Indonesian Journal of Pharmacy

VOL 33 (3) 2022: 333–352 | REVIEW ARTICLE

Somatostatin Analog-Based Radiopharmaceuticals for Molecular Imaging and Therapy of Neuroendocrine Tumors

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Submitted: 21-07-2021
Revised: 02-02-2022
Accepted: 20-07-2022

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ABSTRACT

Somatostatin receptors (SSTRs) are peptide receptors that are overexpressed in a wide variety of cancers including neuroendocrine tumors (NETs). Because of their short biological half-life and low metabolic stability in vivo, natural somatostatin ligands are not suitable for clinical applications. Octreotide is a synthetic somatostatin peptide analog that has been extensively evaluated for the development of SSTR-specific molecular imaging and radionuclide therapy of NETs. In this review, we summarize the development of the radiolabeled octreotide analogs ^{111}In, ^{99m}Tc, and ^{123}I for molecular imaging of NETs via single-photon emission computed tomography (SPECT), ^{68}Ga-labeled somatostatin analog for molecular imaging using positron emission tomography (PET), and ^{177}Lu-, ^{90}Y-, and ^{111}In-labeled somatostatin analogs for peptide receptor radionuclide therapy (PRRT) of NETs. Our review of the literature indicates that these radiolabeled somatostatin analogs exhibit good image quality and high tumor uptake and highlight the potential applications of radiolabeled somatostatin analogs for the molecular imaging and targeted treatment of NETs.

Keywords: somatostatin, peptide, radiopharmaceuticals, therapy, imaging

INTRODUCTION

Cancer is one of the most burdensome and life-threatening diseases in the world (World Health Organization, 2019). More than 19 million cancer cases were estimated worldwide for 2020, with new cases projected to be 28.4 million in 2040 (Sung *et al.*, 2021). Standard primary cancer treatment options such as surgery, chemotherapy, and radiation are available (Harrington *et al.*, 2010), used as single treatments or in combination (Jamous *et al.*, 2013). As an alternative to these standard treatments, radiopharmaceutical therapy (RPT) has been shown to be a safer and more effective approach (Sgouros *et al.*, 2020). Radiopharmaceuticals (radioactive drugs) comprise biologically active molecules labeled with radionuclides. These radioactive molecules have long been used in the field of nuclear medicine to treat a wide variety of diseases including cancers (Payolla *et al.*, 2019) by delivering radiation doses to target cells (Sgouros *et al.*, 2020). Depending on the nature of the radionuclides used (their type of emission), radiopharmaceuticals are categorized as either diagnostic or therapeutic (Payolla *et al.*, 2019). These radioagents can be administered intravenously or locoregionally (Sgouros *et al.*, 2020). The combination of diagnostic radiopharmaceuticals with nuclear molecular imaging modalities enables the visualization of physiological and biological processes in the living body (Payolla *et al.*, 2019). In the case of therapeutic radiopharmaceuticals, these drugs are able to deliver cytotoxic radiation to target sites (Sgouros, 2019). However, as well as their beneficial applications, radiopharmaceuticals with low specificity and selectivity commonly generate toxicity that may eventually limit their efficacy as cancer treatment approaches (Jamous *et al.*, 2013). Accordingly, the development of radiopharmaceutical agents with high specificity is crucial to enable the targeting of cancer cells without harming healthy cells (Jamous *et al.*, 2013; Ramli *et al.*, 2012; Worm *et al.*, 2020).

Biomolecules such as antibodies, peptides, carbohydrates, vitamins, and aptamers are frequently employed to improve specific protein target interaction (Humani *et al.*, 2017; Ramli *et al.*, 2013; Yeole *et al.*, 2013). Peptides offer particular advantages over other targeting moieties (Graham & Menda, 2011; Okarvi, 2008; Yeole *et al.*, 2013). Besides their small size compared to antibodies, they possess high specificity and high tumor penetration, thus enabling them to effectively localize in peptide receptors (Graham & Menda, 2011; Okarvi, 2008; Yeole *et al.*, 2013). Small peptides are relatively easy to synthesize and modify by chemical modifications at large scale, in order to substantially imitate the specific binding of natural peptides in ways that improve their affinity and specificity to particular targets (Graham & Menda, 2011; Okarvi, 2008; Palangka *et al.*, 2019). Peptides can survive extreme reaction conditions (pH, temperature etc.) (Maecke, 2005; Okarvi, 2004). In addition, small peptides demonstrate favorable pharmacokinetic behavior and high target-to-non-target ratios, as well as rapid elimination from the blood and non-target sites (Okarvi, 2008). These features are essential for diagnostic imaging and peptide-receptor-targeted therapy (Graham & Menda, 2011; Okarvi, 2008).

Over the last two decades, extensive development of radiolabeled small peptides for cancer diagnosis and therapy has been carried out (Ambrosini, Fani, *et al.*, 2011; Okarvi, 2004, 2008). This development focuses on the overexpression of peptide receptors that are found in many cancer-cell surfaces (Okarvi, 2008; Reubi, 2004). One of the groups of peptide receptors that has been extensively investigated thus far is the somatostatin receptors (SSTRs) (Ambrosini *et al.*, 2011). SSTRs comprise a group of seven transmembrane domain G protein-coupled receptors that belong to the rhodopsin-like family and that can selectively bind to many intracellular ligand systems (Günther *et al.*, 2018; Reubi, 2003). The family of SSTRs is widely expressed in various tissues, including nervous, pituitary, kidney, lung, and immune tissues (Patel, 1999). Somatostatin ligand binding to SSTRs triggers a wide array of signaling pathways leading to biological responses (Banerjee *et al.*, 2015; Bodei *et al.*, 2009; Gomes-Porras *et al.*, 2020). Up to now, five distinct subtypes of SSTRs (SSTR1–SSTR5) have been identified (Okarvi, 2008). Among the SSTR subtypes found in human cancer cells, SSTR2 is predominant (Ambrosini, *et al.*, 2011; Banerjee *et al.*, 2015; Fani, *et al.*, 2012; Okarvi, 2008).

Somatostatin receptors are widely distributed in healthy tissues, with an expression pattern that differs across the body (Eychenne *et al.*, 2020). In contrast to healthy tissues, high levels of expression of SSTRs can be found in many tumors, and in particular in neuroendocrine tumors (NETs) (Thundimadathil, 2012). NETs are a distinctive group of tumors deriving from dispersed cells that differ in clinical behavior, histology, and naming system (Bodei *et al.*, 2009; Navalkissoor & Grossman, 2019; Oronsky *et al.*, 2017; Tsoli *et al.*, 2019). It has been reported that NETs such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer, and small cell lung carcinoma show excessive expression of these SSTRs (Banerjee *et al.*, 2015; Fani, Maecke, *et al.*, 2012; Okarvi, 2008; Rufini *et al.*, 2006). In addition, gastroentero-pancreatic neuroendocrine tumors (GEP-NETs), including meningioma, neuroblastoma, and medulloblastoma also show a higher density of SSTRs (Banerjee *et al.*, 2015; Fani *et al.*, 2012; Jamous *et al.*, 2013). Other non-NETs, such as renal cancer, breast cancer, lymphoma, hepatocellular cancer, prostate cancer, and gastric cancer, are also SSTR overexpressing (Fani *et al.*, 2012; Okarvi, 2008).

Selective binding of the somatostatin ligand with SSTRs allows specific targeting of radiolabeled somatostatins to SSTRs (Rufini *et al.*, 2006). The present review summarizes the development of radiolabeled somatostatin analogs for diagnostic imaging and peptide receptor radionuclide therapy (PRRT) of NETs. Major emphasis is given to the development of iodine-123 (^{123}I), indium-111 (^{111}In), technetium-99m (^{99m}Tc), and gallium-68 (^{68}Ga) labeled somatostatin analogs for NET imaging using PET or SPECT. For therapeutic purposes, indium-111 (^{111}In), lutetium-177 (^{177}Lu), and yttrium-90 (^{90}Y) labeled somatostatin analogs are described herein.

Somatostatin and its analogs

Somatostatin is a cyclic polypeptide derived from a somatostatin precursor protein that is converted into peptide hormones including somatostatin-14 (SS-14) and somatostatin-28 (SS-28) (Okarvi, 2008). Somatostatin has many biological roles, including acting as a neurotransmitter and neuromodulator in the central nervous system and inhibiting the secretion of peptide hormones such as glucagon, insulin, and growth hormone (Günther *et al.*, 2018).

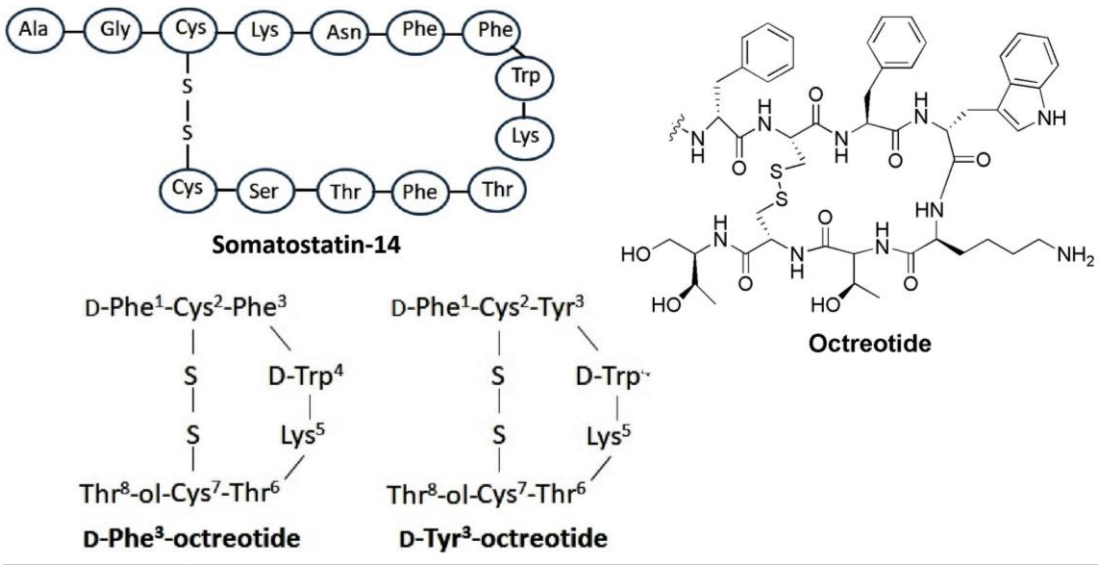

Figure 1. Structure of naturally occurring somatostatin-14, octreotide, Phe[3]-octreotide and Tyr[3]-octreotide (Ambrosini, *et al*., 2011; Okarvi, 2008)

