Editorial Review 2017

The peer-reviewed journal ‘Current Radiopharmaceuticals’ continues to build on its success from previous years. The journal offers a range of article formats including research articles, reviews, communications, editorial letters and perspectives. The 2016 issues contained articles on the use of radiopharmaceuticals in imaging to drug discovery and targeted therapies. All these articles have been peer reviewed by members of the editorial board including guest editors. Here, we would personally like to take this opportunity to thank everyone on the editorial board who have volunteered their time to review the various articles that we have received and the editorial staff at Bentham Science. The journal also compiles thematic ‘Hot Topic’ issues to generate maximum impact of the published material in that particular subject area of radiopharmaceuticals and nuclear medicine. The ninth volume of Current Radiopharmaceuticals contains articles on a wide range of hot topics. The efforts and determination of the editorial board and guest editors have helped promote the journal at various scientific meetings owing to its MEDLINE/PubMed status since 2011.

In this Editorial Review, we have summarized all the abstracts from 2016 issues 1 to 3.

The first issue of 2016 included the final 9 papers of the ‘Thematic Issue: Lutetium-177 Labeled Therapeutics: Emerging Importance for Cancer Treatment and Therapy of Chronic Disease’. The first 10 papers have already been published in Current Radiopharmaceuticals, 2015, 8(2).

The first article of 2016 was on, ‘Overview of Development and Formulation of $^{177}$Lu-DOTA-TATE for PRRT’ by Wouter et al. The background to this paper is about peptide receptor radionuclide therapy (PRRT) using radiolabelled somatostatin analogues. PRRT has become a recognized treatment for patients suffering from inoperable neuroendocrine cancers which are over-expressed in the somatostatin receptors. For PRRT to be effective, the radiolabelled peptide must have a consistently high specific activity to produce the therapeutic efficacy. The aim is not to saturate the surrounding receptors available on the target lesions. The authors of this paper want to exploit the use of $^{177}$Lu-DOTA-TATE in PRRT. They have summarized the data including purity and specific activity of $^{177}$Lu extending to the reaction kinetics profile during labelling of $^{177}$Lu-DOTA-TATE. The radiochemical parameters indicate that the peptide dose can be changed including the formulation and optimization conditions.

The second article in this special issue was on, ‘Lutetium-177 Labeled Peptides: The European Institute of Oncology Experience’, by Carollo et al. The application of peptide receptor radionuclide therapy (PRRT) based on radiolabelled somatostatin analogues have produced encouraging results in various somatostatin receptor positive tumours. This therapeutic approach produced partial remission rates up to 30% and therefore improved the quality of life for the patient. The PRRT works due to the high specific binding of the radiolabelled peptide to somatostatin receptors which are overexpressed by the tumours. The radionuclide $^{177}$Lu has a favourable half-life of 6.7 days and emits beta energy of 0.5 MeV for the treatment and gamma radiation for imaging. The authors continued to build on the success of the European Institute of Oncology (IEO) from the first application of $^{90}$Y labelled peptides towards therapy of neuroendocrine tumours. This gave way to the safe preparation of $^{177}$Lu labelled peptide for the clinical setting. In the design of these radiolabelled somatostatin analogues it was important to understand the chemical purity and specific activity including radiation protection of the healthcare professionals. The article concludes with the quality of these radiolabelled somatostatin analogues and addresses the relevant documentation to produce and deliver these theranostic peptides to the nuclear medicine departments.

The third article on, ‘Lutetium-177 Labeled Bombesin Peptides for Radionuclide Therapy,’ by Reynolds et al. describes the recent advances in $^{177}$Lu-labelled bombesin peptides towards targeted radiotherapy. The rare-earth radionuclides decay by emitting beta particles and have found application in targeted radiotherapy. The lutetium-177 can be produced with a specific activity of 740 GBq/mg by direct neutron capture of enriched lutetium-176 via the nuclear reaction $^{176}$Lu(n,$\gamma$)$^{177}$Lu. This radionuclidic has a half-life of 6.71 days and emits two imageable photons. The application of using lutetium-177 based therapy is to target the gastrin releasing peptide receptor (GRPR) in various disease states. This is due to the fact that GRPR agonists can undergo internalization to develop new theranostic targeting GRP receptor-positive tumours.

