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⁸⁶Y based PET radiopharmaceuticals: radiochemistry and biological applications

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Abstract

Development of targeted radionuclide therapy with ⁹⁰Y labeled antibodies and peptides has gained momentum in the past decade due to the successes of ⁹⁰Y-ibritumomab tiuxetan and ⁹⁰Y-DOTA-Phe¹-Tyr³-octreotide in treatment of cancer. ⁹⁰Y is a pure β^- -emitter and cannot be imaged for patient-specific dosimetry which is essential for pre-therapeutic treatment planning and accurate absorbed dose estimation in individual patients to mitigate radiation related risks. This review article describes the utility of ⁸⁶Y, a positron emitter (33%) with a 14.7-h half-life that can be imaged by positron emission tomography and used as an isotopically matched surrogate radionuclide for ⁹⁰Y radiation doses estimations. This review discusses various aspects involved in the development of ⁸⁶Y labeled radiopharmaceuticals with the specific emphasis on the radiochemistry and biological applications with antibodies and peptides.

Keywords

PET imaging; radiochemistry; ⁹⁰Y; ⁸⁶Y; bioconjugate chemistry; peptides; and antibodies

Introduction

Recent advances in radiochemistry and biomedical sciences offer diverse receptor-avid and immune-derived molecular vectors as well as a plethora of therapeutic radionuclides [1,2]. Several systems are currently being investigated as potential means for targeting of radionuclide to desired site. Of these, largely monoclonal antibodies (mAb) and peptides have successfully been used in clinic [1,2]. Targeted radionuclide therapy with antibodies and peptides are at the forefront of molecular cancer treatment modalities. ⁹⁰Y is one of the promising radionuclides for targeted radionuclide therapy of hematologic malignancies and solid tumors [3–6]. However, ⁹⁰Y labeled antibodies and peptides may pose challenges in managing radiation toxicity if the radiation doses exceed the critical limit to organs such as the bone marrow and the kidneys [7,8]. Since ⁹⁰Y is a pure β^- -emitter, its biodistribution cannot be readily imaged for patient-specific dosimetry which is essential for pre-therapeutic treatment planning and accurate absorbed dose estimation in individual patients to mitigate radiation risks. Attempts have been made to image the Bremsstrahlung radiation generated

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Conflict of Interest: Herceptin[®] and Avastin[®] discussed in the article are manufactured by F. Hoffmann-La Roche, Ltd. TN is an employee of F. Hoffmann-La Roche, Ltd.

by the slowing down of high-energy electrons in tissue. However, the low photon yield and the polychromatic nature of the Bremsstrahlung spectrum result in limited quantitative accuracy with ^{90}Y [9,10].

^{111}In and ^{89}Zr were used as surrogate single photon emission computerized tomography (SPECT) and positron emission tomography (PET) radionuclides for ^{90}Y , respectively; however, disparities were observed in the biodistribution of these radionuclides and the ^{90}Y labeled antibodies and peptides [11–15]. The somatostatin receptor-targeted ^{90}Y -DOTA-Phe¹-Tyr³-octreotide is the most extensively studied radiolabeled peptide in patients for treatment of cancer. Clinical trials performed in several countries showed complete and partial remissions in 10% to 30% of patients [1]. In spite of encouraging efficacy results, loss of renal function or renal failure was observed in some patients treated with ^{90}Y -DOTA-Phe¹-Tyr³-octreotide and therefore pre-treatment radiation dose assessments are critical for ^{90}Y -DOTA-Phe¹-Tyr³-octreotide [1,8]. In a clinical study, a ^{86}Y labeled peptide and ^{111}In labeled peptide were compared for pre-treatment dosimetry assessments of ^{90}Y radionuclide therapy [11]. Compared to ^{86}Y -DOTA-Phe¹-Tyr³-octreotide, dosimetry with ^{111}In -pentetreotide overestimated doses to kidneys and spleen, whereas the radiation dose to the tumor-free liver was then underestimated for ^{90}Y -DOTA-Phe¹-Tyr³-octreotide radiotherapy [11].

