

Design of Radioprobes for Pet and Spect Imaging

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Abstract: Nuclear Cardiology is an important and non-invasive tool for the clinical evaluation of patients with known or suspected coronary artery disease (CAD), one of the leading causes of death in western countries. The advancement of this field depends on the continuous improvement and development of equipment and signal processing technologies. However, its success is primarily determined by the design and development of new radiopharmaceuticals suitable for Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging. Nuclear cardiology started in the mid-1970s with the use of ^{201}Tl -thallous chloride, which has been the firstly approved radiopharmaceutical for perfusion cardiac imaging. Later on, $^{99\text{m}}\text{Tc}$ -Sestamibi was introduced and approved for clinical use. Nowadays, $^{99\text{m}}\text{Tc}$ -Sestamibi is the most used radioprobe for SPECT cardiac imaging. In the case of PET, nuclear cardiology still relies mainly on the use of ^{18}F -2-fluoro-2-deoxy-glucose, which is the gold standard metabolic tracer for cardiac imaging. Until now, a variety of other SPECT and PET radioprobes have been tested as radiopharmaceuticals for cardiac imaging. This contribution reviews representative examples of the chemical/radiochemical strategies that have been used to design perfusion and target-specific radiopharmaceuticals for cardiac imaging.

1 INTRODUCTION

Nuclear Medicine uses radioactive compounds for *in vivo* imaging and therapeutic purposes. Such compounds, named radiopharmaceuticals, are used in very low concentration (10^{-8} - 10^{-12} M), having no pharmacological effect.

For *in vivo* imaging there are two nuclear modalities: Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET), which use γ or β^+ emitting radionuclides, respectively (Table 1) (Correia, 2011); (Morais, 2012a); (Morais 2012b). In the case of SPECT, the radionuclides decay by electron capture (EC) or isomeric transition (IT) with emission of penetrating γ photons having energies in the range 100-250 KeV. In PET, the β^+ particles emitted by the radionuclide react with the electrons from the medium releasing two photons of 511 KeV, as a result of annihilation reactions. In both cases, the resulting photons (100-250 KeV or 511 KeV) are efficiently detected outside the body leading to clinically useful medical images.

Table 1: Examples of radionuclides for medical imaging.

| Nuclide | Physical half-life | Mode of decay (%) | Application |
|---------------------------|--------------------|---|-------------|
| $^{99\text{m}}\text{Tc}$ | 6.0 h | IT (100) | SPECT |
| ^{123}I | 13.2 h | EC (100) | SPECT |
| ^{18}F | 1.83 h | β^+ (97) EC (3) | PET |
| ^{11}C | 20.3 min | β^+ (100) | PET |
| ^{86}Y | 14.7 h | β^+ (33) EC (66) | PET |
| ^{111}In | 2.80 d | EC (100) | SPECT |
| ^{67}Ga | 3.26 d | EC (100) | SPECT |
| ^{68}Ga | 1.13 h | β^+ (99) EC (10) | PET |
| ^{62}Cu | 9.67 min | β^+ (98) EC (2) | PET |
| ^{64}Cu | 12.7 h | β (40), β^+ (19) EC (41) | PET |
| $^{117\text{m}}\text{Sn}$ | 13.6 d | IT (100) | PET |

Perfusion versus Target-specific Radiopharmaceuticals. The biodistribution of radiopharmaceuticals can be determined by their chemical and physical properties – *perfusion radiopharmaceuticals* - or by their biological interactions -

target-specific radiopharmaceuticals (Fig. 1). The biological distribution of *perfusion agents* is determined by blood flow and these agents target high capacity systems, such as phagocytosis, hepatocyte clearance, glomerular filtration. The *target-specific radiopharmaceuticals* target low capacity systems, and their biodistribution is determined by specific protein interactions, for example antigen, enzymatic or receptor-binding interactions (Correia, 2011); (Morais, 2012a); (Morais 2012b).

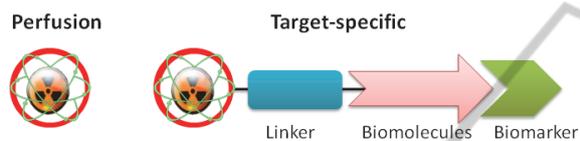


Figure 1: Schematic representation of perfusion and target-specific radiopharmaceuticals.

In this contribution, we review representative examples of the chemical/radiochemical strategies that have been used to design perfusion and target-specific radiopharmaceuticals for cardiac imaging. This will comprise compounds labelled with ^{99m}Tc or ^{18}F but also radioprobes containing less common radionuclides like ^{123}I , ^{64}Cu or ^{117m}Sn .