The fourth article, ‘Radioimmunotherapy of Metastatic Prostate Cancer with $^{177}$Lu-DOTAhuJ591 Anti Prostate Specific Membrane Antigen Specific Monoclonal Antibody,’ by Vallabhajosula et al. aims to design radiopharmaceuticals for the prostate-specific membrane antigen (PSMA) which is present in high levels in prostate cancer. The humanized J591 monoclonal antibody (mAb) can bind to the extracellular domain of PSMA. After binding, the PSMA-antibody complex is internalized into the cell releasing the radionuclide to destroy the tumour. The antibody J591 mAb was labelled with $^{177}$Lu at a high specific activity (10-30 mCi/mg) using DOTA as the bifunctional chelate. Pre-clinical studies have shown that PSMA responds to $^{177}$Lu-J591 mAb complex. Since 2000 this RIT radiopharmaceutical has been involved in five clinical trials for metastatic castration-resistant prostate cancer (CRPC).
‘Development and biological studies of 177Lu-DOTA-rituximab for the treatment of Non-Hodgkin’s lymphoma’, Massiccano et al. is the fifth article. The monoclonal antibody rituximab has been conjugated to different molar amounts of DOTA-NHS-ester. It was found that high radiochemical yield and stability was achieved using a 1:50 molar ratio of rituximab. This resulted in 4.9 ± 1.1 DOTA per rituximab molecule. The radiolabelling with 177Lu was performed in high specific activity and gave good \textit{in vitro} stability. The biodistribution in mice showed tumour uptake and high \textit{in vivo} stability as evidenced by low uptake in bone. These properties of using 177Lu-DOTA-rituximab prepared from DOTA-NHS-ester have potential for the application of 177Lu-labelled antibody in pre-clinical studies.

The sixth article is ‘Evaluation of 177Lu-EDTMP in Dogs with Spontaneous Tumor Involving Bone: Pharmacokinetics, Dosimetry and Therapeutic Efficacy’, by Chakraborty et al. Currently, 177Lu-EDTMP is under investigation for providing palliative care to patients suffering from bone pain due to metastatic skeletal carcinoma. In this article the authors describe the evaluation of 177Lu-EDTMP complex in four different canine patients with different types of primary and metastatic skeletal lesions. The radiopharmaceutical indicated favourable pharmacokinetic profiles such as preferential accumulation at skeletal lesion sites and fast clearance from blood including other non-target organs through the urinary route. The administered dose of the radiopharmaceutical showed excellent therapeutic efficacy towards primary bone cancer.

The seventh article is ‘Pharmacokinetic, Dosimetry and Toxicity Study of 177Lu-EDTMP in Patients: Phase 0/I study,’ Bal et al. The radiopharmaceutical, 177Lu-EDTMP has been proposed as a potent bone pain palliative agent. This is due to the low beta-energy and a suitably long half-life facilitating its wider distribution with less loss from radioactive decay. The results from the study demonstrate that 177Lu-EDTMP has excellent pharmacokinetic and dosimetric properties. In addition to being safe and effective. Along with estimating radiation dose values to certain critical organs, the authors have proposed an MTD for 177Lu-EDTMP that correlated well with toxicity data. The encouraging dosimetry and toxicity data of 177Lu-EDTMP reported the basis for subsequent phases of the studies to establish complete effectiveness and safety of 177Lu-EDTMP as an attractive alternative to other radioactive bone pain palliation agents.

The penultimate article on, ‘77Lu-Labeled Agents for Neuroendocrine Tumor Therapy and Bone Pain Palliation in Uruguay,’ by Balter et al. Lutetium-177 is an emerging radionuclide due to its convenient chemical and nuclear properties. In this paper the authors describe the development and evaluation in Uruguay of the targeted 177Lu labelled radiopharmaceuticals EDTMP (for bone pain palliation) and DOTA-TATE (neuroendocrine tumors). They have optimized the preparation of these 177Lu radiopharmaceuticals including radiolabelling, quality control methods, \textit{in vitro} and \textit{in vivo} stability and their therapeutic application in patients. Radiation dosimetry aspects of 177Lu are also included. These results from the study demonstrate the attractive therapeutic properties of these two 177Lu labelled agents and the feasibility of this metabolic therapy in regions far away from 177Lu producing countries.