In recent years, ^{86}Y has gained popularity as an attractive surrogate for studying ^{90}Y due its half-life (14.7 h) and positron emission (33 % β^+) which allows quantitative imaging over 2–3 days [11,16]. Since the chemical form is identical to ^{90}Y , ^{86}Y labeled antibodies and peptides have identical biodistributions with ^{90}Y labeled antibodies and peptides, and therefore should inherently enable more accurate absorbed dose estimates for ^{90}Y [11,17,18]. This review discusses various aspects involved in the development of ^{86}Y labeled radiopharmaceuticals with the specific emphasis on the radiochemistry and biological applications with antibodies and peptides.

Radiochemistry

Yttrium belongs to group IIIB of the periodic table and has an atomic radius of 2.3 Å and electronegativity of 1.22. ^{86}Y can be produced via the (p,n) or (d,2n) nuclear reaction on enriched ^{86}Sr (^3He ,2n) on natural rubidium, (p,3n) on enriched ^{88}Sr , or (d,x) reaction on natural zirconium target [19,20]. However, the $^{86}\text{Sr}(\text{p,n})^{86}\text{Y}$ reaction is the more commonly used method as it can be applied on medical cyclotrons by irradiating SrCO_3 or SrO with 2–6 μA of beam current for <4 h [21,22]. As compared to SrCO_3 , SrO is a superior target because it can withstand at least a 6 μA of beam current, which is a significant improvement over a maximum of 2 μA on the SrCO_3 target, resulting in yields that are almost double with minimum contaminants [21]. After irradiation, ^{86}Y is separated from the target material using a commercially available $\text{Sr}(\text{II})$ selective resin and purified in order to accomplish efficient radiolabeling [22]. Electrochemical method of separation is also commonly used to produce no-carrier-added ^{86}Y of high purity [23]. Other separation techniques include the combination of co-precipitation and cation-exchange chromatography and ion specific resin chromatography, or paper filtration from alkaline solution [18,19,24].

Once high purity ^{86}Y is produced, it is then attached to the targeting vector such as an antibody and a peptide via a chelating agent. A chelating agent is a molecule containing more than one ligand or an atom such as N, O and S that can donate a lone pair of electrons. The oxidation state and electronegativity play a major role in the formation of metal-ligand complexes. Yttrium is a transition metal ion that exists in a tricationic state, $\text{Y}(\text{III})$, that can readily reach coordination numbers of 8 and 9 in its complexes and prefers octadentate coordinating ligands. Acyclic polyaminocarboxylates such as ethylenediaminetetraacetic

acid (EDTA) and diethylenetriamine pentaacetic acid (DTPA) and macrocyclic polyaminocarboxylates such as 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) have been used as chelating agents for yttrium (Figure 1).

The chelating agents themselves are modified to provide a method to link them to antibodies and peptides (e.g., cyclic and mixed anhydrides of DTPA), alternatively linking groups such as isothiocyanatobenzyl group (SCN-Bz) are incorporated to the chelating agent by covalent linkage to the carbon backbone of the chelating agents [25]. In a pre-clinical study, the biodistribution of yttrium- and indium-labeled mAb B72.3 was compared in athymic mice bearing human colorectal cancer LS-174T tumors using three different chelate conjugates (SCN-Bz-EDTA, Cyclic anhydride-DTPA (ca-DTPA), and SCN-Bz-DTPA) [26]. The yttrium uptake in the bone with the SCN-Bz-EDTA and ca-DTPA conjugated mAb was greater than 14 and 11% ID/g, respectively, while ^{88}Y -SCN-Bz-DTPA-B72.3 showed only 3% ID/g. In contrast, the ^{111}In -labeled B72.3 uptake in the bone with all three chelate conjugates was 2–3% ID/g. The differences in yttrium- versus indium-labeled mAb biodistributions demonstrates the differences in the *in vivo* stability of different forms of acyclic polyaminocarboxylates for In(III) and Y(III); all three chelating agents were stable for ^{111}In , but only the full DTPA with 3 amines and 5 carboxylate donors bound to the Y(III) was stable for ^{88}Y , thereby elucidating the need for both better and more stable chelating agents for Y(III) and the need for a radioisotopically matched imageable yttrium radionuclide to predict more accurate biodistribution and dosimetry of ^{90}Y -labeled agent [26].

