in Alzheimers disease; 5. measurement of receptor and gene expression.

Currently [$^{18}$F]fluoro-deoxyglucose (FDG) is the workhorse of PET and is abundantly applied in the detection of primary tumors and metastases (Shukla, 2006). FDG is not very specific since it is also taken up in inflammatory tissues and its uptake is sometimes increased in hypoxic tissues. On one hand this results in a high sensitivity in detecting tumor lesions, but its specificity to evaluate therapy is hampered. To optimally utilize PET in therapy evaluation, more suitable validated tracers beyond FDG are required.

An ever-increasing number of newly discovered biological targets (often of poorly understood function) is available for study since the recent publication of the human genome. However, the repertoire of well-characterized PET radiotracers for in vivo imaging is limited. Radiochemists therefore play a continuing crucial role in the discovery and development of PET imaging probes to enable the study of novel biological targets in humans. Several criteria should be considered in the development of novel PET probes for in vivo imaging, such as choice of radionuclide, position of labelling, metabolism, non-specific binding and radiolabelling strategies. The development of new PET imaging probes relies mainly on the radionuclides $^{11}$C and $^{18}$F. However other useful PET-radionuclides are emerging such as copper-64, gallium-68, zirconium-89 and iodine-124. These radionuclides have their specific characteristics with respect to half-life, positron energy (resolution), positron abundance and availability. Depending of the biological target of interest and the properties of the PET-radiopharmaceutical the proper radionuclide should be selected (Table 1).

## $^{11}$C-radiochemistry

Carbon-11 is the radionuclide of choice for radiolabelling the investigational drug. Replacement of naturally occurring

**Table 1.**

| | Half life resolution | $\beta$ ± Abundance | Availability |
|---|---|---|---|
| $^{11}$C | 20 min Intermediate | High | Cyclotron |
| $^{18}$F | 110 min | High High | Cyclotron |
| $^{64}$Cu | 12.7 h | High Low | Linited |
| $^{68}$Ga | 68 min | Low High | Generator |
| $^{89}$Zr | 78 h | High Low | Limited |
| $^{124}$I | 100 h | Low Low | Limited |

carbon-12 by carbon-11 does not alter the (bio)chemical properties of a molecule. Many synthetic routes to $^{11}$C-compounds are already available and several others are still under development.

Most of these synthetic routes are based on $^{11}$C-methylation reactions (Wuest, 2007). These reactions are being performed by reaction of [$^{11}$C]methyl iodide of triflate with the corresponding desmethyl precursor. Well-known examples of these PET-radiopharmaceuticals are $^{11}$C-raclopride, $^{11}$C-methionine, $^{11}$C-choline and $^{11}$C-PIB. To expand the assortment of $^{11}$C-compounds new PET-radiochemistry should be developed. An interesting new development is based on $^{11}$C-carbon monoxide. Thus far it has been problematic and technically challenging to trap and concentrate $^{11}$C-CO into a small reaction volume (Karimi, 2003). Recently, a simple solution to this by using Xe-gas as carrier was developed (Eriksson, 2011). Via this way $^{11}$C-CO could be trapped very efficiently at room temperature without any pressure buildup. Subsequent reactions to amides proceeded in radiochemical yields of >80% in the presence of Pd-catalysts (Figure 1).

## 18F-radiochemistry

The second radionuclide is fluorine-18, mainly due to its adequate physical and nuclear characteristics. There is still a need to simplify $^{18}$F-chemistry to allow better dissemination of PET which may become comparable to conventional SPECT.