Two native somatostatin ligands, SS-14 and SS-28, exist in the human body (Okarvi, 2008). However, these naturally occurring somatostatins are known to undergo extremely fast enzymatic degradation (half-life of three minutes) in plasma and tissues by peptidase, making them unsuitable for clinical use (Gomes-Porras *et al.*, 2020; Okarvi, 2008; Wängberg *et al.*, 1997). The synthesis of somatostatin-modified analogs is therefore required to produce more metabolically stable peptides (Gomes-Porras *et al.*, 2020; Okarvi, 2008). In the early 1980s, the somatostatin analog octreotide (

Figure 1) was developed and approved for clinical application (Bodei *et al.*, 2009). Octreotide (SMS 201-995), marketed under the name Sandostatin®, is an octapeptide somatostatin analog and the first agonist peptide analog to be approved by the Food and Drug Administration (FDA) (Eychenne *et al.*, 2020; Gomes-Porras *et al.*, 2020). It has been used for the treatment of acromegaly and GEP-NETs over the past 20 years (Anthony & Freda, 2009). Octreotide is characterized by its high affinity for SSTR2 and moderate affinity for both SSTR5 and SSTR3 (Bodei *et al.*, 2009; Reubi *et al.*, 2000). In addition, octreotide has an antiproliferative effect that can inhibit the proliferation of gastric cells mediated by P300-histone acetyltransferase (P300-HAT) (Wang *et al.*, 2017). Moreover, this octapeptide agonist peptide has a longer half-life (90–120 min) and greater metabolic stability than native somatostatin (Anthony & Freda, 2009). Structurally, when Phe[3] in octreotide (D-Phe[3]-octreotide) (

Figure 1) is replaced by Tyr[3], affinity toward SSTR2 is increased (Eychenne *et al.*, 2020). To the best of our knowledge, octreotide- based peptides are the most widely used somatostatin analog for clinical applications (Ambrosini, *et al.*, 2011). A significant number of publications have reported the development of radiolabeled octreotide-based peptides for diagnosis and therapy of NETs (Romer *et al.*, 2014; Wild *et al.*, 2013). Radiolabeled peptides have drawn considerable attention in relat ion to their properties for the diagnosis and therapy of NETS. The application of radionuclide-labeled somatostatin analogs for the treatment of NETs has been widely employed over the last two decades. The radiolabeled peptides used for targeting receptors are composed of various components, namely targeting peptide vectors, linkers, and radionuclides that are coupled to bifunctional chelating agents (BFCA) or chelators (Maecke, 2005; Okarvi, 2008). The chelators are either directly conjugated to the targeting moiety or attach via a linker (

Figure *2*) (Maecke, 2005; Okarvi, 2008; Teodoro *et al.*, 2011).

radiolabeled with diagnostic radionuclides (SPECT or PET radionuclides) for diagnosis or imaging of disease. SPECT and PET are nuclear molecular

Table I. Characteristics of radionuclides commonly used for diagnosis and radiotherapy of NETs

Radionuclides	Type of rays	Half-life (h)	Energy (keV)	Source	Purpose
^{99m}Tc	γ	6.02	140	Generator	Diagnosis
^{123}I	γ	13.2	159	Cyclotron	Diagnosis
^{68}Ga	γ	1.13	511	Generator	Diagnosis
^{18}F	γ	1.82	511	Cyclotron	Diagnosis
^{111}In	γ Auger electron Conversion electron	67.2	173 and 247 keV to 19 to 244	Cyclotron	Diagnosis Therapy
^{90}Y	β	64.1	2.288	Reactor/generator	Therapy
^{177}Lu	β γ	160.8	500 113-208	Reactor	Therapy

A linker is usually used for pharmacokinetic modulation of the targeted radiopharmaceuticals (Liu & Edwards, 2001). The first radiopharmaceutical developed for PRRT was ^{111}In-diethylentriaminepentaacetic acid-octreotide (^{111}In-DTPA-octreotide, OctreoScan®).

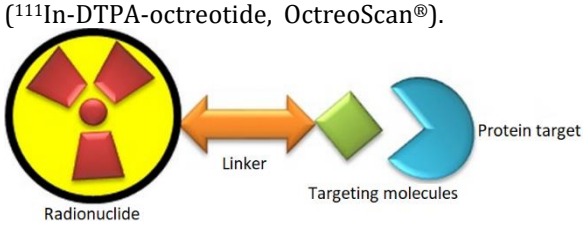

Figure 2. A general strategy of receptor targeted radiopharmaceuticals (Okarvi, 2008) with modification

Gamma radiation of ^{111}In can be used for SPECT imaging of NETs (Bodei *et al.*, 2009; Navalkissoor & Grossman, 2019; Rufini *et al.*, 2006). In addition, this radiolabeled peptide was the first approved by the FDA for the imaging of NETs (Bodei *et al.*, 2009; Navalkissoor & Grossman, 2019; Rufini *et al.*, 2006). OctreoScan also exhibits the therapeutic efficacy associated with the release of short-penetrating Auger electrons that cause cell death (Bodei *et al.*, 2009; Navalkissoor & Grossman, 2019). However, the high cost, unfavorable nuclear properties, and restricted availability of ^{111}In are the main factors limiting the application of this radiolabeled peptide (Ambrosini *et al.*, 2011).

The selection of radionuclides for radiolabeling of targeting molecules such as peptides and antibodies depends on the purpose of the application. The targeting vector can be

imaging techniques used for early detection of and therapeutic response to disease (Brust *et al.*, 2014). Both nuclear imaging techniques allow the visualization, characterization, and measurement of biological processes of radiolabeled molecules in vivo (Dobrucki & Sinusas, 2010; Palumbo *et al.*, 2014). For molecular SPECT imaging, the targeting moiety is labeled by gamma (γ)-emitting radionuclides (100-250 keV) (Maecke, 2005). Both SPECT and PET offer many advantages, including high sensitivity, good spatial resolution, and unlimited penetration depth, making them pivotal players in molecular imaging for preclinical and clinical studies (Lu & Yuan, 2015). SPECT radionuclides include ^{99m}Tc and ^{123}I (Maecke, 2005), while PET radionuclides include fluorine-18 (^{18}F) and ^{68}Ga. (Maecke, 2005; Sugiura *et al.*, 2014). For therapeutic applications, the targeting vector must be labeled with a high linear energy transfer (LET) radionuclide that can kill tumor tissues (Maecke, 2005; Sofou, 2008). LET is defined as the amount of energy transferred per unit of path length by the emitted particles–mainly beta (β^-)-particle emitting radionuclides (Sofou, 2008), alpha (α)-emitters (Dadachova, 2010), and Auger-electron-emitters (Ku *et al.*, 2019). The most widely used radionuclides in nuclear medicine for NET imaging and therapeutic purposes (Duijzentkunst *et al.*, 2017; Okarvi, 2008; Sugiura *et al.*, 2014; Wang *et al.*, 2013) (Table I).

As mentioned earlier, small peptides can be radiolabeled with radionuclides of choice for diagnosis and/or therapy (Okarvi, 2008). It is therefore of great importance that the radiolabeling methods used deliver high

radiolabeling yield, radiochemical purity, and specific activity (Mikołajczak & Maecke, 2016; Palangka *et al.*, 2019). Reubi *et al.* evaluated affinity profiles of various somatostatin analog conjugates and radioconjugates toward human somatostatin receptors (SSTR1-SSTR5) (Reubi *et al.*, 2000). They found that small structural alterations, chelating agent substitution, or metal replacement significantly influence the binding affinity for receptors (Reubi *et al.*, 2000).

In addition, small modifications of peptides also affect receptor subtype selectivity (Reubi *et al.*, 2000). It is also of great importance that labeling strategies retain the affinity of small peptides for receptors (Mikołajczak & Maecke, 2016). Two methods of introducing radionuclides to peptides have been described in the literature (Maecke, 2005), the first of which is direct radiolabeling. One example of direct radiolabeling is radioiodination of peptides via electrophilic substitution, usually occurring at the amino acid portions of peptide-bearing phenyl ring systems such as tyrosine or histidine (Mikołajczak & Maecke, 2016). Another strategy is indirect radiolabeling, effectively performed by conjugating the peptide to radionuclides via BFCAs (Sugiura *et al.*, 2014). This approach is commonly employed for radiometals such as ^{111}In, ^{99m}Tc, ^{68}Ga, ^{177}Lu, and ^{90}Y, due to difficulties in coupling them with the targeting peptide vector (Mikołajczak & Maecke, 2016).

Radiolabeled somatostatins for the imaging of NETs

[^{123}I]-[3-iodo-Tyr^3]-octreotide

^{123}I is a cyclotron-produced radionuclide with a half-life of 13 hours emitting gamma energy of 159 keV (Morphis *et al.*, 2021). The first radiolabeled peptide of [^{123}I]-[3-iodo-Tyr^3]-octreotide was developed by a research group in Rotterdam that studied the *in-vivo* localization of endocrine-associated tumors (Krenning *et al.*, 1989) and *in-vivo* somatostatin receptor scintigraphy (SRS) of radioiodinated Tyr^3-octreotide (Bakker *et al.*, 1990). In this development, Phe^3 was replaced by Tyr^3, resulting in an improvement of affinity to SSTR2 (IC_{50}=2.0±0.7nM) and an enhanced rate of accumulation in human tumors (Lamberts *et al.*, 1990; Maecke, 2005). Despite the good image outcomes of this radiolabeled peptide (Lamberts *et al.*, 1990), it appears that the radiotracer is not an ideal diagnostic imaging agent (Maecke, 2005). The difficulties of radiolabeling strategy and the high lipophilicity of this radioiodinated tracer are considered as the main features that limit its application (Fischman *et al.*, 1993; Krenning *et al.*, 1993).

^{111}In-DTPA-octreotide

^{111}In radionuclide has a 2.8-day physical half-life and produces two gamma emissions, at 171 and 245 keV (Zhang *et al.*, 2017). Radiolabeling peptides with ^{111}In usually achieved via chelators such as DTPA and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). In an attempt to develop improved somatostatin analog-based radiopharmaceuticals for somatostatin receptor scintigraphy (SRS), ^{111}In-DTPA-octreotide (OctreoScan™, Mid-South Imaging & Therapeutics, Memphis, TN) was developed (Kwekkeboom *et al.*, 2000; Maecke, 2005; Rufini *et al.*, 2006). This radiopharmaceutical became the first FDA-approved radiodiagnostic molecular probe. The hydrophilic nature of this radiopeptide improves its pharmacokinetic profile, in that it is eliminated from the body via the kidneys (Maecke, 2005). However, this radiopeptide exhibits a rather low affinity for human SSTR2 (IC_{50}=22±3.6nM) accompanied by slow internalization rate (Maecke, 2005).

