Integrated PET/MRI in preclinical studies State of the art

F. Brunotte, MD[1,2,3], H. Haas, PhD[4], B. Collin, PharmD, PhD[2,5], A. Oudot, PhD[2], S. Bricq, PhD[1], A. Lalande, PhD[1,3], X. Tizon, PhD[6], J.M. Vrigneaud, PhD[2], P.M. Walker, PhD[1,3]

[1] *Laboratory of Electronics, Computer Science and Image, UMR CNRS 6306, University of Burgundy, Dijon, France*
[2] *Cancer Center Georges-François Leclerc, Dijon, France*
[3] *University Hospital, Dijon, France*
[4] *Bioscan Molecular Imaging France, a TriFoil Imaging company, Dijon, France*
[5] *Institute of Molecular Chemistry of the University of Burgundy, UMR CNRS 6302, University of Burgundy, Dijon, France*
[6] *Oncodesign Biotechnology, Dijon, France*

Abstract

Brunotte F, Haas H, Collin B, Oudot A, Bricq S, Lalande A, Tizon X, Vrigneaud JM, Walker PM. Integrated PET/MRI in preclinical studies. State of the art. The exquisite tissue contrast of magnetic resonance imaging (MRI), the absence of ionising radiation and the opportunity to obtain new molecular and functional data have strengthened the enthusiasm for coupling MRI rather than computed tomography (CT) to positron emission tomography (PET). When reviewing the current literature one might be surprised by the almost unlimited diversity of what is placed under the name of PET/MRI in the articles. The magnetic field is varying from 0.3 Tesla (T) to 9.4 T, the size of the bore varies also from the wide bore of clinical scanners to volumes limited to a few tens of mL. Many preclinical studies are performed using separate PET and MRI scanners. Sometimes PET and the magnet are in line or sequential. More rarely, fully integrated PET/MRI scanners are used. In that case, mutual interference between PET and MRI has required innovative designs. Initially, the conventional photomultipliers had been installed outside the magnet using long optical fibres. They have now been replaced by avalanche photodiodes (APD), and in the near future silicon photomultipliers (SiPM) could provide an alternative. Tumours and neurological and cardiovascular disorders have been the most studied conditions. Many issues remain to be resolved such as image registration, attenuation correction and animal monitoring. Friendly consoles integrating the control of both imaging modalities also need to be developed.
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Introduction

The idea of multimodal imaging techniques is not new (1). Nowadays, the coupling of positron emission tomography (PET) and computed tomography (CT) is the standard in clinical practice (2) and more recently the integration of single photon emission computed tomography (SPECT) and CT is becoming more and more available (3). These imaging techniques have proven to be extremely effective in diagnosing a variety of diseases (4). Tissue characterisation has been improved by combining the specificity of radiopharmaceuticals and the 3D imaging capabilities of modern CT scanners. Although straightforward, coupling of PET and CT has two serious drawbacks: X-ray exposure contributes to an increased patient irradiation dose and CT tissue characterisation is limited. Magnetic resonance imaging (MRI) has demonstrated a much more convincing ability to provide tissue characterisation through measurement of key parameters such as relaxation times T1 and T2, apparent diffusion coefficient (ADC), tissue perfusion and spectroscopy. One very prolific application has been dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) of tumours, which has permitted an accurate monitoring of tumour perfusion in response to anti-angiogenic treatments (5).

Garlick *et al* described under the name of PANDA (PET and NMR dual acquisition) in isolated, perfused rat hearts in 1997 (6). LSO crystals were inserted in a 9.4 T magnet with a bundle of optical fibres towards external photomultipliers. Fifteen years later the integration of MRI and PET has generated considerable enthusiasm in the clinical field (7) since nuclear medicine specialists are in need of several requirements that MRI can offer: (i) reduction of the radiation exposure of the patients, especially in case of repeated examinations and in paediatrics, (ii) improvement of soft tissue characterisation by simple addition of the advantages of both techniques and finally (iii) the access to additional physiological parameters that could be derived only by combining both approaches. All these advantages could make PET/MRI a tool of importance especially when focusing on a given organ with the aim of monitoring the effect of a treatment.