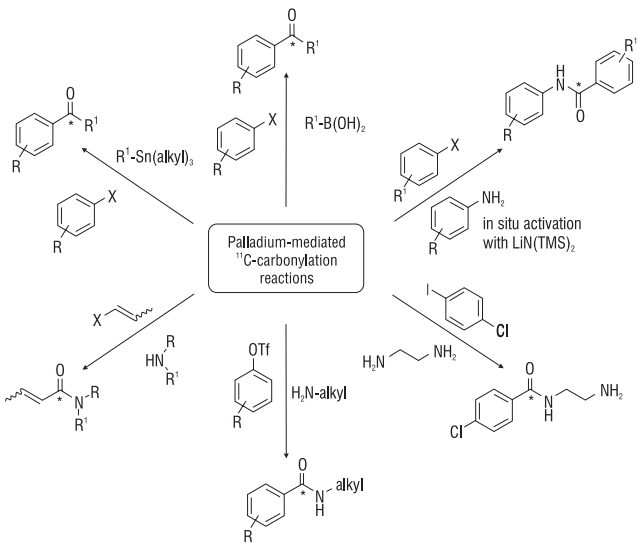


**Figure 1.**

Fluorine-18 is the most often used radionuclide for diagnostic PET imaging since the decay properties of $^{18}$F provide significant advantages. Among the routinely produced positron emitters, the relatively longer half-life of $^{18}$F poses less constraints on synthesis time and permits longer imaging protocols to investigate processes of slower tracer kinetics up to about 6 hours (Miller, 2008).

Standard [$^{18}$F]fluorination productions involve nucleophilic substitutions of tosylates, triflates, iodides, nosylates by azeotropically dried [$^{18}$F]fluoride, often followed by a fluoroalkylation or a hydrolysis step. Finally, purification and formulation steps are needed. Examples of such production methods are FDG, FLT, FAZA, FMISO and fluorocholine.

However, rapid and direct non carrier-added $^{18}$F-labeling of complex biomolecules such as peptides is not straight forward. The main approach to label peptides with $^{18}$F is via fluorination of prosthetic groups which are then conjugated to the biomolecule. For example, [$^{18}$F]Galacto-RGD is labeled via $^{18}$F-acylation with 4-nitrophenyl-2-[$^{18}$F]fluoropropionate. The acylation methodology is however complex and time consuming. Another strategy involves chemoselective oxime formation between the aminooxy functionality of the peptide and the carbonyl group of the $^{18}$F-labeled prosthetic group 4-[$^{18}$F]fluorobenzaldehyde (Hausner, 2008).

Recently, the copper(I)-catalysed Huisgen 1,3-dipolar cycloaddition reaction (CuAAC) between terminal alkynes and azides resulting in 1,4-disubstituted 1,2,3-triazoles has found its way in radiopharmaceutical chemistry. The main advantages of this 'click chemistry' apporoach are selectivity, reliability and short reaction times while only mild reaction conditions are required. The $^{18}$F-labeling of peptides has been the area that has benefited the most from click chemistry (Campbell-Verduyn, 2011).

Click chemistry may be very useful since a $^{18}$F-functional group can easily be coupled to new generation complex molecules that will be investigated for multimodality imaging.

Another important development in $^{18}$F-labelling of peptides is NOTA chelation of an $AlF^{2+}$ complex. The NOTA-chelator is traditionally used for complexation of radiometals. McBride et al. (McBride, 2011) discovered that the $AlF^{2+}$ complex can also be complexed by NOTA. Using this method no time consuming methods including azeotropically drying are needed. After preparation of the $AlF^{2+}$ complex and addition to the NOTA-conjugated peptide reactions are performed at 90 degrees. The overall synthesis time is 15 minutes.

One of the most recent developments is the preparation of electrophilic $^{18}$F with high specific activity. In organic chemistry the fast majority of fluorinations involve electrophilic fluorine, but these methods cannot be applied for PET because the production of electrophilic $^{18}$F involve addition of cold fluorine resulting in low specific activities. Lee et al. published the ability of a Pd-complex to trap high specific activity nucleophilic $^{18}$F-fluoride (Lee, 2011) (Figure 2). By intramolecular electron shifts, the $^{18}$F is subsequently "reacting" as electrophilic $^{18}$F-fluorine with aromatic systems. The scope and limitations of this new method requires further investigations.

As described above, there are many options to radiolabel candidate compounds with $^{18}$F for potential applications, and as the chemistry methods to incorporate $^{18}$F continue to evolve, more molecules will be developed. It can thus be expected that there will be an ever-growing list of $^{18}$F-radiotracers for studying