^{99m}Tc-labeled somatostatin analog

The continuing effort to provide better-quality images of somatostatin-receptor-positive neuroendocrine cancers has also been pursued through the development of ^{99m}Tc-based radiopharmaceuticals. ^{99m}Tc radionuclide is the most widely employed diagnostic radionuclide, owing to its favorable nuclear and physical properties (Boschi *et al.*, 2019). ^{99m}Tc has a physical half-life of six hours and emits pure gamma energy of 140 keV that is suitable for SPECT medical imaging (Saptiama *et al.*, 2016). In addition, ^{99m}Tc radionuclide is widely available worldwide and can be obtained from commercial ^{99}Mo/^{99m}Tc generators (Boschi *et al.*, 2019). Numerous studies investigating ^{99m}Tc-based radiopeptides have been reported (Kuzmanovska *et al.*, 2011; Maina *et al.*, 2002; Mikołajczak, 2009; Widyastuti *et al.*, 2007). The radiolabeling of peptides with ^{99m}Tc can be performed by direct and indirect methods (Okarvi, 2008). The former approach typically occurs through disulfide bonds (S-S) or thiol groups of peptides, while indirect radiolabeling requires BFCAs. Preparation of ^{99m}Tc-labeled peptides via indirect approaches using BCF As such as mercaptoacetyltriglycine (MAG3) and hydrazinonicotinamide (HYNIC) are reported in the literature (Teodoro *et al.*, 2011). The HYNIC ligand is frequently used BFCAs for the preparation

of octreotide somatostatin analog (Liepe & Becker, 2018).

Table II. ^{99m}Tc- and ^{68}Ga-labeled somatostatin analog for imaging purpose

Peptide	Affinity profiles towards SSTRs	References
^{99m}Tc-depreotide (P829; NeoTect)	SSTR2, SSTR3, and SSTR5	(Menda & Kahn, 2002)
^{99m}Tc-Demotate	SSTR2 K(d) = 0.07 nM	(Maina *et al*., 2002; Okarvi, 2008)
^{99m}Tc-EDDA/HYNIC-TOC	SSTR2, and SSTR5	(Kuzmanovska *et al.*, 2011)
^{99m}Tc-EDDA/HYNIC-TATE	SSTR2	(Deveci *et al*., 2013; Hubalewska-Dydejczky, A. Fross-Baron *et al*., 2006)
^{68}Ga-DOTA-TOC	SSTR2 (2.5 ± 0.5 nM) SSTR5 (73 ± 21 nM)	(Hennrich & Benešová, 2020; Reubi *et al*., 2000; Zhang *et al*., 2011)
^{68}Ga-DOTA-TATE	SSTR2 (0.2 ± 0.04 nM)	(Poeppel *et al*., 2011; Reubi *et al*., 2000)
^{68}Ga-DOTA-NOC	SSTR2, SSTR3, and SSTR5	(Wild *et al*., 2013)

Demotate = [N4,Tyr^3]octreotate; EDDA = ethylenediamine-N,N'-diacetic acid; HYNIC = hydrazinonicotinic acid;TOC = Tyr^3-octreotide; TATE = Tyr^3-octreotate; DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; NOC = 1-Nal^3-octreotide

The presence of coligands such as EDDA and tricine may significantly improve the radiolabeling yield and pharmacokinetics of ^{99m}Tc radiolabeled peptides (Kuzmanovska *et al.*, 2011). The preparation of ^{99m}Tc-EDDA/HYNIC-TOC achieves a radiochemical yield of more than 90%. The diagnostic efficiency of ^{99m}Tc-EDDA/HYNIC-TOC and ^{99m}Tc-EDDA/HYNIC-octreotate have been evaluated (Deveci *et al.*, 2013; Kuzmanovska *et al.*, 2011). ^{99m}Tc-EDDA/HYNIC-TOC produces comparable images to ^{111}In-DTPA-Octreotide (OctreoScan) (Gabriel *et al.*, 2003). In addition, ^{99m}Tc-EDDA/HYNIC-TOC exhibits a higher sensitivity as an imaging radiopeptide than OctreoScan (Table II). Despite the progress of SPECT imaging of NETs using ^{99m}Tc-based radiopharmaceuticals, the lower spatial resolution and sensitivity of SPECT modality compared to PET may limit the development of ^{99m}Tc radiolabeled peptides (Duatti, 2021). Nevertheless, efforts to develop novel ^{99m}Tc-based radiodiagnostic probe for the imaging of SSTR-positive NETs continue. The preparation of these new ^{99m}Tc-labeled peptides employs a more robust ^{99m}Tc-tricarbonyl core to achieve high radiolabeling yields and better images (Radford et al., 2017).

^{68}Ga-labeled somatostatin analogs for molecular imaging of NETs

Positron emission tomography (PET) is a non-invasive functional nuclear molecular imaging technique that employs biomolecules labeled with short half-life PET radionuclides (e.g. ^{18}F, ^{11}C, ^{68}Ga, etc.) for in-vivo visualization and collection of quantitative information about physiological, biochemical, and pharmacological processes in the living organism at the molecular or cellular level (Ametamey *et al.*, 2008; Jacobs *et al.*, 2003; Paans & Vaalburg, 2000; Phelps, 2000; Ritawidya *et al.*, 2019; Wuest, 2005). PET scans are based on the coincident detection of one pair of 511 keV photons produced through the so-called annihilation process taking place when the positrons (β^+) emitted by the PET radionuclide after the injection of PET tracers into the living body combine with electrons in the tissue observed (Alauddin, 2012). Three-dimensional (3D) images of radiolabeled PET probe concentration within the body are generated using appropriate software and analysis (Alauddin, 2012). PET imaging has shown great efficacy for diagnostic applications in the fields of oncology, cardiology, and neurology for clinical diagnostics, as well as for basic human investigations, research, drug development and evaluation, and preclinical research using non-human primates and rodents (Ametamey *et al.*, 2008; Lobrano & Singha, 2003; Paans & Vaalburg, 2000).

PET radionuclides are commonly produced in a particle-accelerating machine known as a cyclotron (Lystad & Pollard, 2009; Wuest, 2005). Due to the short half-lives of PET radionuclides, cyclotrons are usually placed close to where the PET scanner is located (Lystad & Pollard, 2009; Turner & Jones, 2003). However, some PET radionuclides can also be produced by generators (e.g. ^{68}Ga and ^{82}Rb) (Dash & Chakravarty, 2019).

The availability of such generators allows the on-site preparation of PET radiopharmaceuticals in small institutes or facilities and supports independence from the presence of accelerators (Dash & Chakravarty, 2019; Hennrich & Benešová, 2020). A study comparing cyclotron ^{68}Ga production and ^{68}Ge/^{68}Ga produced by generators for radiolabeling and biological investigation of ^{68}Ga-NOTA-BBN2 was reported by Nelson *et al.* (2020). The findings show that cyclotron-produced ^{68}Ga gave a higher radiolabeling yield than ^{68}Ga derived from generators in the preparation of ^{68}Ga-NOTA-BBN2. In addition, cyclotron ^{68}Ga production delivers comparable or better quality ^{68}Ga than generator-produced ^{68}Ge/^{68}Ga. In addition, a comparable biodistribution profile was obtained for both sources of ^{68}Ga (Nelson *et al.*, 2020). The attractive physical properties of ^{68}Ga (half-life of 68 minutes) and its availability from generators offers wide potential for developing ^{68}Ga-based PET radiotracers for diagnosis of various cancers that show higher expression of peptide receptors, including SSTRs, that are widely expressed in NETs (Jalilian, 2016).

^{68}Ga radionuclide has attracted increasing interest because this radiometal allows 'theranostic' approach for personalized medicine. The comparable chemical properties of therapeutic radionuclides (e.g. ^{177}Lu, ^{90}Y, etc.) with diagnostic or imaging radionuclide (^{68}Ga) allows them to be coupled with similar targeting vectors and is regarded as one of the key features of the application of ^{68}Ga radiopharmaceuticals (Hennrich & Benešová, 2020; Jalilian, 2016). PET or SPECT molecular imaging may enable the prediction of patients who meet the criteria and will most likely benefit from PRRT, allowing personalized nuclear medicine (Turner, 2018). Therefore, following the accumulation of diagnostic radiopharmaceuticals in tumor tissue positive receptors of interest is the injection of the peptide-targeting probe or its analog labeled with a therapeutic radionuclide to eradicate tumor cells (Hennrich & Benešová, 2020). ^{68}Ga has a half-life of 68 minutes, making it suitable for PET scans. In addition, it is a positron-emitting radionuclide (88%). Similarly to ^{111}I, ^{177}Lu, and ^{90}Y, ^{68}Ga can be effectively complexed by a macrocylic DOTA chelator (Zhang *et al.*, 2017b). In contrast to DTPA, a DOTA chelator can result in a thermodynamically and kinetically stable complexation of trivalent radiometals (Liu & Edwards, 2001). The substitution of DTPA, as in ^{111}In-DTPA-octreotide (OctreoScan), with macrocyclic polyaminopolycarboxy chelator DOTA resulted in the advent of various DOTA-peptide conjugates, namely DOTA-(Tyr^3)-octreotide (DOTA-TOC), DOTA-(Tyr^3)-octreotate (DOTA-TATE), and DOTA-[1-Nal^3-octreotide] (DOTA-NOC) (Ambrosini, Campana, *et al.*, 2011). This is mainly due to the inability of DTPA complexation with some trivalent radiometals (Kaltsas *et al.*, 2005) including ^{68}Ga. The radiopeptide conjugates ^{68}Ga-DOTA-TOC/TATE/NOC listed in Table exhibit affinity for SSTR2 and SSTR5, with ^{68}Ga-DOTA-NOC also demonstrating a good affinity toward SSTR3 (Ambrosini, Campana, *et al.*, 2011; Wild *et al.*, 2013).

^{68}Ga-DOTA-TOC/, ^{68}Ga-DOTA-TATE, and ^{68}Ga-DOTA-NOC are the most widely used somatostatin analogs in clinical settings for diagnosis, staging, prognosis, and evaluation of the outcomes of NET treatment (Hofmann *et al.*, 2001; Srirajaskanthan *et al.*, 2010; Wild *et al.*, 2013), due to their pharmacokinetics, blood clearance, and target localization, which are appropriate for ^{68}Ga half-life (68 min) (Velikyan, 2014). Wild *et al.* prospectively compared ^{68}Ga-DOTA-NOC and ^{68}Ga-DOTA-TATE PET/CT in 18 patients with GEP-NETs, as well as investigating the clinical outcome of ^{68}Ga-DOTA-NOC PET/CT (Wild *et al.*, 2013). The results showed that ^{68}Ga-DOTA-NOC detected more tumors than ^{68}Ga-DOTA-TATE (93.5% vs. 85.5%). It appeared that the better performance of ^{68}Ga-DOTA-NOC resulted from a higher detection rate of liver metastases than tumor differentiation level. Despite its better sensitivity for detecting more lesions than ^{68}Ga-DOTA-TATE, this study suggested further larger investigations were needed to confirm clinical significance of the results (Wild *et al.*, 2013). A similar study evaluating both ^{68}Ga-labeled somatostatin analogs has been reported for eight patients with well-differentiated NETs (WDNETs) grade 1, eight patients with WDNETs grade 2, one patient with poorly differentiated NET, and four with mixed NETs (a total of 20 patients) (Kabasakal *et al.*, 2012). This study revealed similar excellent image quality and comparable body distribution in ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-NOC. Furthermore, ^{68}Ga-DOTA-TATE demonstrated higher lesion uptake compared to ^{68}Ga-DOTA-NOC, pointing to the potential application of this SSTR2-specific radiolabeled analog (Kabasakal *et al.*, 2012).