In animals many of the rationale retained for clinical studies also apply. The animal irradiation due to CT images can be as high as

several tenths of grays (8). Therefore, reduction of the ionising radiation exposition is also an issue in animal studies especially when studies are repeated. Translational research from animal to human requires the same type of imaging. It is now well recognised that imaging can reduce the duration of drug development and the attrition rate of newly developed drugs (9). The availability of PET/MRI both in preclinical and clinical studies will boost this multimodal imaging technique as a key tool in pharmacological research. Nowadays, integrated PET and MRI is developing in a parallel manner in the preclinical and clinical fields and any improvement achieved finds quickly application in the other field, thus making PET/MRI a truly translational imaging modality.

General design of integrated PET/MR scanner

In recent years, the acquisition of PET and MR images of the same animal has been realised using different imaging strategies. So far, most studies have been performed on separate scanners with subsequent registration of the images, but new and more integrated systems are now available.

1. Separate scanners

In developing multimodality systems, the idea of separate systems makes sense since it offers the possibility to perform sequential studies using various imaging modalities (10), the only requirement being the design of the animal handling cell in which the animal is positioned and which has to fit the different modalities. This enables to use sequentially any combination of imaging modalities (optical, SPECT, PET, MRI). Another advantage of this approach is to allow the use of the scanners for different experiments at the same time. Regarding PET/MRI, this might be also an advantage by allowing the use of magnets with different field strengths in combination with the same PET scanner. It also allows MRI to be performed outside of the area dedicated to radioactivity handling.

The University of Burgundy and Bioscan, Inc., jointly developed parallel imaging in Phase I of the IMAPPI (Integrated Magnetic resonance and PET in Preclinical Imaging) project in the framework of the 'invest for the future' program of the French government (11). The installation in a room accredited for the use of radioactivity of a PET/CT and a MRI system allows easy switching from one system to the other (figure 1). The system configuration allows the use of both scanners at their optimal performances due to the lack of interference between both scanners. However, the system has two major drawbacks: firstly, it is impossible to position the animal in a reproducible manner that makes the use of registration software mandatory, and secondly, simultaneous acquisition is obviously impossible.

To meet the objectives of the project a special animal handling cell with a new miniature gating and acquisition module has been developed. This animal cell can be easily moved from one scanner and docked to the other scanner and vice versa. Data is transmitted through a small bi-directional high-speed optical communication device whereas the module is supplied