To further understand and improve the *in vivo* stability, additional studies were performed with backbone-substituted forms of the SCN-Bz-DTPA and DOTA [27]. In this study, the biodistribution of yttrium- and indium-labeled mAb, B3, using two different chelate conjugates, i.e. 2-(p-SCN-Bz)-6-methyl-DTPA (1B4M-DTPA) and 2-(p-SCN-Bz)-1,4,7,10-tetraazacyclododecane tetraacetic acid (C-DOTA) (Figure 1) were compared in tumor bearing athymic mice [27]. Mice injected with indium and yttrium labeled 1B4M-DTPA-B3 showed a similar biodistribution in all tissues except the bones, where significantly higher accretion of yttrium than indium was observed, with 2.8% $\pm$ 0.2% vs. 1.3% $\pm$ 0.16% ID/g in the femur at 168 h, respectively ($P < 0.0001$) [27]. In contrast, mice receiving indium and yttrium labeled C-DOTA-B3 showed significantly higher accumulation of indium than yttrium in most tissues, including the bones and therefore further illustrating the differences between two radionuclides and the chelating agents. From these studies, it was observed that the SCN-Bz substituted onto the carbon backbone of DTPA for use in linkage to the antibody and the methyl groups incorporated onto the backbone sterically hindered the release of yttrium from the chelate and therefore demonstrated the superiority of backbone-substituted DTPA chelating agents over cyclic anhydride-DTPA chelating agents.

With a better understanding of the coordination chemistry and geometry of DTPA derivatives, a cyclohexyl derivative of DTPA (CHX-DTPA) was developed, which demonstrated excellent stability *in vitro* and *in vivo* [25,28,29]. Interestingly, the stereochemistry of CHX-DTPA played a major role in the *in vivo* stability of yttrium labeled agents and subsequent bone uptake. The single enantiomeric [(*R*)-2-amino-3-(4-isothiocyanatophenyl)propyl]-trans-(*S,S*)-cyclohexane-1,2-diamine-pentaacetic acid (CHX-A''-DTPA) radioimmunoconjugate was found to be more stable as compared to the corresponding diastereomeric pair of CHX-B-DTPA radioimmunoconjugates (Figure 1). After 7 days post-injection, bone uptake of the yttrium labeled CHX-B'-DTPA or CHX-B''-DTPA radioimmunoconjugates was 5 times higher than that of the yttrium labeled CHX-A''-DTPA radioimmunoconjugate [28,30]. For labeling of peptides at the *N*-terminus, an *N*-hydroxysuccinimidyl penta-*tert*-butyl ester derivative of CHX-A''-DTPA featuring a glutaric acid spacer was developed (Figure 2) [31]. In order to further improve the stability,

DOTA derivatives such as SCN-Bz-DOTA were explored for radiolabeling antibodies and peptides with yttrium [32–34]. In a comparative study, it was found that DOTA conjugated antibody was more stable than the DTPA conjugated [33]. Since then, numerous pre-clinical and clinical studies have been published reporting DTPA and DOTA based chelating agents for ^{90}Y radionuclide therapy and thus extrapolating to ^{86}Y for PET imaging [15,16,31,35].

For *in vivo* applications, kinetic inertness of yttrium–chelator complexes or conjugates is more relevant than thermodynamic stability [36]. For yttrium, acyclic chelating agents are less kinetically inert than macrocyclic complexes of comparable stability, but at the same time acyclic chelating agents have faster metal-binding kinetics at room temperature compared with their macrocyclic analogues, which can be a significant advantage for radiolabeling of antibodies which are thermosensitive.