In 2005, studies of ^{68}Ga-DOTA-TOC for imaging of meningiomas showed higher tumor-to-background ratios of ^{68}Ga-DOTA-TOC than those obtained by [^{18}F]-2-fluoro-2-deoxy-D-glucose

([^{18}F]FDG) (Henze *et al.*, 2005). Recently, ^{68}Ga-DOTA-TOC was approved by the FDA for the imaging of somatostatin-receptor-positive GEP-NETs using PET in adult and pediatric patients (FDA, 2019; Hennrich & Benešová, 2020). In European countries including Austria, Germany, and France, this ^{68}Ga-labeled peptide was approved and marketed under the name IASOtoc® (IASON GmbH, Graz, Austria) (IASON GmbH, 2016) (Hennrich & Benešová, 2020) and TOCscan® (ITM AG, Muenchen, Germany) (Hennrich & Benešová, 2020; ITM, 2018) in 2016 and 2018, respectively. In December 2016, ready-to-use DOTA-TOC kits (SomaKit TOC®, AAA, a Novartis company, Saint-Genis-Pouilly, France) were made available in Europe and approved by the European Medicine Agency (EMA) (EMA, 2016). In the same year, the DOTA-TATE kit (NETSPOT™, AAA, a Novartis company, Saint-Genis-Pouilly, France) was approved by the FDA for use in the US for ^{68}Ga generator-based radionuclide radiopharmaceuticals (AAA, 2016). DOTA-TATE demonstrated a 10-fold higher affinity for SSTR2 than DOTA-TOC (Reubi *et al.*, 2000). However, no statistically significant difference between the uptake of these ^{68}Ga-labeled somatostatin analogs could be detected in vitro in monkey brain tissue or in-vivo/ex-vivo rat organ positive SSTRs including pancreas, adrenals, or pituitary. This finding suggested that the complicated surroundings in vitro and in vivo eliminated the difference detected in transfected cell line binding (Velikyan *et al.*, 2012).

PRRT using radiolabeled somatostatin analogs

^{111}In-DTPA-octreotide

PRRT generally comprises a radionuclide attached via a chelating agent to a peptide vector that specifically binds to peptide receptors on the cancer cell surface, enabling the delivery of radiation (Das *et al.*, 2019). ^{111}In-DTPA-octreotide (OctreoScan®) was the first radiolabeled somatostatin analog used in PRRT. The potential for application of this radiopharmaceutical lies in its therapeutic Auger electron emission (Valkema *et al.*, 2002). Auger electrons possess high LET (energy of less than 25 keV; 0.02–10 μm of tissue penetration), making them useful for cancer therapy (Ku *et al.*, 2019; Valkema *et al.*, 2002). Phase I study of radiolabeled octreotide was performed evaluating 40 patients (Valkema *et al.*, 2002). Twenty one patients showed therapeutic responses; of these, one patient and six patients demonstrated partial and minor remission, respectively, indicating the potential therapeutic application of radiolabeled octreotide (Valkema *et al.*, 2002). Kidney toxicity is relatively mild; however, bone marrow toxicity may be observed when the accumulated administered dose is higher than 100 GBq. Furthermore, three of six patients who obtained a cumulative dose of higher than 100 GBq progressed to myelodysplastic syndrome and leukemia (Valkema *et al.*, 2002). As a result, it was concluded that 100 GBq is the maximum tolerable dose (Valkema *et al.*, 2002).

The therapeutic outcomes of ^{111}In-DTPA-octreotide were also evaluated in SSTR-positive rat pancreatic CA20948-expressing SSTR2 from Lewis rats (Capello *et al.*, 2005). The results showed complete responses (up to 50%) in animals bearing small tumors following at least three administrations of 111 MBq or a single injection of 370 MBq of ^{111}In-DTPA-octreotide, resulting in a dose of 6.3–7.8 mGy/MBq (1–10 g tumor). Partial responses were seen in rats bearing larger tumors. The investigation revealed higher expression of SSTRs in tumors that regrew following PRRT, following initial reduction in tumor size (Capello *et al.*, 2005). It can be posited that this higher SSTR density may lead to higher uptake of radiolabeled peptide, suggesting that repeated administration of radiolabeled peptide might be favorable.

Recently, Pool *et al.* investigated the outcome of intra-arterial (IA) injection of ^{111}In-DTPA-octreotide on tumor uptake in preclinical and clinical studies to enhance PRRT response in GEP-NET liver metastases (Pool *et al.*, 2014). The preclinical findings in rats bearing hepatic SSTR2-expressing tumors demonstrated twice the tumor uptake of ^{111}In-DTPA-octreotide following IA injection than in IV post-injection. Dosimetry study simulations with ^{177}Lu in one patient applying radiation dose of up to 23 Gy showed that IA injection led to 2.9-fold improvement in mean tumor-radiation dose. This study concluded that despite outcome variability in patients after IA injection, IA administration showed significant incremental radioactivity uptake in GEP-NET liver metastases up to 72 hours after injection, as indicative of preclinical and clinical results (Pool *et al.*, 2014).

Since ^{111}In is an Auger electron emitter with shorter tissue penetration than β-emitters, short-range radiotoxicity level is produced (Kaltsas *et al.*, 2005; Van Essen *et al.*, 2007). Thus ^{111}In-DTPA-octreotide is regarded as not being ideal as a somatostatin- analog-based radiopharmaceutical

for PRRT (Kaltsas *et al.*, 2005; Van Essen *et al.*, 2007).

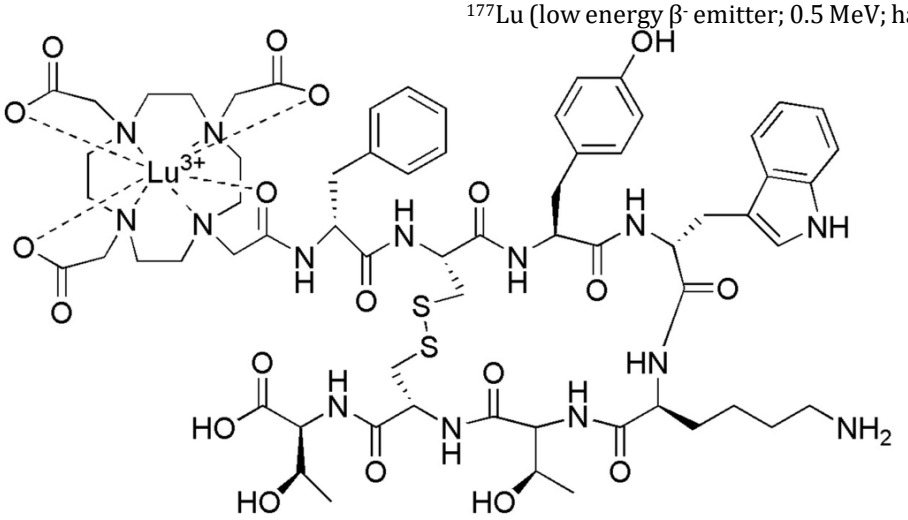

Figure 3. Chemical structure of FDA approved ^{177}Lu-DOTA-TATE for PRRT (Hennrich & Kopka, 2019)

Radionuclide-labeled somatostatin analogs for PRRT of NETs

Octreotide labeled with therapeutic β^- emitting radionuclides such as ^{90}Y and ^{177}Lu has proven efficacy in PRRT for therapy of NETs (Van Essen *et al.*, 2007). The preparation of octreotide labeled with therapeutic radiometals can effectively be performed by chelation with a BFCA. In contrast to ^{111}In, which can form stable complexation with acyclic chelator DTPA, these trivalent radiometals show less stable metal-ligand complexation with DTPA chelating agents (Breeman, 2012). Thus, attempts to prepare a stable radiometallic conjugates in vivo is required for PRRT. This is of great importance because the free radiometal nuclides that are degraded *in vivo* can bind to the bone marrow and lead to hematopoietic toxicity as a result of bone marrow irradiation (Otte *et al.*, 1997). Therefore, a wide variety of macrocyclic BFCAs have been developed to improve stability in vivo of radiolabeled somatostatin analogs. Significant progress in the development of PRRT was achieved by the success of conjugation of somatostatin analogs with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), a BFCA (De Jong *et al.*, 1998; Ritawidya *et al.*, 2016).

These conjugate ligand DOTA-octreotide peptides are found to be thermodynamically and kinetically stable in a complex form with all M^{3+} radiometals for medical applications, including ^{90}Y (high energy β^- emitter; 2.28 MeV; half-life of 64 h), ^{177}Lu (low energy β^- emitter; 0.5 MeV; half-life of 6.7 d), and β^+-emitting radionuclides (e.g. ^{68}Ga), thus allowing the application of radionuclides for therapy and imaging (Breeman *et al.*, 2001; Kwekkeboom *et al.*, 2000; Okarvi, 2008; Schottelius & Wester, 2009). The success of ^{68}Ga-DOTA-TOC has triggered the use of this DOTA-TOC conjugate ligand in PRRT for NETs. The superiority of DOTA over other chelators such as EDTA and DTPA has been intensively investigated in several studies (Banerjee *et al.*, 2015; De León-Rodríguez & Kovacs, 2008). However, DOTA-based biologically active molecules suffer from slow kinetic formation that may limit their use (Chong *et al.*, 2002; De León-Rodríguez & Kovacs, 2008). Consequently, high temperatures are usually employed to accelerate complex association (Cooper *et al.*, 2006; De León-Rodríguez & Kovacs, 2008).

^{177}Lu- and ^{90}Y-labeled peptides in PRRT represent an effective strategy and a promising approach in the treatment of metastatic neuroendocrine tumor-overexpressing somatostatin receptors (Cremonesi *et al.*, 2018; Navalkissoor & Grossman, 2019). Because of their ideal nuclear properties there has been extensive investigation of ^{177}Lu and ^{90}Y labeled-DOTA conjugates in Europe for NETs and other cancers (De León-Rodríguez & Kovacs, 2008).