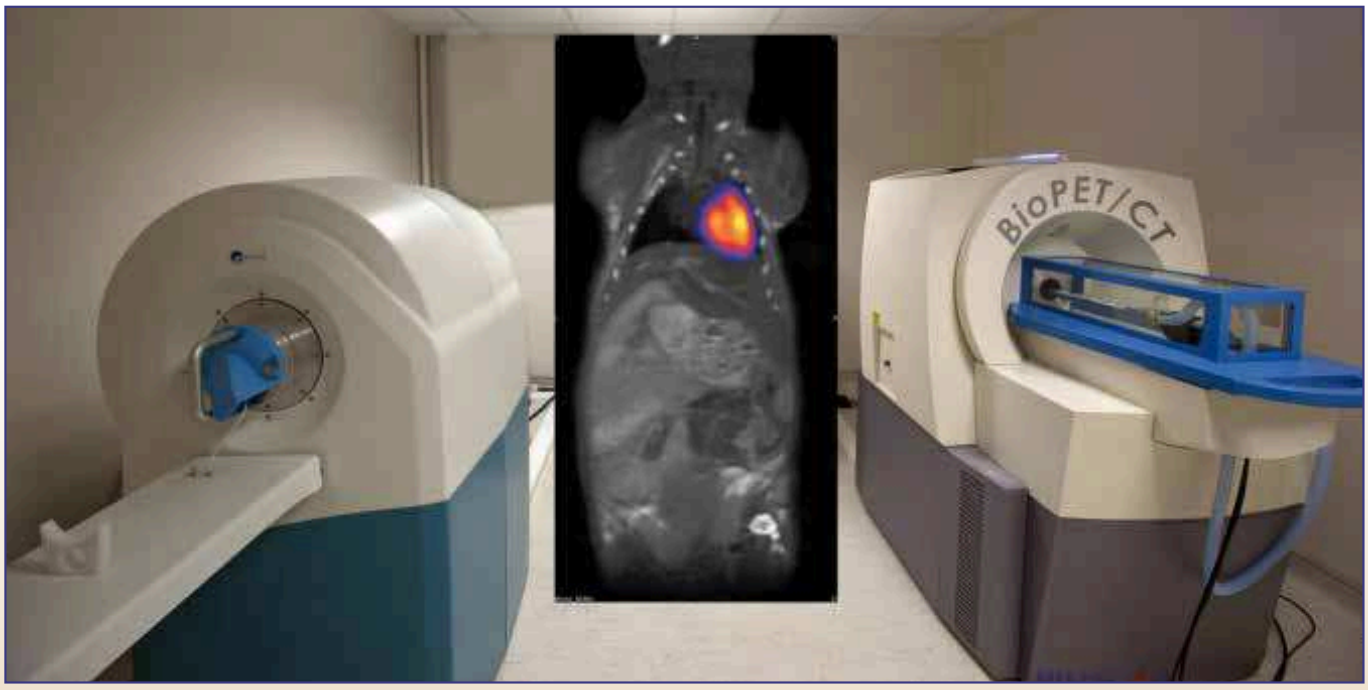

Figure 1. IMAPPI Phase I: Two separate imaging systems installed in the preclinical imaging room. On the right, the PET/CT system with the universal animal handling cell and on the left the MRI 3.0T system with the identical animal cell completely inside the magnet bore.

with standard compatible animal sensors for ECG and respiratory gating.

In several studies, clinical scanners have been used for preclinical imaging with some success (12, 13). These studies usually belong to the 'separate imaging' modality and have the advantage of allowing the choice of different magnetic fields for MRI acquisitions.

2. In-line (or sequential) PET/MRI

Several companies are marketing systems consisting in existing PET scanners installed in the vicinity of a magnet. The bores of both systems are aligned in order to allow a smooth displacement of the animal between both scanners as shown in figure 2. Philips is using a similar configuration in clinical nuclear medicine (13, 14). Among the strong disadvantages, the effect of the magnetic field even outside the magnet might be significant. Of course it is impossible to use such systems for independent, parallel experiments.

3. Fully integrated PET/MRI scanners

Although cost-effective and efficient for a preclinical lab, permitting the use of magnets of different fields, both system configurations, parallel and in-line, do not allow for simultaneous acquisition of PET and MR images. Yet, a fully integrated PET/MRI scanner is the most promising technology (15, 16). Moreover, the animal is studied in the same position and under the same physiological conditions for both techniques. One of the strong points of the technique is the possibility of reducing the total examination time and consequently the duration of the anaesthesia. Two designs of the integrated scanner are possible: a fully integrated PET ring inside the MRI scanner or a removable PET insert. Many teams found removable inserts useful in order to benefit from the possible separate use of both imaging techniques.

Figure 2. IMAPPI Phase II: One integrated in-line PET/MR imaging system with the PET ring mounted in front of the MRI and the MR-compatible motorised conveyance system with the animal cell positioned inside the scanner.

What is the ideal magnetic field for MRI coupled with PET?

One important question is the choice of the magnetic field to be used. This is a key question for those wishing to move towards that technology. The magnet size, its weight and costs increase rapidly with the size of the bore and the main magnetic field (B0). In order to get the best possible signal to noise ratio, a high field of 7 T or more is preferable. High field magnets with strong gradients offer an unprecedented spatial resolution. When performing magnetic resonance spectroscopy (MRS), the spectral resolution is better and smaller voxels can be studied. For that reason, most of the preclinical magnets installed in the world belong to that category. Unfortunately, since many of these magnets have not been installed in areas dedicated to handling of radioactive substances, it appears often difficult to use them as part of a PET/MRI project.