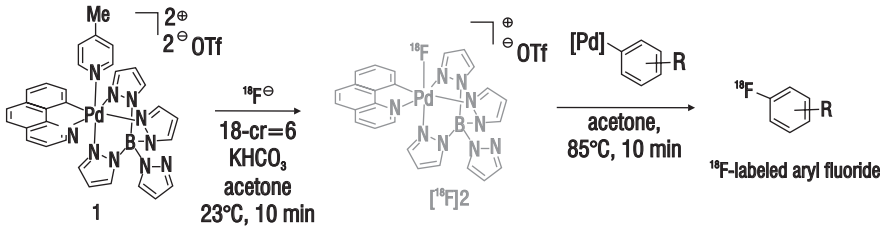


**Figure 2.**

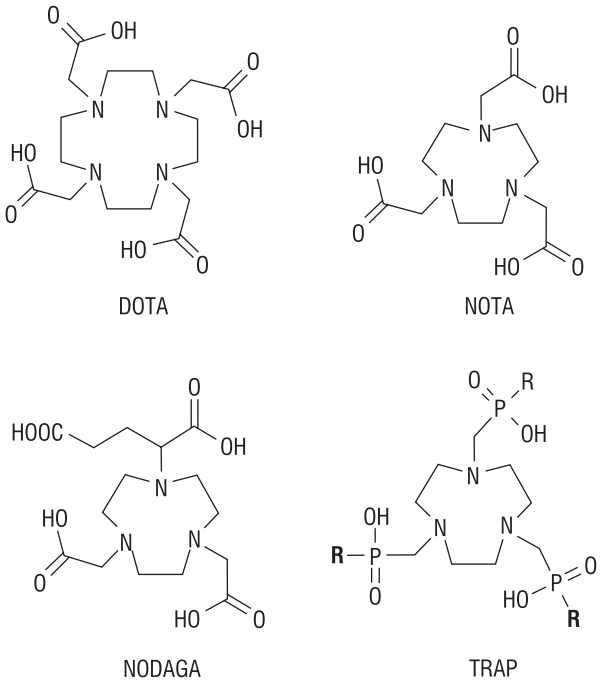


**Figure 3.**

the receptors, transporters, enzymes and other functions involved in normal and pathological processes of the human brain.

The relatively longer half-life of $^{18}$F also permits the distribution of $^{18}$F-labelled radiopharmaceuticals to clinical services approachable within a few hours of transport. The initiatives of several small and medium companies made possible the regular supply of GMP grade $^{18}$F-labelled radiopharmaceuticals from a single cyclotron/PET radiopharmaceutical production facility to several clinical PET centers. 'Cyclotron-PET satellite' concept is a successful business venture in many parts of the world and significantly contributed to the growth in the number of PET/CT cameras installed all over the world.

## Radiometals

Finally metal-based PET-radionuclides such as $^{64}$Cu, $^{89}$Zr and $^{68}$Ga are increasingly used thereby building on the longlasting experience that the community gained with SPECT-radiopharmaceuticals. These radionuclides are mainly being used for radiolabelling of peptides, proteins and antibodies. Since $^{64}$Cu and $^{89}$Zr have a relatively long half life they may easily be distributed over long distances and can be used to produce a wide range of peptides and antibodies. Recenty, $^{68}$Ga has become available through a GMP-compliant generator and is very suitable to produce radiolabelled peptides (Prata, 2012). Several potent new chelators for $^{68}$Ga have been published in addition to NOTA and DOTA. A promising chelator is TRAP (Figure 3). The presence of phosphorous groups results in very efficient trapping. A 10–30 fold lower concentration of the peptide is needed, therefore resulting in higher specific activities. The chelator allows for easy access to multimeric tracers by derivatization of the 3 phosporous group with targeting chemical entities (Notni, 2012). The metal based radionuclides have the advantage that they can be available without having the expensive cyclotron infrastructure.

$^{64}$Cu and $^{89}$Zr also deserve increased interest as with their relatively long half lives they are very suitable for labeling of molecules with slow pharmacokinetics and enables distribution over long distances. For example $^{89}$Zr has been applied to a number of monoclonal antibodies, that are conjugated with a desferal chelating group. $^{89}$Zr-labelled monoclonal antibodies allow PET scanning up to 7 days, where usually maximal target over nontarget ratio is being reached at 3–4 days post injection (van Dongen, 2010).

## Centralized versus noncentralized production of PET-radiophamaceuticals

Because of the growing interest of PET, the supply of PET-radiopharmaceuticals has attracted attention from industry. Since several years FDG is commercially produced and distributed to hospitals without a cyclotron. Costs for application of FDG-PET for specific medical indication are reimbursed by health insurance.