Biological applications

^{86}Y labeled peptides

^{86}Y labeled somatostatin receptor-targeted peptides were evaluated in rodents, non-human primates and humans [11,18,31]. For peptides, CHX-A''-DTPA, a widely applicable chelating agent for yttrium was modified via standard succinimidyl ester coupling chemistry for *N*-terminal conjugation to somatostatin peptide [31]. Briefly, an *N*-hydroxysuccinimidyl penta-*tert*-butyl ester derivative of CHX-A''-DTPA with a glutaric acid spacer moiety was developed to lessen steric effects and interactions of the chelator–metal complex on peptide–receptor binding affinity. CHX-A''-DTPA-octreotide was radiolabeled with ^{86}Y and evaluated in AR42J tumor bearing male rats. ^{86}Y -CHX-A''-DTPA-octreotide was prepared with high radiochemical yields (> 97 %) and specific activity of 6.49×10^6 MBq/mmol. Somatostatin-receptor mediated uptake was observed in the AR42J tumor (0.94 ± 0.22 % ID/g) in addition to somatostatin receptor expressing organs such as pituitary gland (1.70 ± 0.08 % ID/g), adrenal glands (0.95 ± 0.30 % ID/g), and pancreas (0.65 ± 0.24 % ID/g) [31]. Tumor was clearly visualized at 4 h after injection by PET imaging [31].

In order to quantify the *in vivo* parameters of ^{90}Y -DOTA-DPhe¹-Tyr³-octreotide and the radiation doses delivered to healthy organs, the analogue ^{86}Y -DOTA-DPhe¹-Tyr³-octreotide was synthesized and its uptake measured in baboons using PET [18]. ^{86}Y -DOTA-DPhe¹-Tyr³-octreotide was further evaluated in a Phase I clinical study involving 24 patients with somatostatin-receptor positive neuroendocrine tumors [15]. Most patients were injected with 370 MBq of ^{86}Y -DOTA-DPhe¹-Tyr³-octreotide along with amino acids to reduce renal uptake. PET scans were performed at 4, 24 and 48 h after injection. Primary and metastatic lesions were clearly visualized at 4, 24 and 48 h after injection [15]. In another study comprising 8 patients with progressive metastatic neuroendocrine tumors, ^{86}Y -DOTA-DPhe¹-Tyr³-octreotide was compared with ^{111}In -pentetreotide for predicting the radiation doses after 3 cycles of ^{90}Y -DOTA-DPhe¹-Tyr³-octreotide [11]. The range of doses (mGy/MBq ^{90}Y -DOTA-Phe¹-Tyr³-octreotide) for kidneys, spleen, liver and tumor masses was 0.6–2.8, 1.5–4.2, 0.3–1.3 and 2.1–29.5 (^{86}Y -DOTA-Phe¹-Tyr³-octreotide), respectively, versus 1.3–3.0, 1.8–4.4, 0.2–0.8 and 1.4–19.7 (^{111}In -pentetreotide), with wide inter-subject variability. Compared with ^{86}Y -DOTA-Phe¹-Tyr³-octreotide, dosimetry with ^{111}In -pentetreotide overestimated doses to kidneys and spleen, whereas the radiation dose to the tumor-free liver was underestimated [11].

^{86}Y labeled peptides targeting the alpha-melanocyte stimulating hormone (alpha-MSH) and gastrin-releasing peptide receptors have also been reported [37,38]. The α -MSH targeted DOTA-ReCCMSH(Arg¹¹) was labeled with ^{64}Cu and ^{86}Y and evaluated in tumor bearing mice [37]. Tumor concentration for both the ^{86}Y - and ^{64}Cu -complexes reached a maximum at 30 min, while co-administering 20 μg of unlabeled complex reduced tumor uptake