High field magnets may have limitations. The first is the limited possible translation to clinical imaging. In the foreseeable future, clinical imaging will be mainly performed at magnetic field strengths of 1.5 T and 3 T, and these will remain the highest fields used in routine MRI. Since the behaviour of MRI contrast agents depends on the field strength of the magnet, it could be interesting to stay at field strengths similar to those used in human imaging situations. Most of the encountered artefacts, including PET/MRI mutual interference increase with the magnetic field intensity. For these reasons, other groups have developed scanners at fields as low as 0.3 T (17). Imaging at low fields has some advantages due to a better tissue contrast with or without contrast agents. Low field magnets have the advantage of low weight, transportability and even bench top imaging. Hence, they are easy to install in areas dedicated and licensed for the use of radioactive sources. The bore is usually limited in size, allowing imaging of small rodents typically mice and rats, and the magnetic field is relatively low (between 0.3 T and 3 T) with a limited image quality, requiring long acquisition times and limited temporal resolution thus reducing the dynamic acquisition capability of these magnets.
When considering the integration of a PET detector inside the bore of a magnet, additional requirements apply, since the PET detector ring will reduce the available space for the animal, monitoring devices, the installation of gas supply and intravenous lines. The minimal bore diameter of the magnet cannot be less than 30 cm if mice or rats are imaged.

PET technology compatible with magnetic fields

Acquiring simultaneously PET and MRI datasets is technically very demanding due to mutual interactions between magnetic fields and the electronics of the PET detectors. Coincidence detection in PET requires scintillation crystals, light amplification,

electric wiring and some X-ray shielding. Interactions between the magnetic field and these electronic devices require new approaches, which have been developed in the late 1990's. The nature of the best PET scintillation crystals has been debated, but it has been shown that sodium iodide, cesium iodide, lutetium orthosilicate (LSO), or lutetium-yttrium oxyorthosilicate (LYSO) cause limited MRI artefacts. Due to the presence of gadolinium in the LGSO and GSO crystals, causing MRI artefacts (18), LSO (19) and LYSO (20) seem to be the preferred crystals for PET/MRI. Since conventional photomultipliers cannot be used in a magnetic field without severe artefacts, long light guides of 2 m with light amplification outside the magnet (3 T) have been used (21). In another approach a split magnet of 1 T has been used to allow the magnetic-sensitive components to be placed outside the magnet (22). Some groups have pursued this approach using shortened light fibres and PSMTs (Position Sensitive Photomultiplier Tubes) (16).

Since conventional photomultipliers are extremely sensitive to magnetic fields, two other approaches have been used: avalanche photodiodes (APD) and silicon photomultipliers (SiPM). APDs have been proposed in 1997 by Pichler *et al* as compatible with magnetic fields as high as 9.4 T (23).

The SiPM is a relatively new photodetector (24) consisting of a Geiger-mode avalanche (G-APD) photodiode described in the nineties (25). These photodetectors have also been named avalanche photodiodes based on MRS (Metal Resistor-Semiconductor) (26, 27), multipixel photon counter (MPPC) or solid-state photon counter (SSPC). They are now referred to as SiPM. Systems for imaging small animals based on LGSO crystals and SiPMs have been developed (28, 29). It has been suggested that a SiPM with 50 µm pixels gives the best results for developing high-resolution PET (30). SiPMs combine the advantages of conventional photomultipliers and APDs with high gain, high signal to noise, excellent timing properties and insensitivity to magnetic fields (31). Nevertheless, interference between PET and MRI may persist (32). A fully digital implementation of a SiPM has been developed, simplifying the overall PET detector design while reducing the sensitivity to temperature variations and electronic noise susceptibility (33). Regarding the way PET crystals and coils are installed in the magnet, PET scanners have been configured differently across the different research groups. As mentioned earlier, a split magnet has been proposed by the group at Cambridge with a PET scanner installed between the two halves of the MRI (22). Field cycled MRI has been used with a PET detector based on conventional photomultipliers. In that case, PET acquisition occurs only when the 0.3 T magnetic field is switched off (34).