The final article in this special issue is on, ‘Theranostic Applications of Lutetium-177 in Radionuclide Therapy’, by Das and Banerjee. In this article, the possibility of using two 177Lu-based agents such as 177Lu-EDTMP and 177Lu-DOTATATE for theranostic applications in metastatic bone pain palliation (MBPP) are reviewed. In the case of 177Lu-EDTMP, the whole-body images obtained are compared with those recorded using 99mTc-MDP in the same patient. Pre-therapy images were acquired using 177Lu-DOTATA-E and compared with similar images obtained with standard agents. These imaging agents included 99mTc-HYNIC-TOC (SPECT) and 68Ga-DOTA-TOC (PET) which were used in the same patient. The advantage of the long physical half-life of 177Lu has been utilized in mapping the pharmacokinetics of two additional agents. These include 177Lu-labelled hydroxyapatite (HA) in radiation synovectomy of knee joints and 177Lu-HA for therapy of hepatocellular carcinoma. The conclusion of these imaging studies suggest that 177Lu as a theranostic radioisotope role in nuclear medicine.

The first article of issue 2 was on, ‘Small-Animal Molecular Imaging for Preclinical Cancer Research: \textmu PET and \textmu SPECT,’ by Cucurullo et al. In this paper the authors set about the discussion of using small PET and SPECT scanners to evaluate pre-clinical imaging of disease states. In this case, small animal scanners usually have a higher sensitivity and spatial resolution compared to larger scanners used for humans. The benefits of using small animal scanners are to elucidate various animal models to work out the various mechanism of disease from pathology and translational pharmacology towards human disease states. The advantage of molecular imaging in the PET and SPECT mode is that the animals were not sacrificed and this approach allows experiments to be repeated to obtain robust results. Numerous animal models have investigated the human pathology including the development of new imaging and therapeutic agents. These small scanners are useful in oncology to image neoplastic phenotypes, tumour grafts, the promotion of tumour genesis and many others. The advent of small animal molecular imaging is becoming an essential tool in biomedical research and will continue to grow in the development of radiopharmaceuticals.

The next article on, ‘Radioguided Surgery for Localization of Nonpalpable Breast Lesions A Mini-Review’, by Langhans et al. investigates patients with nonpalpable breast lesions that may be eligible for breast conserving surgery guided by lesion localization methods. The current standard is wire-guided localization (WGL) which has several disadvantages. The major disadvantage is that most patients have an insufficient resection margin and require further operations. Radioguided surgery (RGS) offers a new approach including radioguided occult lesion localization (ROLL). In addition, to the technique called radioactive seed localization (RSL). Ultrasound is used to guide both procedures especially using a small titanium seed containing radioactive iodine-125 (1-10 MBq). The seed is set in the middle of the non-palpable breast lesion. During the operation, the seed can be located with a hand-held gamma probe. Limited studies have been carried out using RSL and include one randomized trial. The results indicated no superior benefits compared to WGL. Using the RSL technique, the patient experience less discomfort
and the radioactive seed can be placed a few days before surgery compared to the wire used in WGL. Currently, RSL is becoming more popular in surgical and radiological procedures and an important tool for preoperative localization of nonpalpable breast lesions.

The next article is on, ‘Optimising the Azeotropic Drying of 18F-Fluorine Way to Improve the 18F-Fluorocholine Radioc hemical Yield’, by Hassan et al. The background to this paper is the use of 18F-fluorocholine ion in the imaging of prostate tumour using positron emission tomography/computed tomography (PET/CT) hybrid scanner. This radiotracer is not available in Malaysia due to the relatively low radiopharmaceutical yield and logistics. This article provides improvements to the radiosynthesis of [18F]-fluorocholine. In the previous study azeotropic drying of the non-carrier-added 18F-fluorine in the reactor carried out at atmospheric pressure in a shorter time interval. The authors have studied the azeotropic drying of non-carried-added [18F]-fluorine at a high vacuum pressure. They concluded that the 18F-fluorocholine radiochemical yields improved after azeotropic drying.

The article on, ‘Convenient and Efficient Method for Quality Control Analysis of 18F-Fluorocholine: For a Small Scale GMP-based Radiopharmaceuticals Laboratory Set-up’, is presented by Hassan et al. Prostate cancer continues to be the most widespread cancer in men in Malaysia. The radiotracer 18F-fluorocholine is the gold standard for diagnostic imaging of prostate cancer. Today, only 18F-fluorodeoxyglucose (18F-FDG) is available and used in most oncology cases in Malaysia. The aim is to put Malaysia on the road map to 18F-fluorocholine by providing support to GMP radiopharmaceutical facilities and nuclear medicine departments.