significantly. Non-target organ concentration was considerably lower with ^{86}Y -DOTA-ReCCMSH(Arg¹¹) than its ^{64}Cu analogue, except in the kidneys, where the ^{64}Cu complex had lower accumulation at all time points [37]. In order to improve specific activity, CHX-A"-DTPA as chelating agent for ReCCMSH(Arg¹¹) was examined due to its rapid and efficient metal chelation properties [39]. CHX-A"-DTPA has been reported to chelate yttrium and other trivalent metal cations nearly instantaneously at a chelator/metal ratio of 1:1 at 22°C, whereas a minimum molar ratio of DOTA-ReCCMSH(Arg¹¹)/radiometal of 20:1 and incubation at $\geq 75^\circ\text{C}$ were necessary for efficient peptide labeling and therefore post-labeling purification is required [39]. Gastrin-releasing peptide receptors targeted peptide, MP2346 was conjugated with DOTA and radiolabeled with ^{64}Cu and ^{86}Y [38]. ^{64}Cu and ^{86}Y labeled MP2346 were evaluated in mice bearing PC-3 tumor xenografts. Biodistribution in PC3 tumor-bearing mice demonstrated higher tumor uptake, but lower liver retention, in animals injected with ^{86}Y -MP2346 compared to ^{64}Cu -MP2346. It was possible to delineate PC-3 tumors *in vivo* with ^{64}Cu -MP2346, but superior ^{86}Y -MP2346-PET images were obtained due to lower uptake in clearance organs and lower background activity and therefore the ^{86}Y analogue demonstrated superior targeting characteristics than ^{64}Cu analogue [38]. The studies with α -MSH and gastrin-releasing peptide receptors targeted peptides demonstrated the superiority of ^{86}Y labeled over ^{64}Cu labeled peptides.

^{86}Y labeled antibodies

Numerous ^{90}Y labeled intact monoclonal antibodies were evaluated in pre-clinical and clinical settings [7,40–43]. Of the numerous ^{90}Y labeled mAbs evaluated, ^{90}Y -ibritumomab tiuxetan (Zevalin[®]) was approved by the US FDA in 2002 for treatment of patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL), including patients with rituximab refractory follicular NHL[43]. Since then many antibodies and proteins have been labeled with ^{86}Y for PET imaging and dosimetry of counterpart ^{90}Y labeled antibodies and proteins [16,22,44]. Human epidermal growth factor 2 (HER2) targeted intact IgG₁ mAb, Trastuzumab (Herceptin[®]) was approved by US FDA in 1999 for treatment of cancer [43].

1B4M-DTPA-trastuzumab was radiolabeled with ^{86}Y and ^{111}In , and evaluated in LS-174T tumor bearing athymic mice [22]. The biodistribution study revealed that ^{111}In -1B4M-DTPA-trastuzumab, while a suitable surrogate for ^{90}Y in the major organs, did not parallel the uptake of ^{86}Y -1B4M-DTPA-trastuzumab in the bone, and thus may not accurately predict the level of ^{90}Y accumulation in the bone for clinical radioimmunotherapy applications [22]. Examination of the results for the uptake of the two radiolabeled antibodies at the bone over time revealed that ^{111}In -1B4M-DTPA-trastuzumab reached a maximum of 2.15 ± 0.49 %ID/g at 12 h and remained constant until 72 h. The amount of radioactivity in the bone declined thereafter at 120 h to 1.07 ± 0.41 %ID/g. On the contrary, accumulation of ^{86}Y -1B4M-DTPA-trastuzumab in the bone was observed over a period of 120 h. The level of ^{86}Y -1B4M-DTPA-trastuzumab at 12 h was higher than ^{111}In -1B4M-DTPA-trastuzumab (2.69 ± 0.71 %ID/g, $p = 0.345$), however the differences were not found to be significant. This trend continued until the 72 h time point when a marked increase in the ^{86}Y -1B4M-DTPA-trastuzumab level was noted (3.07 ± 0.63 %ID/g versus 1.83 ± 0.19 %ID/g; ^{86}Y versus ^{111}In , $p = 0.019$), which was a significant difference. Finally, the level of ^{86}Y in the bone at the 120 h time point continued to increase from being merely 25% greater than the comparable ^{111}In value at 72 h to 331% greater than the comparable ^{111}In value at 120 h. This study once again exemplified the requirement of employing appropriate matched pair isotopes for imaging and therapy to insure that dosimetry considerations may be addressed accurately [22].