The key issue of inserting a PET detector into a magnet is the mutual interference between PET and MRI. PET detectors and electronics can decrease the homogeneity of the main magnetic field (B0) and of the radiofrequency (RF) field (B1) induced by the coils. The presence of PET detectors can make the coil tuning difficult. RF radiations and noise can be emitted by the PET detector and picked up by the receiver coil. On the other hand, eddy currents can be induced in the PET detector by switching the MR gradients used for MRI.

When inserting a PET detector inside a magnet, one question arises regarding the respective position of the RF coils and the PET detector. Different solutions have been proposed. Yoon et al have placed the RF coil inside the PET ring (35). When the RF coils are inside the PET detectors, the PET detectors are outside the field of view of the MR and thus will create less artifacts. Other designs of integrated PET/MRI have been proposed and sometimes, scintillator, diodes and analogue electronics have been installed inside the RF coils and thus in the MR field of view (36). In animal imaging, the issue of the field of view is of lesser importance than in humans where omitting the patient's arms in the field of view of MRI is a significant limitation for attenuation correction in PET (37). The presence of coils inside the PET field of view can induce attenuation artefacts that are difficult to take into account as MR coils are not visible on MR images (38).

Other key issues of PET/MRI in preclinical imaging

Besides the design of the PET/MRI system, many other issues have to be addressed in order to establish integrated PET/MRI as a tool for routine preclinical imaging. The recording of the physiological signals inside the magnet is mandatory for MR imaging of anatomical structures concerned with respiratory and cardiac motion. MR compatibility is obviously the most demanding requirement for ECG and respiratory monitoring devices which should be optimised for high magnetic fields and gradients. Other devices such as blood samplers are also very important (39). After selecting the best MR-compatible PET hardware, the MRI scanner has to be optimised for image quality. The design of the MR gradients, RF coils and acquisition sequences has to be carefully optimised to avoid artefacts. In most studies the consoles for PET and MRI acquisition control are different, making the experiments somewhat tedious. So an important objective is the design of one unique user-friendly console for controlling both tasks of PET and MRI.
New adapted software to analyse acquired data also has to be developed. Firstly, software for registration of PET and MRI data sets without the use of CT is required (figure 3). CT produces irradiation that is not negligible even in small animals and it would not make sense to use CT in PET/MRI studies. Several studies have been reported regarding registration of MRI and PET (40-42). Bagci et al have described PET/MRI co-segmentation of breast cancer xenografts implanted in mice (43). Registration might not be limited to parallel or in-line imaging modalities since movement of the animal is still possible even in a fully integrated PET/MRI scanner. Secondly, software needs to be developed for attenuation correction. Despite the limited size of rodents, attenuation correction is preferable even in mice (44, 45). Attenuation correction using CT scans is straightforward. However, using MR requires

converting anatomical information obtained from MRI into an attenuation map that can be used for attenuation correction (46). Most of the work has been done in the clinical setting or in relatively large animals like rabbits (12), whereas in preclinical studies MR attenuation correction is still a topic of research. Several methods have been suggested. It is possible to convert maps obtained by 3- or 4-class tissue segmentation into attenuation maps (47). Atlases might also be used (48). After registration of the acquired data with an atlas, attenuation correction is performed according to the attenuation maps of the atlas. Another method is to obtain images of bone using ultra short echo times (UTE) (49). One interesting method has been proposed for the brain which consists of performing an additional PET with ^{18}F-NaF permitting a clear identification of the skull with a low uptake in the brain (50). As mentioned before, the correction of the attenuation induced by MR coils is another important challenge. Another field of interest in PET/MR imaging is the development of MR-based motion correction for PET (51). In animals the advantages of MRI to correct motion in PET have been shown in rabbits and monkeys (52).