The article ‘Evaluation of a Labelled Bacteriophage with 99mTc as a Potential Agent for Infection Diagnosis’, is contributed by Cardoso et al. The design of novel imaging probes especially to target the biochemistry of the human body could lead to early diagnosis of disease states caused by infection. However, scintigraphic imaging can locate the infection in the body. The radiolabelling technique requires size exclusion purification of the 99mTc-phage to obtain a radiochemical purity greater than 90%, during 18 hours post labelling period. The imaging revealed low levels of accumulation of 99mTc-phage in the stomach, small intestine and large intestine including the thyroid. This was indicative of no in vivo reoxidation taking place and the complex eliminated in the urine. Calculations are compared against the target/normal ratio (T/NT) for sterile inflammation and infection. The values obtained indicated significant differences between sterile inflammation and infection by Pseudomonas aeruginosa. The targeted biodistribution profile including the T/NT ratios were reasonable enough to distinguish between infection caused by Pseudomonas aeruginosa and sterile inflammation.

The next article is ‘Preparation and Administration of I-125 Labeled Seeds for Localization of Nonpalpable Breast Lesions’, by Langhans et al. Radioactive seed localization (RSL) is a new technique for surgical identification of non-palpable breast lesions. The authors describe the preparation of the needle using iodine-125 seeds which are deposited into breast lesions guided by ultrasound imaging. The study calculated the amount of seed activity required to produce a reasonable response from a gamma probe and limit the level of exposure to the staff. The clinical study included eleven patients each of whom received the radioactive seed which was placed into the breastbone using an 18-gauge needle guided by ultrasound and a gamma probe. The radiation exposure to the medical staff was below the acceptable limit using this radioguided surgical procedure.

In the final issue of 2016 the article, ‘Radiolabeled Sugars Used for PET and SPECT Imaging’, by Barrios-Lopez and Bergström discusses novel methods in the development of sugar-based probes to be utilized in human clinical studies in the application of molecular imaging. The incorporation of radioactive labels into carbohydrates can be used to investigate biochemical processes in living systems. The most used sugar probe in PET imaging is 2-deoxy-2-18F-fluoro-D-glucose (18F-FDG), especially in oncology. The authors of this review focus on the merits of 18F-FDG and other related sugars towards the design of new PET and Single Photon Emission Computed Tomography (SPECT) imaging probes.

The next article on ‘Gallium-68 in Medical Imaging’, by Martinova et al. discusses the emerging field of gallium-68 positron emission tomography (PET) imaging probes in the clinical setting. Gallium-68 is produced using a germanium-68/gallium-68 generator. This generator is easily transportable and more cost-effective than PET radioisotopes produced from a cyclotron. Also, gallium-68 has an acceptable working half-life of 68 minutes to provide radioactivity for various PET imaging procedures and radiation dose to patients.

The following article on, ‘Production of 68Ga-citrate Based on a SnO2 Generator for Short-Term Turpentine Oil-Induced Inflammation Imaging in Rats’ by Mirzaei et al. The gallium-68 citrate is used in PET imaging of infections and inflammatory processes. The authors of this paper are interested in developing models of the gallium-68 tracer in the inflammation process. They prepared the gallium-68 citrate from 68Ga-GaCl3, by eluting from a SnO2 based 68Ge/68Ga generator with sodium citrate. The radiation dose was administered to normal and turpentine-oil induced rats for PET/CT imaging studies. The gallium-68 citrate was produced in high radiochemical purity and the specific activity range was 28-30 GBq/mM. The PET/CT imaging studies indicated that gallium-68 citrate was able to detect the early onset of inflammation in animal models over a scanning period of 80 minutes.

In this article entitled, ‘Radiosynthesis of [18F]-fluorobenzoate-doxorubicin Using Acylation Approach’, by Kumar et al. the aim was to radiolabel doxorubicin with [18F] using the acylation method. They had already previously radiolabelled doxorubicin with [99mTc] and evaluated its potential use as a SPECT imaging agent to detect tumours in mice. The PET imaging precursor pentamethylbenzyl-4-(trimethylammonium trifluoromethanesulfonate) benzotate prepared from 4-[18F]-fluorobenzoic acid (FBA) followed by acylation to give the corresponding radiolabelled doxorubicin. The synthesis was achieved within 1 hour
and produced a radiolabelling efficiency of 59.0%. The radiochemical yield for \(^{18}\text{F}\)-FBA and \(^{18}\text{F}\)-fluorobenzoate-doxorubicin were 19.0-29.0% and 12.0-14.0% respectively. This research proved that the radiosynthesis of \(^{18}\text{F}\)-fluorobenzoate-doxorubicin by acylation was a reasonable approach and further synthetic methodology is required to improve the radiolabelling strategy.