^{86}Y -trastuzumab was further evaluated in mice bearing intraperitoneal ovarian (SKOV-3) and colorectal (LS-174T) tumors [35,45]. Both these studies demonstrated the utility of ^{86}Y -

trastuzumab as a PET surrogate for ^{90}Y -trastuzumab distribution. ^{86}Y -trastuzumab localized to sites of disease with minimal normal organ uptake as revealed in microPET and MRI data (Figure 3) [35,45]. Dosimetry calculations with ^{86}Y -trastuzumab in intraperitoneal ovarian carcinoma model revealed the absorbed dose to the kidneys was 0.31 Gy/MBq for ^{90}Y -trastuzumab [35]. The liver received 0.48 Gy/MBq, and the spleen received 0.56 Gy/MBq and the absorbed dose to tumors varied from 0.10 Gy/MBq for radius = 0.1 mm to 3.7 Gy/MBq for radius = 5 mm [35]. Cetuximab (Erbix[®]), panitumumab (Vectibix[®]) and bevacizumab (Avastin[®]) are other mAbs that are approved by the US FDA for treatment of cancer. Cetuximab and panitumumab target HER1, whereas bevacizumab targets vascular endothelial growth factor (VEGF). All these mAbs have been radiolabeled with ^{86}Y and evaluated in pre-clinical models [16,17,46].

^{86}Y -CHX-A"-DTPA-panitumumab was developed as a noninvasive molecular imaging tool for selecting patients for HER1-targeted panitumumab therapy and for dosimetry assessment for possible targeted ^{90}Y therapy [16]. Panitumumab was modified with the CHX-A"-DTPA at a 10:1 molar excess of chelate to protein, yielding a final chelate-to-protein ratio of 1.6 chelate molecules per protein molecule. The ^{86}Y -CHX-A"-DTPA-panitumumab conjugate was successfully prepared, with the radiochemical yields ranging from 60% to 75% and specific activity exceeding 2 GBq/mg [16]. Biodistribution, non-compartmental pharmacokinetics, and imaging data revealed HER1-mediated uptake of ^{86}Y -CHX-A"-DTPA-panitumumab and accumulation in HER1-expressing tumor xenografts [16]. Similarly, ^{86}Y -CHX-A"-DTPA-bevacizumab was developed as a potential PET imaging agent of VEGF-A mediated tumor angiogenesis and as a surrogate marker for ^{90}Y -based radioimmunotherapy [17]. *In vivo* biodistribution and PET imaging studies were performed on mice bearing VEGF-A-secreting human colorectal (LS-174T), human ovarian (SKOV-3) and VEGF-A-negative human mesothelioma (MSTO-211H) xenografts. Biodistribution and PET imaging studies demonstrated highly specific tumor uptake of the radioimmunoconjugate. In mice bearing VEGF-A-secreting LS-174T, SKOV-3 and VEGF-A-negative MSTO-211H tumors, the tumor uptake at 3 days post-injection was 13.6 ± 1.5 , 17.4 ± 1.7 and 6.8 ± 0.7 % ID/g, respectively [17]. The corresponding tumor uptake in mice co-injected with 0.05 mg cold bevacizumab were 5.8 ± 1.3 , 8.9 ± 1.9 and 7.4 ± 1.0 % ID/g, respectively at the same time point, demonstrating specific blockage of the target in VEGF-A-secreting tumors. The LS-174T and SKOV3 tumors were clearly visualized by PET imaging after injecting 1.8–2.0 MBq ^{86}Y -CHX-A"-DTPA-bevacizumab [17].