An adapted quality control of PET as well as MRI is an important requirement including the separate control of image quality obtained both by PET and MRI, and the study of the effects of their mutual interference. It is of course mandatory that the PET scanners, to be inserted in a magnet, reach a performance similar to that of the best stand-alone PET scanners (53-55). Fluids adapted to phantoms have been proposed for PET/MRI (56).

Biological studies involving PET/MR acquisitions

1. Tumour imaging

Most of the studies coupling MRI and PET have been carried out in tumour-bearing animals. Many radiopharmaceuticals have proven useful in investigating experimental tumours. ^{18}F-FDG has been, by far, the most widely used radiopharmaceutical. The overexpression of the glucose transporter membrane transporter (GLUT1I) in many cancer cells makes ^{18}F-FDG an ideal tracer (57). Modifications of ^{18}F-FDG uptake in response to treatment had been shown in the 1990s of the 20th century (58) and were confirmed in many animal models (59). Nowadays, ^{18}F-FDG is used daily in the clinical setting as a surrogate marker of pathological response and of survival (60). Most of the clinical and preclinical studies have been performed using PET or PET/CT. Using MRI instead of CT reduces the irradiation of the animals and its potential effects on the biology of the tumour. More importantly, MRI provides high resolution and high contrast anatomical and functional imaging. It is in particular very easy to differentiate central necrosis from surrounding viable tumour, to analyse perfusion, water diffusion which is related to cellular density, and to assess the concentration of metabolites detected by magnetic resonance spectroscopy.

It has been shown that simultaneous PET/MRI of tumours can yield images of the biodistribution of ^{18}F-FDG or of a radiolabelled anti-carcino-embryonal-antigen (CEA) antibody along with MRI, including ADC mapping (61). One of the interests of coupling MRI and PET is to benefit from DCE-MRI, which is a well validated technique in exploring tumour perfusion and vascular permeability (62). Tumour uptake of ^{18}F-fluoromisonidazole (^{18}F-Fmiso) and DCE-MRI have been compared in prostate cancer of the rat (63) by performing PET and MRI sequentially and registering the images with the aid of positioning moulds (64). PET/MRI experiments have also allowed the comparison of total choline concentration at H-MRS performed in a 3 T clinical magnet and ^{18}F-fluoromethylcholine uptake at PET in rat rhabdomyosarcoma (65). The authors suggest a complementary role of both techniques rather than redundancy. Magnetic resonance spectroscopic imaging of hyperpolarised ^{13}C-pyruvate metabolism has also been compared to 18F-FDG uptake in hepatocellular carcinoma bearing rats (66). Coupling MRI and PET has been useful in the evaluation of the effects of radiofrequency on VX2 tumours in rabbits (67).

Many authors have proposed nanoparticles as multifunctional platforms allowing multimodal imaging, particularly PET/MR imaging. Iron oxide nanoparticles have been encapsulated in human serum albumin and labelled with ^{64}Cu-DOTA and Cy5.5 dye, thus being detectable by PET, MRI and near infrared fluorescence (NIRF) (68). Nanoparticles are very flexible platforms and can be used in PET/MR imaging of specific biological target such as tumour $\alpha_v\beta_3$ integrin using Arginine-Glycine-Aspartic (RGD) conjugated nanoparticles (69). This kind