With the situation of commercial distribution on one hand and the small scale in house production at sites with cyclotron on the other hand, the discussion has emerged whether centralized or non-centralized production is preferred. The choice for one or the other is very dependent on the specific situation, but the following considerations can be taken into account:

1. Costs of the healthcare system could be reduced by centralized production by more efficient investment of equipment. On the other hand loss of radioactivity by decay during transportation and impact of transportation (timing, traffic, costs) should not be ignored.
2. Which tracers, mainly $^{18}$F, will be centrally produced ? It can be anticipated that only the blockbusters that gain commercial profit will be centrally produced, whereas the specialties will be produced on-site. In this case the effect on tracer development and innovation should be considered. Will research groups continue to develop $^{18}$F-tracers if these tracers will be taken over by industry?
3. Since FDG is centrally produced, is there still a need for sites to produce FDG for in house purposes? Arguments to continue

in house FDG production are preservation of expertise on $^{18}$F-production and infrastructure. An argument to discontinue in house FDG-production is reallocation of workload to innovation or other activities and can be based on financial reasons.

4. Does legislation still allow small scale in-house production. In case of compliance to industrial Good Manufacturing Production (GMP) regulations, the constraints and investments can be too high for PET-sites. In addition, authorities may require Marketing Authorization.

## Regulations and good manufacturing practice

In Europe, radiopharmaceuticals are considered as a special group of medicines. Therefore, their preparation and use are regulated by a number of EU directives, regulations and rules that have been adopted by member states.

Radiopharmaceuticals may be prepared within a Marketing authorization (MA) track. Small scale preparations in non-industrial sites such as hospital pharmacies, nuclear medicine departments, or PET centres indeed represent an increasingly important segment of application. The "Guidelines on Good Radiopharmacy Practice", and "Guidance on current good radiopharmacy practice (cGRPP) for the small scale preparation of radiopharmaceuticals", issued by the Radiopharmacy Committee of EANM are useful references for quality assurance related to the small-scale preparation of radiopharmaceuticals and their non-radioactive precursors. In-house prepared radiopharmaceuticals may be used for routine clinical (diagnostic or therapeutic) purposes or to investigate physiological functions disease related or new therapeutic approaches (Elsinga, 2010).

However, the current EU-directive poses severe constraints to the small scale radiopharmacies, which make its clinical trial applications a challenging task. The most critical points may be summarized as follows:

1. requirements for large clinical trials conducted by large pharmaceutical companies are virtually the same as for small academic units in hospitals or at universities. This is a specific problem for radiopharmaceuticals, that in many cases are used within clinical trials not as an investigational medicinal product themselves, but as surrogate imaging biomarkers of the consequences or effects of the treatment of medicinal product(s) used in the clinical trial;
2. most radiopharmaceuticals are considered as Investigational Medicinal Products (IMPs), due to the lack of a specific E.P. Monograph, even if their efficacy and safety have been demonstrated in numerous clinical studies and used for decades in humans;
3. it should be stressed that, based on risk assessment analysis, radiopharmaceuticals usually show an excellent safety profile,
4. another major problem of the directive is the need for full GMP compliance in the manufacturing of investigational radiopharmaceuticals. In general, the logistic (e.g. size of the facility, number of available radiochemistry labs), personnel and economic availability in a typical PET Centre or Nuclear Medicine Dept. make it very difficult and expensive to fully comply with GMP, especially considering that often the clinical trials are conducted on a relatively small number of patients.

To this regard, the EANM has taken the action to provide a series of documents and guidelines with the aim to help the community to comply with EU legislation and also to give a contribute to general debates and discussions about the above issues. In this context, the Radiopharmacy Committee of the EANM has recently prepared a guidance document on "Good Radiopharmaceutical Practice (cGRPP) for small scale production of radiopharmaceuticals", which had the ambition to provide a more sustainable alternative to the classic "Good Manufacturing Practice" that apply to the pharmaceutical industry, while maintaining the same quality, safety and efficacy standards. cGRPP should provide a general framework for the preparation of radiopharmaceutical on a "small scale" basis, which cover all the practical aspects that include the preparation of PET, SPECT and therapeutic RPs. It is the opinion of the EANM Radiopharmacy Committee that there would be no reason to set such a differentiation between RPs prepared for "in-house" and clinical trials use, as the instrumentation, environment, procedures, analytical procedures, characterizations, etc., are in most cases performed in the same way and no real distinctions may be operated.

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