Human mindin homologue, mindin/RG-1, is expressed in >80% of prostate cancers metastatic to bone or lymph nodes as well as in locally recurrent tumors in androgen-unresponsive patients [47,48]. A fully human antibody, 19G9, was generated against mindin/RG-1 protein and conjugated with CHX-A"-DTPA, and radiolabeled with either ^{111}In , ^{90}Y , or ^{86}Y for *in vivo* imaging and radionuclide therapy [47]. PET with ^{86}Y -CHX-A"-DTPA-19G9 showed very specific accumulation of the antibody in LNCaP tumor xenografts with clear tumor delineation apparent 4 h after injection [47]. Based on the imaging data with ^{86}Y -CHX-A"-DTPA-19G9 the therapeutic efficacy of ^{90}Y -CHX-A"-DTPA-19G9 was evaluated in mice bearing LNCaP xenografts. A dose-finding study identified a nontoxic therapeutic dose to be approximately 2.7 MBq. Significant antitumor effects were seen with a single administration of radiolabeled antibody to animals bearing 200 to 400 mm³ tumors [47]. To further develop mindin/RG-1-targeted radionuclide therapy, 19G9 was engineered to obtain the matched diabody, single-chain variable domain (scFv) and novel miniantibody format. The intact antibody, 19G9 and its fragments were conjugated with CHX-A"-DTPA and radiolabeled with ^{86}Y for PET imaging and *in vivo* evaluation in tumor bearing mice [48].

The size of the construct profoundly affected the pharmacokinetic characteristics of each agent (Figure 4) [48]. The smallest construct (scFv) was rapidly and efficiently extracted from the blood and removed, primarily via the renal system, before significant tumor accumulation. In contrast, the largest construct (IgG) demonstrated prolonged blood retention and significant tumor uptake. PET detected IgG tumor deposition at 24 h. The diabody and miniantibody fragments both demonstrated intermediate blood clearance and tumor localization. Diabody blood levels were rapidly reduced during the initial hours, and tumor deposition was probably not sufficient for radiotherapy. High kidney levels were found for the diabody at 3 and 6 h. PET of the diabody at 48 h did, however, show comparable tumor delineation to that of the IgG and miniantibody [48]. The above studies demonstrate the utility of ^{86}Y labeled antibody not only in understanding the biodistribution of ^{90}Y labeled antibody but also selection of the optimum construct for improved outcomes.

Besides antibodies and peptides, there are other reported applications of ^{86}Y . ^{86}Y -citrate was used as an analog of the commercially available radiotherapeutic ^{90}Y -citrate [20]. Additionally, a mirror-image oligonucleotide (L-RNA) was radiolabeled with ^{86}Y for PET imaging [49].

Discussion

Antibodies and peptides function as carriers of cytotoxic substances, such as radioisotopes for treatment of cancer [1,43]. In NHL, anti-CD20 radiolabeled antibodies have superior antitumor activity compared with their unconjugated antibody counterparts, but there is increased, albeit manageable, hematological toxicity if the careful pretreatment planning and dosimetry is performed [7,41]. Similarly, for neuroendocrine and somatostatin receptor expressing tumors, radiolabeled peptides have demonstrated superior antitumor activity than unlabeled peptides [1,6]. However, renal toxicity is a primary concern and therefore careful pretreatment dosimetry and screening is required [8].

For ^{90}Y labeled agents, ^{86}Y offers an attractive alternative to ^{111}In for pretreatment dosimetry and imaging. In pre-clinical studies, the superiority of ^{86}Y over ^{111}In in predicting ^{90}Y has been demonstrated [11,22]. However, ^{86}Y itself has some limitations such as the high-energy gamma-emission and a lack of adequate commercial availability (as compared to ^{111}In). More than 65% of ^{86}Y decays are accompanied by additional gamma-rays with energies from 200 to 3,000 keV that are mostly emitted simultaneously with positron emissions and the subsequent annihilation photons resulting into increased scatter and random events [50,51]. The resulting large number of non-true coincidences evoke a low-frequency background noise that decreases the contrast in reconstructed images and may lead to erroneous quantitation of the ^{86}Y radioactivity concentration in individual regions of interest, thus resulting in false ^{90}Y organ doses [50,51]. Successful attempts have been made to improve the image characteristics of ^{86}Y by developing methods to correct for scatter fractions and spurious coincidences [50–52]. Image reconstruction algorithms have been developed, which include models of the statistical nature of nuclear decays and tomography responses that improve the spatial resolution and at the same time reduce the image noise [52,53]. Further advances in instrumentation and image processing may additionally improve spatial resolution and the ability to perform more accurate quantitative analysis with ^{86}Y .