2 RADIOPHARMACEUTICALS FOR CARDIAC IMAGING

Nuclear Cardiology is an important and non-invasive tool for the clinical evaluation of patients with known or suspected coronary artery disease (CAD), one of the leading causes of death in western countries (Notghi, 2011); (Osborn, 2012). The clinical importance of nuclear cardiology stems from the unique advantages of *Nuclear Imaging Modalities* (SPECT and PET), such as their high intrinsic sensitivity, non-invasiveness and specificity. The advances on nuclear cardiology depend on the continuous improvement and development of instrumentation and signal processing technologies. However, its success is primarily determined by the design, development and validation of new, more sensitive and specific radiopharmaceuticals.

2.1 SPECT Radioprobes

Nuclear cardiology started in the mid-1970s with the use of ^{201}Tl -thallous chloride, which has been the firstly approved radiopharmaceutical for perfusion

cardiac imaging by SPECT. ^{99m}Tc is the most widely used SPECT radionuclide, due to its ideal nuclear properties, low-cost and availability from commercial $^{99}\text{Mo}/^{99m}\text{Tc}$ generators. Later on, an alternative ^{99m}Tc -based cardiac perfusion agent - ^{99m}Tc -Sestamibi (Fig. 2) – was introduced for SPECT cardiac imaging, overcoming the limitations associated with the unfavourable decay properties of ^{201}Tl (Maria, 2009). ^{99m}Tc -Sestamibi corresponds to an organometallic Tc(I) compound, which is synthesized in aqueous solution starting from the Tc(VII) permethylate anion ($^{99m}\text{TcO}_4^-$) that is reduced prior to its complexation by the isonitrile ligands (Wackers, 1989).

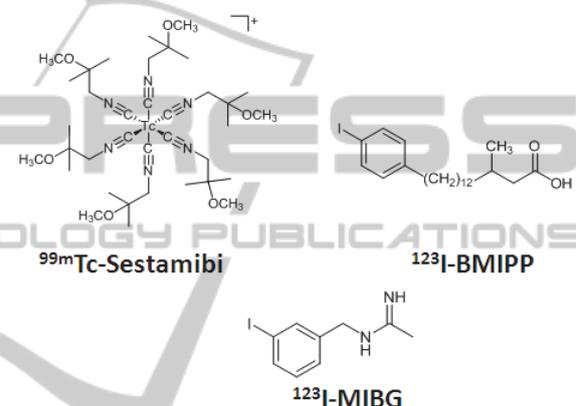


Figure 2: Selected examples of SPECT radioprobes for cardiac imaging.

Other radiometals, like ^{67}Ga , ^{111}In or the less common ^{117m}Sn (see Table 1), are also relevant for SPECT imaging. For instance, it has been recently reported that the target-specific agent ^{117m}Sn -DOTA-Annexin (TA) has potential for in vivo imaging of vulnerable plaque (Strauss, 2013). This agent corresponds to a Sn(II) complex with a macrocyclic DOTA ligand functionalized with Annexin-V for the targeting of phosphatidylserine (PS) that is externalized in cells undergoing apoptosis. Interestingly, ^{117m}Sn is a very promising radionuclide for the development of theranostic radiopharmaceuticals, as it decays via isomeric transition with the emission of monoenergetic conversion electrons. The pre-clinical evaluation of ^{117m}Sn -DOTA-Annexin in ApoE $^{-/-}$ mouse has shown that this radioconjugate has some therapeutic potential for the stabilization of vulnerable plaques (Strauss, 2013).

Besides metal-based compounds, several examples of radioiodinated molecules, such as ^{123}I -BMIPP and ^{123}I -MIBG (Fig. 2), have also shown promising for SPECT cardiac imaging. The methyl-

p-[^{123}I]-iodophenyl-pentadecanoic acid (BMIPP) is a radiolabeled branched fatty acid with the ability to assess *in vivo* the viability of cardiac tissue, playing an important role for identifying ischemia (Kontos, 2010). The meta-[^{123}I]-iodobenzylguanidine (MIBG) is a norepinephrine analogue that allow the *in vivo* imaging of cardiac innervation, being useful to assess the severity of heart failure and prognosis (Tamaki, 2011). ^{123}I -BMIPP and ^{123}I -MIBG can be obtained by isotopic exchange of stable ^{127}I by ^{123}I in BMIPP and MIBG, respectively, using Cu(II) salts as catalyst in the presence of a reducing agent. High specific activity ^{123}I -MIBG is achievable by electrophilic radioiodination of adequate stannylated precursors (Vallabhajosula, 2011).