^{90}Y-DOTA-TOC

Several phase I and II investigations of ^{90}Y-DOTA-Tyr-3-octreotide (^{90}Y-DOTA-TOC,

OctreoTher™) have been conducted in various countries (Van Essen *et al.*, 2007). Otte *et al.* performed the first study of promising therapeutic application of DOTA-TOC labeled with ^{90}Y for the treatment of a patient with abdominal metastases of neuroendocrine tumor with unknown sites (Otte *et al.*, 1997). The study results confirmed tumor response and symptomatic relief (Otte *et al.*, 1997).

Radiolabeled somatostatin analogs are eliminated by the kidneys (Das *et al.*, 2019; Jamar *et al.*, 2003). Reabsorption of these drugs in the proximal tubules can result in nephrotoxicity leading to kidney damage (Das *et al.*, 2019). Owing to their greater particle range, this phenomenon is more severe in ^{90}Y-labeled somatostatin analogs than in other β^- emitters, such as ^{177}Lu (Das *et al.*, 2019). To overcome this drawback, co-injection of positively charged amino acids such as lysine and/or arginine may lead to reduced initial renal absorption of radiolabeled agents (Jamar *et al.*, 2003).

With an average β^- energy of 940 keV and depth of tissue penetration of up to 11 mm (Kim *et al.*, 2010), ^{90}Y-DOTA-TOC is suitable for PRRT of larger tumors and tumors with non-homogeneous receptors, due to its better cross-fire effect (Bodei *et al.*, 2012). Additionally, its shorter half-life (2.7 days) than ^{177}Lu (6.7 days) permits a higher dose rate (Bodei *et al.*, 2012). ^{90}Y is a pure β^- emitter, therefore, detection of this radiotracer following its administration is challenging (Hennrich & Kopka, 2019). The nuclear imaging of ^{90}Y is possible with bremsstrahlung imaging and PET; however, the resulting images are poor (Elschot *et al.*, 2013; Kim *et al.*, 2011; Wright *et al.*, 2015).

^{177}Lu-DOTA-TATE

DOTA-TATE is an analog of DOTA-TOC in which the C-terminal threoninol in the octapeptide is substituted by threonine (Reubi *et al.*, 2000). DOTA-TATE is characterized by its higher affinity and selectivity for SSTR2 in comparison to that of DOTA-TOC (Reubi *et al.*, 2000). Radiolabeling of DOTA-TATE with a therapeutic radionuclide such as ^{177}Lu ($t_{1/2}$ = 6.7 days) has led to growing interest in PRRT for treatment of cancers (Baum, n.d.; Hennrich & Kopka, 2019). ^{177}Lu has emerged as a radionuclide therapy for PRRT due to its favorable nuclear properties (Banerjee *et al.*, 2015). ^{177}Lu is a moderate β^- particle emitter (β^- max = 498.3 keV and average β^- =134.2 keV) accompanied by average tissue penetration of 2.2 mm, making it sufficient to deliver radiation doses to smaller tumors (Hennrich & Kopka, 2019). In addition, the cross-fire effect of ^{177}Lu can spread up to a diameter of 20 cells, allowing surrounding cells that express a sufficient concentration of related receptors to be affected (Banerjee *et al.*, 2015). Furthermore, its γ emissions at 113 keV (3%) and 210 keV (11%) (Hennrich & Kopka, 2019) can be used to perform SPECT imaging in cancer patients (Hennrich & Kopka, 2019). ^{177}Lu can be produced in high activity levels with high specific activities in nuclear reactors available worldwide (Knapp, 2009). Two methods for ^{177}Lu production using a nuclear reactor are available: direct and indirect (Dash *et al.*, 2015). The direct or carrier-added approach uses enriched ^{176}Lu as the irradiation target, while the indirect approach uses an enriched ytterbium (^{176}Yb) target for irradiation (Vogel *et al.*, 2021). The high level of specific activity of ^{177}Lu is of great importance for the application of targeted radionuclide therapies such as PRRT, in particular for the preparation of a wide variety of therapeutic radioligands based on peptides and antibodies (Dash *et al.*, 2015).

In January 2018, following its approval in Europe in September 2017, the FDA approved ^{177}Lu-DOTA-TATE (Lutathera®) for the treatment of GEP-NETs in adult patients (Hennrich & Kopka, 2019; Mittra, 2018). ^{177}Lu-DOTA-TATE is widely used as part of a pair of theranostic agents with diagnostic PET/CT agent ^{68}Ga-DOTA-TATE or ^{68}Ga-DOTA-TOC (Hennrich & Kopka, 2019; Wang *et al.*, 2020). The complexation of ^{177}Lu in ^{177}Lu-DOTA-TATE occurs at DOTA BFC. Additionally, the DOTA chelator binds to the TATE moiety.

De Jong *et al.* studied the biodistribution and radionuclide therapy application of ^{177}Lu-DOTA-TATE (**Error! Reference source not found.**) in tumor-bearing SSTR pancreatic rat tumors (De Jong *et al.*, 2001). The results showed that the energy of ^{177}Lu was sufficient for scintigraphy (De Jong *et al.*, 2001). Furthermore, it was found that the highest uptake of ^{177}Lu-DOTA-TATE was in pancreatic tumors and other SSTR2-expressing organs such as adrenals, pituitary, and pancreas (De Jong *et al.*, 2001). ^{177}Lu-DOTA-TATE demonstrated promising results in radionuclide therapy in particular in animals bearing smaller tumors (De Jong *et al.*, 2001).

Future perspectives

All the radiolabeled somatostatin analogs discussed are SSTRs agonists. A complex of radioactive somatostatin agonists with a receptor is readily internalized into tumor cells, allowing the accumulation of radioactivity (Ginj *et al.*, 2006). To

the best of our knowledge, the internalization of radioconjugates is of great importance for the receptor-mediated diagnosis and therapy of SSTR-positive tumors (Fani *et al.*, 2017). However, recently a paradigm shift has occurred toward the application of antagonist somatostatin analogs. Antagonist peptide analogs differ from agonists in terms of their inability to provoke receptor internalization (Ginj *et al.*, 2006). Somatostatin antagonists that have been developed include CYN-154806, PRL-2970, and sst3-ODN-8 and non-cyclic antagonist peptides such as BIM-23056 and BIM-23627 (Eychenne *et al.*, 2020). Interestingly, the absence of the internalization of the radioligand receptor complex has shown more effectiveness in in-vivo receptor binding. In addition, Ginj *et al.* proposed that SSTR antagonists may perform better than peptide agonists by binding to more receptor binding sites, leading to greater uptake of radioligands (Ginj *et al.*, 2006). Radiolabeled antagonist peptides may possess better pharmacokinetic properties and faster renal elimination. The evidence obtained from many studies provides for a new direction of interest away from agonists and toward antagonist radiotracers (Fani *et al.*, 2017). The first clinical results for the radiolabeled somatostatin antagonist ^{111}I-DOTA-BASS were reported (Wild *et al.*, 2011). The findings of clinical studies in five patients confirmed preclinical results suggesting that ^{111}I-DOTA-BASS demonstrated higher tumor uptake and better visualization than the FDA-approved ^{111}In-DTPA-Octreotide (OctreoScan). The promising therapeutic application of radiolabeled peptide antagonist ^{177}Lu-DOTA-JR11 was evaluated and compared with ^{177}Lu-DOTA-TATE in clinical studies in four patients with metastatic NETs (Wild *et al.*, 2014). ^{177}Lu-DOTA-JR11 may be superior to the agonist ^{177}Lu-DOTA-TATE, the former characterized by its favorable pharmacokinetics and biodistribution (Wild *et al.*, 2014). Further larger clinical investigation is required to confirm the superiority of this radiolabeled antagonist over agonists. However, for certain radionuclides aiming for improved effects in PRRT, the receptor-mediated internalization induced by the agonist that allows the specific accumulation of radionuclides inside tumor cells is favorable (Worm *et al.*, 2020). Comparison studies between a highly affine antagonist ^{68}Ga-NODAGA-JR11 and two agonist radiotracers ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-TATE for SSTR imaging in ZR-7-5-1, a luminal breast cancer model, were reported (Dude *et al.*, 2017). The results from biodistribution studies showed higher tumor uptake of agonist ^{68}Ga-DOTA-TOC than ^{68}Ga-DOTA-TATE. Interestingly, the antagonist ^{68}Ga-NODAGA-JR11 had lower tumor uptake than both agonist radiotracers (Dude *et al.*, 2017). This research finding was not in agreement with results obtained in other studies (Fani, Braun, *et al.*, 2012). This aspect requires further investigation to evaluate radiolabeled somatostatin antagonists for the treatment of breast cancer (Dude *et al.*, 2017).

CONCLUSION

SSTRs offer potential for targeted diagnosis and therapy of NETs. Over the last three decades, octreotide somatostatin analogs have been the most widely used peptides studied so far. The development of radiolabeled octreotide somatostatin analogs with different diagnostic or therapeutic radionuclides has shown their efficacy as specific targeting radioligands for diagnosis and therapy of SSTR-positive cancers in particular NETs. ^{68}Ga-DOTA-TOC has been approved and found to be a promising diagnostic PET radiopharmaceutical imaging agent for NETs. ^{68}Ga-DOTA-TOC has attracted growing interest in theranostic applications with PRRT agent ^{177}Lu-DOTA-TATE. Recently, the development of radiopharmaceutical approaches based on somatostatin agonist analogs has shifted toward antagonist peptides. Given the promising potential of these radiolabeled antagonists for NET diagnosis and therapy, the approach requires further clinical studies and evaluation that may eventually lead to their clinical use.

REFERENCES

AAA. (2016). *FDA letter of approval of NETSPOT TM (Somakit-TATE), a Kit for the Preparation of Gallium Ga68 Dotatate for Neuroendocrine Tumor Detection*. https://www.globenewswire.com/news-release/2016/06/02/845561/0/en/Advanced-Accelerator-Applications-Announces-FDA-Approval-of-NETSPOT-Somakit-TATE-a-Kit-for-the-Preparation-of-Gallium-Ga-68-Dotatate-for-Neuroendocrine-Tumor-Detection.html

Alauddin, M. M. (2012). Positron emission tomography (PET) imaging with 18F-based radiotracer. *American Journal of Nuclear Medicine and Molecular Imaging*, *2*(1), 55–76.

Ambrosini, V., Campana, D., Tomassetti, P., Grassetto, G., Rubello, D., & Fanti, S. (2011).