The available choice of radionuclides used for PET imaging of antibodies and peptides are ^{124}I , ^{64}Cu , ^{89}Zr , ^{86}Ga , ^{18}F and ^{86}Y . Each of these radionuclides has their own specific advantage and drawback. For rapidly internalizing antibodies and peptides, ^{124}I will be dehalogenated rapidly *in vivo* and result in poor tumor to background ratio. ^{64}Cu -TETA-1A3 has previously been reported for clinical PET imaging of metastatic colorectal cancer [54]. Detection of lung and liver metastasis was seriously hindered by non-specific

uptake in the liver and the blood due to dissociation of the ^{64}Cu from the currently used chelates for radiolabeling mAbs [54]. ^{89}Zr is an attractive positron emitter due its longer half-life, however preparation of ^{89}Zr labeled mAbs is a multi-step, tedious process and ^{89}Zr has been shown to dissociate from the currently used chelates and to localize in the bone thereafter [55,56]. While for peptides and antibody fragments, ^{68}Ga has gained immense popularity in the recent years [57–59], despite the lack of the availability of radiopharmaceutical grade $^{86}\text{Ge}/^{68}\text{Ga}$ generator remains an issue (at least in the United States). Clinical translation of all these unconventional radionuclides will largely depend on the commercial availability and supply of radiopharmaceutical grade radionuclide. Availability and high energy gamma emission poses the biggest challenge for clinical translation of ^{86}Y .

It is clear from the selected examples cited in this report that efforts are continuing to develop ^{86}Y labeled radiopharmaceuticals as PET imaging agents and for dosimetry of ^{90}Y labeled radiopharmaceuticals. ^{86}Y labeled radiopharmaceuticals hold significant promises, but several scientific and non-scientific challenges such as availability have to be conquered before realizing its true potential in PET imaging agents and as a surrogate radioisotope for dosimetry of ^{90}Y .

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List of abbreviations

mAbs	Monoclonal antibodies
PET	Positron emission tomography
MRI	Magnetic resonance imaging
EDTA	Ethylenediaminetetraacetic acid
DTPA	Diethylenetriamine pentaacetic acid
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
SCN-Bz	Isothiocyanatobenzyl
ca	Cyclic anhydride
% ID/g	Percent injected dose per gram
alpha-MSH	Alpha-melanocyte stimulating hormone
NHL	Non-Hodgkin's lymphoma
HER	Human epidermal growth factor
VEGF	Vascular endothelial growth factor
scFv	Single-chain variable domain antibody fragment
IgG	immunoglobulin

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Figure 1. Chemical structures of acyclic and macrocyclic polyaminocarboxylates chelating agents used for radiolabeling with yttrium

Figure 2. Succinimidyl ester coupling chemistry for *N*-terminal conjugation of octreotide with *N*-hydroxysuccinimidyl penta-*tert*-butyl ester derivative of CHX-A''-DTPA with a glutaric acid spacer.

Figure 3. PET maximum intensity projections (3 d p.i.) of female athymic mouse bearing (A) subcutaneous LS-174T and (B) intraperitoneal LS-174T tumors injected with ^{86}Y -CHX-A"-DTPA-trastuzumab. (C) MRI of the female athymic mouse bearing intraperitoneal LS-174T tumors indicating the localization of the radiolabeled antibody in the tumor sites (C). White arrows indicate tumor sites. This figure is adapted from Milenic et al. [45].

Figure 4. Comparison of PET imaging of ^{86}Y labeled IgG, scFv, diabody and miniantibody construct of 19G9 in tumor bearing mice. Reprinted by permission of the Society of Nuclear Medicine from Schneider et al. [48]