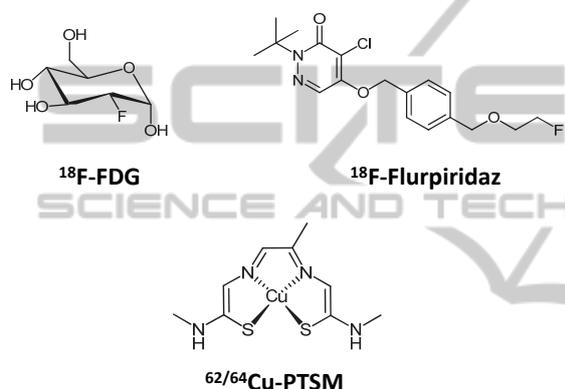


Figure 3: Selected examples of PET radioprobes for cardiac imaging.

2.2 PET Radioprobes

Until recently, the cyclotron-produced carbon-11 (^{11}C) and fluorine-18 (^{18}F) (Table 1) were the most explored PET radionuclides on the design of molecular imaging agents. Usually, labelling with ^{11}C frequently involves introduction of a [^{11}C]methyl group in the biomolecule via selective *N*- and *O*-methylation (Ametamey, 2008). However, the very short-life of this radionuclide ($T_{1/2} = 20.4$ min) limits its use to on-site cyclotron facilities, and requires rapid one-step radiosynthesis. The longer half-life of ^{18}F ($T_{1/2} = 110$ min) allows for multistep radiosynthesis, longer *in vivo* investigation and commercial distribution to other clinical PET centers. Radiofluorination reactions can be achieved with either electrophilic or nucleophilic radioactive fluoride. However, reactions with the less reactive nucleophilic radiofluoride are more selective and provide ^{18}F -labeled compounds in higher yields and higher specific activity (Ametamey, 2008). For all these reasons, ^{18}F remains the most used PET radionuclide in radiopharmaceutical research.

In the particular case of nuclear cardiology PET imaging relies mainly on the use of [^{18}F]-2-fluoro-2-deoxy-glucose, which has emerged several years ago as the gold standard metabolic tracer for cardiac imaging. (Strauss et al., 2013) Nowadays, ^{18}F -FDG is produced worldwide in a large number of PET facilities and under GMP conditions, based on a nucleophilic reaction between a mannose triflate precursor and [^{18}F]fluoride.

More recently, ^{18}F -flurpiridaz (Fig. 2) a structural analog of pyridaben obtained by radiofluorination of a toluenesulfonate ester precursor, started to be clinically evaluated as a PET tracer for myocardial perfusion imaging. ^{18}F -flurpiridaz targets the mitochondrial complex I (MC-1), a mitochondrial protein found primarily in myocardial cells, presenting a rapid uptake and slow washout in cardiomyocytes. These characteristics allow for a fast and sustained accumulation in the heart (Ya, 2011).

There are several positron emitter radiometals that are relevant the design of PET probes for cardiac imaging, as is the case of ^{68}Ga and $^{62/64}\text{Cu}$ (Table 1) (Cutler, 2013). ^{68}Ga is a positron emitter readily accessible from the $^{68}\text{Ge}/^{68}\text{Ga}$ generator, offering the possibility to obtain on site a PET radionuclide without needing the presence of a nearby cyclotron. This possibility might open the way to an important role for ^{68}Ga in PET imaging, similarly to the role played by $^{99\text{m}}\text{Tc}$ in SPECT imaging during the past few decades. Recently, several cationic and lipophilic Ga(III) complexes with hexadentate ligands have been synthesized and pre-clinically evaluated as radioactive probes for myocardial perfusion imaging (Hsiao, 2009). Despite some encouraging results, none of the reported Ga(III) complexes has shown potential to be clinically evaluated as a PET probe for cardiac imaging. So far, $^{62/64}\text{Cu}$ -PTSM has been the unique metal-based compound that showed promising biological properties as a PET perfusion imaging agent. Although the mechanism is not fully understood, it is considered that this small-sized, neutral and lipophilic Cu(II) complex is retained in the cells due to its intracellular reduction to Cu(I), followed by release of the bis(thiosemicarbazone) ligand (H_2PTSM) (Paterson, 2011).

In summary, the chemical and structural diversity of PET and SPECT radioprobes allowed the design of several perfusion, metabolic and target-specific agents for cardiac imaging, some of them already in clinical use and others undergoing clinical evaluation. Despite this success, there is still room to investigate new radioprobes for nuclear

cardiology, aiming at their translation from the bench to the patient bedside.

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