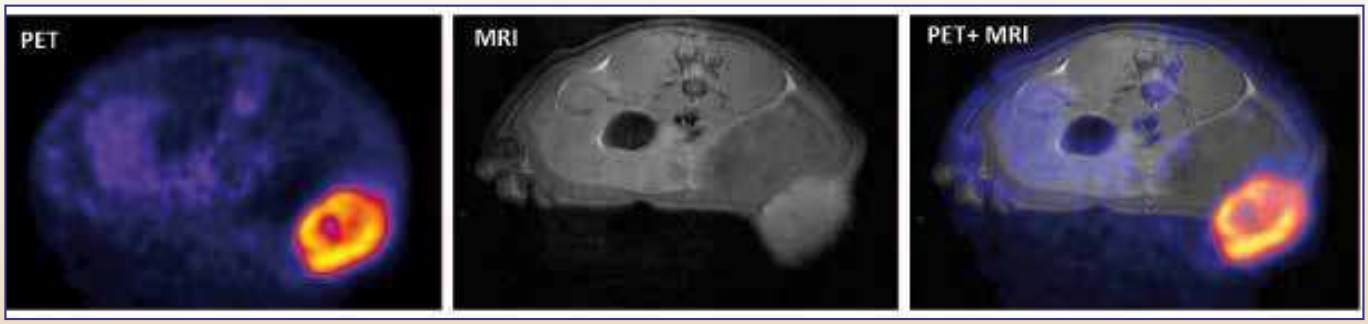

Figure 3. FDG-PET, MRI and co-registered PET/MRI of a mouse bearing a PC3 prostate tumour.

of approach paves the way towards theranostics as proposed by Yang *et al* with nanoparticles RGD-functionalised and conjugated with doxorubicin (70). Recently, liposomes functionalised by octreotide and labelled by gadolinium (Gd) and ^{89}Zr have shown affinity for tumours expressing sstr2 receptor as demonstrated in mice by MRI at 4.7 T and PET (71).

2. Brain imaging

Brain imaging might benefit enormously from coupling both imaging modalities. MRI benefits from an unsurpassed resolution and tissue contrast for brain study. Moreover, MRI has the ability to assess oxygenation using the blood oxygen level dependent (BOLD) effect, perfusion from the ADC measurements and neuronal viability from n-acetyl aspartate (NAA) concentration measurements using spectroscopy. On the other hand, the sensitivity of PET permits an accurate study of receptors such as serotonin 5-HT$_{1A}$ receptor imaging co-registered with rat and mouse MRI templates (72). Combining PET and MRI is very promising in the field of brain metabolism and perfusion studies. MRI has been proved useful to provide anatomical localisation as in FDG-PET studies of brain metabolism coregistered with MRI at 4.7 T (73). Cerebral blood flow was studied by Watabe *et al* using ^{15}O PET registered with separately acquired brain MRI at 0.3 T (74). PET provides a gold standard for MRI to validate imaging protocols as in the study of Bos et al comparing arterial spin labelling at 7 T and biodistribution to ^{68}Ga or ^{64}Cu-labelled microspheres (75).

Brain tumours have benefited from the excellent spatial resolution and tissue characterisation provided by MRI combining, T1-, T2-weighted images, ADC imaging and spectroscopy. On the other hand, PET studies of brain tumours allow the use of many radiopharmaceuticals, which have been proved to be efficient in studying brain tumours. Coupling MRI, MRS and PET would probably improve the comprehensive study of brain tumours and the subsequent follow-up of the effects of new targeted drugs. Belloli *et al* investigated a preclinical model of glioblastoma multiforme (76). In that study, gadolinium enhanced MRI was acquired in a 3 T clinical magnet to assess tumour morphology and growth separately from brain PET using ^{18}F-FAZA to assess hypoxia and ^{18}F-FDG to assess brain metabolism. Many other tracers have been investigated in preclinical models such as choline, thymidine or amino-acids. Two tumour phenotypes of glioblastoma (angiogenic and infiltrative) have been studied by co-registered 7 T MRI and PET performed separately, showing that ^{11}C-methionine (MET) accumulation was more specific of angiogenic gliobastoma in comparison with infiltrative glioblastoma than ^{18}F-fluorothymidine (FLT) (77).

3. Cardiovascular imaging

In the field of cardiovascular diseases, MRI combined with PET will be an important tool since X-ray attenuation is similar for blood, the myocardium and vessel walls. Therefore, using CT, these different tissues are not distinguishable without injection of an iodine-based contrast agent. MRI has the unique advantage of showing spontaneous contrast between blood, myocardium and vessel wall. Moreover, dynamic imaging is possible, allowing visualisation of heart and vessel motion without contrast agent. MRI makes it easy to combine cardiovascular dynamics with PET study of tracer uptake. This has been proved useful for studying vulnerable plaques and differentiate myocardial scar from myocardium with residual viability.