The article, ‘Dual Nuclear/Fluorescence Imaging Potential of Zinc(II) Phthalocyanine in MIA PaCa-2 Cell Line’, by Lambrecht et al. in relation to pancreatic cancer. This type of cancer is difficult to diagnose in the early stage using various imaging techniques. The best approach is to use hybrid imaging systems incorporating optical imaging. The study used zinc(II) phthalocyanine \([\text{Zn(II)}\text{Pc}]\) radiolabelled with iodine-131 to be employed in an \textit{in vitro} study. The intracellular uptake studies of radiolabelled \([\text{Zn(II)}\text{Pc}]\) were performed using WI-38 and MIA PaCa-2 cell lines. The results indicated an intracellular uptake efficiency of radiolabelled \([\text{Zn(II)}\text{Pc}]\) in MIA PaCa-2 cells and gave two-fold higher than WI-38 cells. The fluorescence imaging (FI) efficiency of \([\text{Zn(II)}\text{Pc}]\) has been investigated in MIA PaCa-2 cells and significant uptake observed. The conclusion of the study indicated that \([\text{Zn(II)}\text{Pc}]\) has the potential to be a new imaging agent for dual fluorescence/nuclear imaging of pancreatic cancer.

The next article is on, ‘\(^{18}\text{F}\)-FDG-PET/CT in Patients Affected by Differentiated Thyroid Carcinoma with Positive Thyroglobulin Level and Negative \(^{131}\text{I}\) Whole Body Scan. It’s Value Confirmed by a Bicentric Experience’, by Bertagna et al. The authors are interested in the application of \(^{18}\text{F}\)-FDG-PET/CT hybrid imaging systems towards differentiated thyroid cancer (DTC). The objective of the study was to analyze the diagnostic value of \(^{18}\text{F}\)-FDG-PET/CT in patients treated with \(^{131}\text{I}\)-Iodine. In addition, to negative \(^{131}\text{I}\)-Iodine-WBS in the presence of Tg levels higher than 1ng/mL after TSH stimulation. The patient sample was from September 2005 to December 2014 and included 154 patients affected by DTC treated with \(^{131}\text{I}\)-Iodine with negative \(^{131}\text{I}\)-Iodine-WBS and Tg > 1ng/mL underwent \(^{18}\text{F}\)-FDG-PET/CT. The study showed that 66 patients (43%) had a negative \(^{18}\text{F}\)-FDG-PET/CT while 88 (57%) a positive scan. These scans consisted of bone, pulmonary, lymph node metastases and local recurrences imaging. The study concluded that \(^{18}\text{F}\)-FDG-PET/CT hybrid imaging could be useful in the evaluation of patients affected by differentiated thyroid cancer.

The final article of issue 3 was on, ‘Automated PET Radiotracer Manufacture on the BG75 System and Imaging Validation Studies of \(^{18}\text{F}\)fluoromisonidazole (\(^{18}\text{F}\)FMISO)’, by Yuan et al. The PET tracer, 1-[\(^{18}\text{F}\)]fluoro-3-(2-nitro-1\text{H}-imidazol-1-yl)-propan-2-ol (\(^{18}\text{F}\)FMISO) was the first radiotracer developed for hypoxia PET imaging. This tracer showed potential in the diagnosis and prognosis of cancer. Unfortunately, the access to \(^{18}\text{F}\)FMISO radiotracer is in short supply due to being cyclotron produced. The aim was to develop an automated approach to \(^{18}\text{F}\)FMISO based on the BG75 system. This set-up produced \(^{18}\text{F}\)FMISO in a radiochemical purity >99%. The biodistribution of \(^{18}\text{F}\)FMISO in both tumour models was consistent with reported studies when observed in the bladder and large intestines. \(^{18}\text{F}\)FMISO autoradiography and EF5 hypoxia staining indicated high hypoxia specificity. Therefore, this investigation showed that \(^{18}\text{F}\)FMISO could be produced on the BG75 system in an automatic configuration to generate dose-on-demand using single dose disposable cards.

The journal is gaining pace, and so is its reputation amongst researchers in pharmaceutical (imaging) companies, institutions and universities; all of this will lead to the continued future success of \textit{Current Radiopharmaceuticals}.

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