PET/CT with 68Gallium-DOTA-peptides in NET: An overview. *European Journal of Radiology*, *80*(2), e116–e119. https://doi.org/10.1016/j.ejrad.2010.07.022

Ambrosini, V., Fani, M., Fanti, S., Forrer, F., & Maecke, H. R. (2011). Radiopeptide imaging and therapy in Europe. *Journal of Nuclear Medicine*, *52*(12 (Suppl)), 42S-55S. https://doi.org/10.2967/jnumed.110.085753

Ametamey, S. M., Honer, M., & Schubiger, P. A. (2008). Molecular imaging with PET. *Chemical Reviews*, *108*(5), 1501–1516. https://doi.org/10.1021/cr0782426

Anthony, L., & Freda, P. U. (2009). From somatostatin to octreotide LAR: Evolution of a somatostatin analogue. *Current Medical Research and Opinion*, *25*(12), 2989–2999. https://doi.org/10.1185/03007990903328959

Bakker, W. ., Krenning, E. P., Breeman, W. A., & Al., E. (1990). Receptor scintigraphy with radioiodinated somatostatin analogue: radiolabeling, purification, biologic activity, and in vivo application in animals. *J Nucl Med*, *31*, 1501–1509.

Banerjee, S., Pillai, M. R. A., & Knapp, F. F. (2015). Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications. *Chemical Reviews*, *115*(8), 2934–2974. https://doi.org/10.1021/cr500171e

Baum, R. (n.d.). *177Lu-DOTA-TATE for Peptide Receptor Radionuclide Therapy (PRRT) of Metastatic Progressive Neuroendocrine Tumors*.

Bodei, L., Cremonesi, M., Grana, C. M., Chinol, M., Baio, S. M., Severi, S., & Paganelli, G. (2012). Yttrium-labelled peptides for therapy of NET. *European Journal of Nuclear Medicine and Molecular Imaging*, *39*(Suppl 1), S93–S102. https://doi.org/10.1007/s00259-011-2002-y

Bodei, L., Ferone, D., Grana, C. M., Cremonesi, M., Signore, A., Dierckx, R. A., & Paganelli, G. (2009). Peptide receptor therapies in neuroendocrine tumors. *Journal of Endocrinological Investigation*, *32*(4), 360–369.

Boschi, A., Uccelli, L., & Martini, P. (2019). A picture of modern Tc-99m radiopharmaceuticals: Production, chemistry, and applications in molecular imaging. *Applied Sciences (Switzerland)*, *9*(12), 1–16. https://doi.org/10.3390/app9122526

Breeman, W. A. P. (2012). Practical aspects of labeling DTPA-and DOTA-peptides with 90Y, 111In, 177Lu, 68Ga for peptide-receptor scintigraphy and peptide-receptor radionuclide therapy in preclinical and clinical applications. *University of New Mexico Health Sciences Center, College of Pharmacy*, *16*(0039), 1–34.

Breeman, W., de Jong, M., Kwekkeboom, D., Valkema, R., Bakker, W., Kooij, P., Visser, T., & Krenning, E. (2001). Somatostatin receptor-mediated imaging and therapy: basic science, current knowledge, limitations and future perspectives. *European Journal of Nuclear Medicine and Molecular Imaging*, *28*(9), 1421–1429.

Brust, P., van den Hoff, J., & Steinbach, J. (2014). Development of 18F-labeled radiotracers for neuroreceptor imaging with positron emission tomography. *Neuroscience Bulletin*, *30*(5), 777–811. https://doi.org/10.1007/s12264-014-1460-6

Capello, A., Krenning, E., Bernard, B., Reubi, J. C., Breeman, W., & De Jong, M. (2005). 111In-labelled somatostatin analogues in a rat tumour model: Somatostatin receptor status and effects of peptide receptor radionuclide therapy. *European Journal of Nuclear Medicine and Molecular Imaging*, *32*(11), 1288–1295. https://doi.org/10.1007/s00259-005-1877-x

Chong, H.-S., Garmestani, K., Ma, D., Milenic, D. E., Overstreet, T., & Brechbiel, M. W. (2002). Synthesis and biological evaluation of novel macrocyclic ligands with pendent donor groups as potential yttrium chelators for radioimmunotherapy with improved complex formation kinetics. *Journal of Medicinal*, *45*(16), 3458–3464.

Cooper, M. S., Sabbah, E., & Mather, S. J. (2006). Conjugation of chelating agents to proteins and radiolabeling with trivalent metallic isotopes. *Nature Protocols*, *1*, 314–317.

Cremonesi, M., Ferrari, M. E., Bodei, L., Chiesa, C., Sarnelli, A., Garibaldi, C., Pacilio, M., Strigari, L., Summers, P. E., Orecchia, R., Grana, C. M., & Botta, F. (2018). Correlation of dose with toxicity and tumour response to 90Y- and 177Lu-PRRT provides the basis for optimization through individualized

treatment planning. *European Journal of Nuclear Medicine and Molecular Imaging*, *45*(13), 2426–2441.

Dadachova, E. (2010). Cancer therapy with alpha-emitters labeled peptides. *Seminars in Nuclear Medicine*, *40*(3), 204–208. https://doi.org/10.1053/j.semnuclmed.2010.01.002

Das, S., Al-toubah, T., El-haddad, G., & Strosberg, J. (2019). 177Lu-DOTATATE for the treatment of gastroenteropancreatic neuroendocrine tumors. *Expert Review of Gastroenterology & Hepatology*, *13*(11), 1023–1031. https://doi.org/10.1080/17474124.2019.1685381.177

Dash, A., & Chakravarty, R. (2019). Radionuclide generators : the prospect of availing PET radiotracers to meet current clinical needs and future research demands. *American Journal of Nuclear Medicine and Molecular Imaging*, *9*(1), 30–66.

Dash, A., Pillai, M. R. A., & Knapp Jr, F. F. (2015). *Production of 177Lu for Targeted Radionuclide Therapy: Available Options*. *49*, 85–107. https://doi.org/10.1007/s13139-014-0315-z

De Jong, M., Bakker, W. H., Breeman, W. A. P., Bernard, B. F., Hofland, L. J., Visser, T. J., Srinivasan, A., Schmidt, M., Béhé, M., Mäcke, H. R., & Krenning, E. P. (1998). Pre-clinical comparison of [DTPA0] octreotide, [DTPA0,Tyr3] octreotide and [DOTA0,Tyr3] octreotide as carriers for somatostatin receptor-targeted scintigraphy and radionuclide therapy. *International Journal of Cancer*, *75*(3), 406–411. https://doi.org/10.1002/(SICI)1097-0215(19980130)75:3<406::AID-IJC14>3.0.CO;2-6

De Jong, M., Breeman, W. A. P., Bernard, B. F., Bakker, W. H. B., Chaar, M. S., Van Gameren, A. V, Bugaj, J. E. B., Erion, J., Schmidt, M., Srinivasan, A., & Krenning, E. P. (2001). [177Lu-DOTA0,Tyr3]octreotate for somatostatin receptor-targeted radionuclide therapy. *International Journal of Cancer*, *92*, 628–633.

De León-Rodríguez, L. M., & Kovacs, Z. (2008). The synthesis and chelation chemistry of DOTA-peptide conjugates. *Bioconjugate Chemistry*, *19*(2), 391–402. https://doi.org/10.1021/bc700328s

Deveci, E. K., Ocak, M., Bozkurt, M. F., Türker, S., Kabasakal, L., & Uğur, Ö. (2013). The diagnostic efficiency of 99mTc-EDDA/HYNIC-Octreotate SPECT-CT in comparison with 111In-Pentetrotide in the detection of neuroendocrine tumours. *Molecular Imaging and Radionuclide Therapy*, *22*(3), 76–84. https://doi.org/10.4274/mirt.68552

Dobrucki, L. W., & Sinusas, A. J. (2010). PET and SPECT in cardiovascular molecular imaging. *Nature Reviews Cardiology*, *7*(1), 38–47. https://doi.org/10.1038/nrcardio.2009.201

Duatti, A. (2021). Review on 99mTc radiopharmaceuticals with emphasis on new advancements. *Nuclear Medicine and Biology*, *92*, 202–216. https://doi.org/10.1016/j.nucmedbio.2020.05.005

Dude, I., Zhang, Z., Rousseau, J., Hundal-Jabal, N., Colpo, N., Merkens, H., Lin, K.-S., & Bénard, F. (2017). Evaluation of agonist and antagonist radioligands for somatostatin receptor imaging of breast cancer using positron emission tomography. *EJNMMI Radiopharmacy and Chemistry*, *2*(1). https://doi.org/10.1186/s41181-017-0023-y

Duijzentkunst, D. A. S., Kwekkeboom, D. J., & Bodei, L. (2017). Somatostatin receptor 2-targeting compounds. *Journal of Nuclear Medicine*, *58*(9), 54S-60S. https://doi.org/10.2967/jnumed.117.191015

Elschot, M., Vermolen, B. J., Lam, M. G., de Keizer, B., van den Bosch, M. A., & de Jong, H. W. (2013). Quantitative comparison of PET and bremsstrahlung SPECT for imaging the in vivo Yttrium-90 microsphere distribution after liver radioembolization. *PLoS One*, *8*(2), e55742. https://doi.org/10.1371/journal.pone.0055742

EMA. (2016). *Authorization Details for SomaKit TOC® in Europe*. https://www.ema.europa.eu/en/documents/overview/somakit-toc-epar-summary-public_en.pdf

Eychenne, R., Bouvry, C., Bourgeois, M., Loyer, P., Benoist, E., & Lepareur, N. (2020). Overview of Radiolabeled Somatostatin Analogs for Cancer Imaging and Therapy. *Molecules*, *25*(17). https://doi.org/10.3390/molecules25174012

Fani, M., Braun, F., Waser, B., Beetschen, K., Cescato, R., Erchegyi, J., Rivier, J. E., Weber, W. A., Maecke, H. R., & Reubi, J. C. (2012). Unexpected sensitivity of sst 2 antagonists to N-terminal radiometal modifications. *Journal of Nuclear Medicine*, *53*(9), 1481–1489. https://doi.org/10.2967/jnumed.112.102764

Fani, M., Maecke, H. R., & Okarvi, S. M. (2012). Radiolabeled peptides: valuable tools for the detection and treatment of cancer. *Theranostics*, *2*(5), 481–501. https://doi.org/10.7150/thno.4024

Fani, M., Nicolas, G. P., & Wild, D. (2017). Somatostatin Receptor Antagonists for Imaging and Therapy. *Journal of Nuclear Medicine*, *58*(Suppl 2), 61S-67S. https://doi.org/10.2967/jnumed.116.186783

FDA, U. S. (2019). *FDA letter of approval for [68Ga]Ga-DOTA-TOC*. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/210828Orig1s000ltr.pdf

Fischman, A. J., Babich, J. W., & Strauss, H. W. (1993). A ticket to ride: peptide radiopharmaceuticals. *Journal of Nuclear Medicine*, *34*(12), 2253–2263.

Gabriel, M., Decristoforo, C., Donnemiller, E., Ulmer, H., Rychlinski, C. W., Mather, S. J., & Moncayo, R. (2003). An intrapatient comparison of 99mTc-EDDA/HYNIC-TOC with 111In-DTPA-octreotide for diagnosis of somatostatin receptor-expressing tumors. *Journal of Nuclear Medicine*, *44*(5), 708–716.