Stegger *et al* have shown that left ventricular volumes of mice can be measured either using MRI at 6.3 T or ^{18}F-FDG-PET (78). Results were similar except for a slight overestimation of left ventricular diastolic volume by PET. Both techniques permitted adequate triggering at heart rates over 500 beats/min. Quantification of regional myocardial oxygenation by MRI has been validated by PET in dogs (79). Using a clinical 1.5 T MRI scanner and a dedicated PET, it has been shown that the myocardial defect of ^{18}F-FDG uptake correlated with late enhancement observed with gadolinium MRI (80). Feasibility of imaging heart mouse with simultaneous PET/MRI was demonstrated at 7 T (81), but myocardial uptake was lower than with high resolution PET. PET/MRI of the heart is also promising in the field of regenerative therapy based on stem cells PET. It has been shown that PET and MRI at 4.7 T were able to follow stem cells labelled with both superparamagnetic iron oxides (SPIO) and a PET tracer (82). PET/MRI of the heart can also be used for early stem cell engraftment in predicting late cardiac functional recovery (83).

PET combined with MRI has been used to study vascular diseases as these two techniques are particularly complementary. MRI allows the anatomical imaging of the vessels and of the atherosclerotic plaques. Angiogenesis in the vessel wall can be delineated using DCE-MRI and inflammation can be outlined by ^{18}F-FDG-PET (84). USPIO can demonstrate the presence of macrophages in the inflammatory wall of the vessels. Nanoparticles labelled with ^{89}Zr have been imaged by PET and anatomically localised using 7 T MRI (85). In another study of atherosclerotic rabbits in a clinical sequential PET/MRI scanner at 3 T, it has been suggested that ^{18}F-FDG was superior to USPIO to assess the effects of atorvastatin (86). PET/MR imaging has been proposed to assess the effect of pioglitazone (87). True simultaneous PET/MRI of intra-arterial thrombus was achieved in the rat at 3 T using a fibrin-targeted probe labelled with gadolinium and ^{64}Cu (88). Especially for the assessment of aortic aneurisms the future of multimodal imaging seems bright (89).

Conclusion

Many of the experimental approaches described in this review have been performed with separate PET and MRI. This separate approach fulfils most of the demands on the coupling of both technologies like irradiation reduction and anatomical co-localisation of images. Nevertheless, the most

interesting perspectives are probably those where the addition of both techniques allows access to new fields of physiological investigation. A very elegant example is shown in the study of Frullano *et al* who described a smart PET/MRI agent, made of a gadolinium chelate labelled with ^{18}F, enabling direct quantification of pH value in vivo (90). In their approach, the MR probe had a relaxivity dependant on the pH and PET permitted absolute quantification of the concentration of the molecular probe. These two simultaneous measurements allowed for adequate pH measurement.

There is no doubt that coupling magnetic resonance imaging and PET will offer an unprecedented comprehensive study of metabolism in many diseases. Scanners integrating PET and MRI offer the brightest perspective to the addition of both modalities. Nevertheless most of the available studies rely on separate instruments. For the foreseeable next five years, it is obvious that all the different approaches will coexist. Before deciding on the acquisition of PET and MRI in a preclinical laboratory, the research objectives should be carefully defined. One may suggest that flexible instruments including a removable insert usable as a standalone PET would be the best compromise for those unable to afford the purchase of several scanners. Imaging of animals larger than rats and mice is also an issue often requiring the use of clinical scanners. Nevertheless the tremendous potential of PET/MRI as a tool for translation from preclinical models to the clinic will probably assure the success of integrated PET/MRI scanners. This might be reinforced by the advent of multimodal molecular probes.

Email-address for correspondence: hein.haas@trifoilimaging.com

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