Ginj, M., Zhang, H., Waser, B., Cescato, R., Wild, D., Wang, X., Erchegyi, J., Rivier, J., Maecke, H. R., & Reubi, J. C. (2006). Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors. *PNAS*, *103*(44), 16436–16441.

Gomes-Porras, M., Cárdenas-Salas, J., & Álvarez-Escolá, C. (2020). Somatostatin analogs in clinical practice: A review. *International Journal of Molecular Sciences*, *21*(5), 1682. https://doi.org/10.3390/ijms21051682

Graham, M. M., & Menda, Y. (2011). Radiopeptide imaging and therapy in the United States. *Journal of Nuclear Medicine*, *52*, 56S-63S. https://doi.org/10.2967/jnumed.110.085746

Günther, T., Tulipano, G., Dournaud, P., Bousquet, C., Csaba, Z., Kreienkamp, H.-J., Lupp, A., Korbonits, M., Castaño, J. P., Wester, H. J., Culler, M., Melmed, S., & Schulz, S. (2018). International union of basic and clinical pharmacology. CV. somatostatin receptors: structure, function, ligands, and new nomenclature. *Pharmacological Reviews*, *70*(4), 763–835. https://doi.org/10.1124/pr.117.015388

Harrington, C. B., Hansen, J. A., Moskowitz, M., Todd, B. L., & Feuerstein, M. (2010). It's not over when it's over: Long-term symptoms in cancer survivors-a systematic review. *International Journal of Psychiatry in Medicine*, *40*(2), 163–181. https://doi.org/10.2190/PM.40.2.c

Hennrich, U., & Benešová, M. (2020). [68Ga]Ga-DOTA-TOC: The first FDA-approved 68Ga-radiopharmaceutical for PET imaging. *Pharmaceuticals (Basel)*, *13*(3), 38.

Hennrich, U., & Kopka, K. (2019). Lutathera®: the first FDA-and EMA-approved radiopharmaceutical for peptide receptor radionuclide therapy. *Pharmaceuticals*, *12*(3), 114. https://doi.org/10.3390/ph12030114

Henze, M., Dimitrakopoulou-strauss, A., Milker-zabel, S., Schuhmacher, J., Strauss, L. G., Doll, J., Mäcke, H. R., Eisenhut, M., Debus, J., & Haberkorn, U. (2005). Characterization of 68Ga-DOTA-D-Phe1-Tyr3-Octreotide kinetics in patients with meningiomas. *Journal of Nuclear Medicine*, *46*(5), 763–770.

Hofmann, M., Maecke, H., Börner, A. R., Weckesser, E., Schöffski, P., Oei, M. L., Schumacher, J., Henze, M., Heppeler, A., Meyer, G. J., & Knapp, W. H. (2001). Biokinetics and imaging with the somatostatin receptor PET radioligand 68Ga-DOTATOC: Preliminary data. *European Journal of Nuclear Medicine*, *28*(12), 1751–1757. https://doi.org/10.1007/s002590100639

Hubalewska-Dydejczky, A. Fross-Baron, K., Mikolajczak, R., Maecke, H. R., Huszno, B., Pach, D., Sowa-Staszczak, A., Janota, B., Szybiński, P., & Kulig, J. (2006). 99mTc-EDDA/HYNIC-octreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results of 3 years' experience. *European Journal of Nuclear Medicine and Molecular Imaging*, *33*, 1123–33.

Humani, T. S., Sutari, Triningsih, Ramli, M., Ritawidya, R., & Haryuni, R. D. (2017).

Preparation of (177Lu-DOTA)n-PAMAM-[Nimotuzumab-F(ab')2] as a therapeutic radioimmunoconjugate for EGFR overexpressed cancer treatment. *Journal of Mathematical and Fundamental Sciences*, *49*(3). https://doi.org/10.5614/j.math.fund.sci.2017.49.3.4

IASON GmbH. (2016). *Authorization Details of IASOtoc ®*. http://www.iason.eu/produkte/iasotoc.html#page-top

ITM. (2018). *Marketing Authorization for TOCscan® (68Ga-Edotreotide) in Germany, Austria and France*. https://itm-radiopharma.com/fileadmin/user_upload/news/PR_ITM_receives_Marketing_Authorization_for_TOCscan.pdf

Jacobs, A. H., Li, H., Winkeler, A., Hilker, R., Knoess, C., Rüger, A., Galldiks, N., Schaller, B., Sobesky, J., Krach, L., Monfared, P., Klein, M., Vollmar, S., Bauer, B., Wagner, R., Graf, R., Wienhard, K., Herholz, K., & Heiss, W. D. (2003). Pet-based molecular imaging in neuroscience. *European Journal of Nuclear Medicine and Molecular Imaging*, *30*(7), 1051–1065. https://doi.org/10.1007/s00259-003-1202-5

Jalilian, A. R. (2016). An overview on Ga-68 radiopharmaceuticals for positron emission tomography applications. *Iranian Journal of Nuclear Medicine*, *24*(1), 1–10.

Jamar, F., Barone, R., Mathieu, I., Walrand, S., Labar, D., Carlier, P., de Camps, J., Schran, H., Chen, T., Smith, M. C., Bouterfa, H., Valkema, R., Krenning, E. P., Kvols, L. K., & Pauwels, S. (2003). 86Y-DOTA0-D-Phe1-Tyr3-octreotide (SMT487) – a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *European Journal of Nuclear Medicine and Molecular Imaging*, *30*(4), 510–518.

Jamous, M., Haberkorn, U., & Mier, W. (2013). Synthesis of peptide radiopharmaceuticals for the therapy and diagnosis of tumor diseases. *Molecules*, *18*(3), 3379–3409. https://doi.org/10.3390/molecules18033379

Kabasakal, L., Demirci, E., Ocak, M., Decristoforo, C., Araman, A., Ozsoy, Y., Uslu, I., & Kanmaz, B. (2012). Comparison of 68Ga-DOTATATE and 68Ga-DOTANOC PET/CT imaging in the same patient group with neuroendocrine tumours. *European Journal of Nuclear Medicine and Molecular Imaging*, *39*(8), 1271–1277. https://doi.org/10.1007/s00259-012-2123-y

Kaltsas, G. A., Papadogias, D., Makras, P., & Grossman, A. B. (2005). Treatment of advanced neuroendocrine tumours with radiolabelled somatostatin analogues. *Endocrine-Related Cancer*, *12*(4), 683–699. https://doi.org/10.1677/erc.1.01116

Kim, Y. C., Kim, Y. H., Uhm, S. H., Seo, Y. S., Park, E. K., Oh, S. Y., Jeong, E., Lee, S., & Choe, J. G. (2010). Radiation safety issues in Y-90 microsphere selective hepatic radioembolization therapy: Possible radiation exposure from the patients. *Nuclear Medicine and Molecular Imaging*, *44*(4), 252–260. https://doi.org/10.1007/s13139-010-0047-7

Kim, Y. C., Kim, Y. H., Um, S. H., Seo, Y. S., Park, E. K., Oh, S. Y., Han, Y. M., & Choe, J. G. (2011). Usefulness of bremsstrahlung images after intra-arterial Y-90 resin microphere radioembolization for hepatic tumors. *Nuclear Medicine and Molecular Imaging*, *45*(1), 59–67. https://doi.org/10.1007/s13139-010-0066-4

Knapp, F. F. (Russ) J. (2009). *Lutetium-177-broad production capabilities are expected to stimulate clinical applications of this important therapeutic radioisotope*. Technical Meeting on Therapeutic Radiopharmaceuticals. https://inis.iaea.org/collection/NCLCollectionStore/_Public/43/004/43004236.pdf?r=1

Krenning, E. ., Kwekkeboom, D. ., Bakker, W. ., Breeman, W. A. ., Kooji, P. P. ., Oei, H. ., van Hagen, M., Postema, P., de Jong, M., Reubi, J., Visser, T., Reijs, A., Hofland, L., Koper, J., Lamberts, S., Postema, P., de Jong, M., Reubi, J., Visser, T., … Lamberts, S. (1993). Somatostatin receptor scintigraphy with [111In-DTPA-d-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. *European Journal of Nuclear Medicine*, *20*(8), 716–731.

Krenning, E., Bakker, W., Breeman, W., Koper, J., Kooij, P., Ausema, L., Lameris, J., Reubi, J., & Lamberts, S. (1989). Localisation of endocrine-related tumours with

radioiodinated analogue of somatostatin. *The Lancet*, *333*(8632), 242–244.

Ku, A., Facca, V. J., Cai, Z., & Reilly, R. M. (2019). Auger electrons for cancer therapy – a review. *EJNMMI Radiopharmacy and Chemistry*, *4*, 27. https://doi.org/10.1186/s41181-019-0075-2

Kuzmanovska, S., Vaskova, O., & Zdraveska Kocovska, M. (2011). "In-house" preparation of 99mTc-EDDA/HYNIC-TOC, a specific targeting agent for somatostatin receptor scintigraphy. *Macedonian Pharmaceutical Bulletin*, *57*(1,2), 65–70. https://doi.org/10.33320/maced.pharm.bull.2011.57.007

Kwekkeboom, D., Krenning, E. P., & De Jong, M. (2000). Peptide receptor imaging and therapy. *Journal of Nuclear Medicine*, *41*(10), 1704–1713.

Lamberts, S. W., Bakker, W. H., Reubi, J. C., & Krenning, E. P. (1990). Somatostatin-receptor imaging in the localization of endocrine tumors. *N Engl J Med*, *323*(18), 1246–1249.

Liepe, K., & Becker, A. (2018). 99mTc-Hynic-TOC imaging in the diagnostic of neuroendocrine tumors. *World Journal of Nuclear Medicine*, *17*, 151–156. https://doi.org/10.4103/wjnm.WJNM

Liu, S., & Edwards, S. D. (2001). Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals. *Bioconjugate Chemistry*, *12*(1), 7–34. https://doi.org/10.1021/bc000070v

Lobrano, M. B., & Singha, P. (2003). Positron emission tomography in oncology. *Clinical Journal of Oncology NUrsing*, *7*(4), 379–385. https://doi.org/10.1093/bmb/ldl013

Lu, F.-M., & Yuan, Z. (2015). PET/SPECT molecular imaging in clinical neuroscience: recent advances in the investigation of CNS diseases. *Quantitative Imaging in Medicine and Surgery*, *5*(3), 433–447. https://doi.org/10.3978/j.issn.2223-4292.2015.03.16

Lystad, R. P., & Pollard, H. (2009). Functional neuroimaging: a brief overview and feasibility for use in chiropractic research. *The Journal of the Canadian Chiropractic Association*, *53*(1), 59–72.

Maecke, H. R. (2005). Radiolabeled peptides in nuclear oncology: influence of peptide structure and labeling strategy on pharmacology. In A. A. Bogdanov & K. Licha (Eds.), *Molecular Imaging* (pp. 43–72). Ernst Schering Res Found Workshop, vol 49. Springer, Berlin, Heidelberg. https://doi.org/10.1007/3-540-26809-x_3

Maina, T., Nock, B., Nikolopoulou, A., & Al., E. (2002). [99mTc]Demotate, a new 99mTc-based [Tyr3]octreotate analogue for the detection of somatostatin receptor-positive tumours: synthesis and preclinical results. *Eur J Nucl Med*, *29*(6), 742–753.

Menda, Y., & Kahn, D. (2002). Somatostatin receptor imaging of non-small cell lung cancer with 99mTc depreotide. *Semin Nucl Meduclear Medicine*, *32*(2), 92–96. https://doi.org/10.1053/snuc.2002.31564

Mikolajczak, R. (2009). Technetium-99m labeled somatostatin analogues and their role in the management of patients with neuroendocrine tumors. *World Journal of Nuclear Medicine*, *8*(3), 141–142.

Mikołajczak, R., & Maecke, H. R. (2016). Radiopharmaceuticals for somatostatin receptor imaging. *Nuclear Medicine Review*, *19*(2), 126–132. https://doi.org/10.5603/NMR.2016.0024

Mittra, E. S. (2018). Neuroendocrine tumor therapy: 177Lu-DOTATATE. *AJR*, *211*(2), 278–285. https://doi.org/10.2214/AJR.18.19953

Morphis, M., van Staden, J. A., du Raan, H., & Ljungberg, M. (2021). Evaluation of Iodine-123 and Iodine-131 SPECT activity quantification: a Monte Carlo study. *EJNMMI Physics*, *8*(1), 1–20. https://doi.org/10.1186/s40658-021-00407-1

Navalkissoor, S., & Grossman, A. (2019). Targeted alpha particle therapy for neuroendocrine tumours: the next generation of peptide receptor radionuclide therapy. *Neuroendocrinology*, *108*(3), 256–264. https://doi.org/10.1159/000494760

Nelson, B. J. B., Wilson, J., Richter, S., Duke, M. J. M., Wuest, M., & Wuest, F. (2020). Taking cyclotron 68Ga production to the next level: Expeditious solid target production of 68Ga for preparation of radiotracers. *Nuclear Medicine and Biology*, *80–81*, 24–31. https://doi.org/10.1016/j.nucmedbio.2020.01.005

Okarvi, S. M. (2004). Peptide-based radiopharmaceuticals: future tools for diagnostic imaging of cancers and other

diseases. *Medicinal Research Reviews*, *24*(3), 357–397. https://doi.org/10.1002/med.20002

Okarvi, S. M. (2008). Peptide-based radiopharmaceuticals and cytotoxic conjugates: Potential tools against cancer. *Cancer Treatment Reviews*, *34*, 13–26. https://doi.org/10.1016/j.ctrv.2007.07.017

Oronsky, B., Ma, P. C., Morgensztern, D., & Carter, C. A. (2017). Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia*, *19*(12), 991–1002. https://doi.org/10.1016/j.neo.2017.09.002

Otte, A., Jermann, E., Behe, M., Goetze, M., Bucher, H. C., Roser, H. W., Heppeler, A., Mueller-Brand, J., & Maecke, H. R. (1997). DOTATOC: a powerful new tool for receptor-mediated radionuclide therapy. *European Journal of Nuclear Medicine*, *24*, 792–795.

Paans, A. M. J., & Vaalburg, W. (2000). Positron emission tomography imaging and drug development. *Current Pharmaceutical Design*, *6*, 1583–1591.

Palangka, C. R. A. P., Hanaoka, H., Yamaguchi, A., Murakami, T., & Tsushima, Y. (2019). Al18F-labeled alpha-melanocyte-stimulating hormone (α-MSH) peptide derivative for the early detection of melanoma. *Annals of Nuclear Medicine*, *33*(10), 733–739. https://doi.org/10.1007/s12149-019-01383-4

Palumbo, B., Buresta, T., Nuvoli, S., Spanu, A., Schillaci, O., Fravolini, M. L., & Palumbo, I. (2014). SPECT and PET serve as molecular imaging techniques and in Vivo biomarkers for brain metastases. *International Journal of Molecular Sciences*, *15*(6), 9878–9893. https://doi.org/10.3390/ijms15069878

Patel, Y. C. (1999). Somatostatin and its receptor family. *Frontiers in Neuroendocrinology*, *20*(3), 157–198. https://doi.org/10.1006/frne.1999.0183

Payolla, F. B., Massabni, A. C., & Orvig, C. (2019). Radiopharmaceuticals for diagnosis in nuclear medicine: A short review. *Ecletica Quimica*, *44*(3), 11–19. https://doi.org/10.26850/1678-4618eqj.v44.3.2019.p11-19

Phelps, M. E. (2000). Positron emission tomography provides molecular imaging of biological processes. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(16), 9226–9233. https://doi.org/10.1073/pnas.97.16.9226

Poeppel, T. D., Binse, I., Petersenn, S., Lahner, H., Schott, M., Antoch, G., Brandau, W., Bockisch, A., & Boy, C. (2011). Functional imaging of neuroendocrine tumors. *Journal of Nuclear Medicine*, *52*(12), 1864–1870. https://doi.org/10.2967/jnumed.111.091165

Pool, S. E., Kam, B. L. R., Koning, G. A., Konijnenberg, M., ten Hagen, T. L. M., Breeman, W. A. P., Krenning, E. P., de Jong, M., & van Eijck, C. H. J. (2014). [111In-DTPA]octreotide tumor uptake in GEPNET liver metastases after intra-arterial administration: an overview of preclinical and clinical observations and implications for tumor radiation dose after peptide radionuclide therapy. *Cancer Biotherapy and Radiopharmaceuticals*, *29*(4), 179–187. https://doi.org/10.1089/cbr.2013.1552

Radford, L., Gallazzi, F., Watkinson, L., Carmack, T., Lewis, M. R., Jurisson, S. S., Papagiannopoulou, D., Hennkens, H. M., Ashley, B., R, L. M., & S, J. S. (2017). Synthesis and evaluation of a 99mTc tricarbonyl-labeled somatostatin receptor-targeting antagonist peptide for imaging of neuroendocrine tumors. *Nuclear Medicine and Biology*, *47*, 4–9. https://doi.org/10.1016/j.nucmedbio.2016.12.002

Ramli, M., Hidayat, B., Ardiyatno, C. N., Aguswarini, S., Rustendi, C. T., Subur, M., Humani, T. S., & Ritawidya, R. (2013). Preclinical study of 177 Lu-DOTA-trastuzumab , a potential radiopharmaceutical for therapy of breast cancer positive HER-2. *Jurnal Ilm*, *2011*(November), 116–122.

Ramli, M., Hidayat, B., Rustendi, C. T., Subur, M., Ardiyatno, C. N., Karyadi, Aguswarini, S., Humani, T. S., Ritawidya, R., Mutalib, A., & Masjhur, J. S. (2012). In Vitro and In Vivo testing of 177Lu-DOTA-nimotuzumab, a potential radioimmunotherapeutical agent of cancers. *ITB Journal of Science*, *44 A*(4), 333–345. https://doi.org/10.5614/itbj.sci.2012.44.4.4

Reubi, J. C. (2003). Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocrine Reviews*, *24*(4), 389–427. https://doi.org/10.1210/er.2002-0007

Reubi, J. C. (2004). Somatostatin and other peptide receptors as tools for tumor diagnosis and treatment. *Neuroendocrinology*, *80*(suppl 1),

51–56. https://doi.org/10.1159/000080742

Reubi, J. C., Schär, J., Waser, B., Wenger, S., Heppeler, A., Schmitt, J. S., & Mäcke, H. R. (2000). Affinity profiles for human somatostatin receptor subtypes SST1 – SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *European Journal of Nuclear Medicine*, *27*, 273–282.

Ritawidya, R., Sutari, S., Setiyowati, S., Subur, M., Alwi, Y., Susilo, V. Y., Humani, T. S., & Ramli, M. (2016). Synthesis of DOTA-TOC conjugate as a precursor of 177Lu-DOTA-TOC radiopharmaceutical for therapy and diagnosis of somatostation receptor positive cancer. *Majalah Polymer Indonesia*, *19*(1), 1–14.

Ritawidya, R., Wenzel, B., Teodoro, R., Toussaint, M., Kranz, M., Deuther-Conrad, W., Dukic-Stefanovic, S., Ludwig, F.-A., Scheunemann, M., & Brust, P. (2019). Radiosynthesis and biological investigation of a novel fluorine-18 labeled benzoimidazotriazine-based radioligand for the imaging of phosphodiesterase 2A with positron emission tomography. *Molecules*, *24*, 4149.

Romer, A., Seiler, D., Marincek, N., Brunner, P., Koller, M. T., Ng, Q. K. T., Maecke, H. R., Müller-Brand, J., Rochlitz, C., Briel, M., Schindler, C., & Walter, M. A. (2014). Somatostatin-based radiopeptide therapy with [177Lu-DOTA]-TOC versus [90Y-DOTA]-TOC in neuroendocrine tumours. *European Journal of Nuclear Medicine and Molecular Imaging*, *41*(2), 214–222. https://doi.org/10.1007/s00259-013-2559-8

Rufini, V., Calcagni, M. L., & Baum, R. P. (2006). Imaging of neuroendocrine Tumors. *Semin Nucl Med*, *36*(3), 228–247. https://doi.org/10.1053/j.semnuclmed.2006.03.007

Saptiama, I., Lestari, E., Sarmini, E., Lubis, H., Marlina, & Mutalib, A. (2016). Development of 99Mo/99mTc generator system for production of medical radionuclide 99mTc using a neutron-activated 99Mo and zirconium based material (ZBM) as its adsorbent. *Atom Indonesia*, *42*(3), 115–121. https://doi.org/10.17146/aij.2016.531

Schottelius, M., & Wester, H. J. (2009). Molecular imaging targeting peptide receptors. *Methods*, *48*(2), 161–177. https://doi.org/10.1016/j.ymeth.2009.03.012

Sgouros, G. (2019). Radiopharmaceutical Therapy. *Health Physics*, *116*(2), 175–178. https://doi.org/10.1097/HP.0000000000001000.RADIOPHARMACEUTICAL

Sgouros, G., Bodei, L., McDevitt, M. R., & Nedrow, J. R. (2020). Radiopharmaceutical therapy in cancer: clinical advances and challenges. *Nature Reviews Drug Discovery*, *19*(9), 589–608. https://doi.org/10.1038/s41573-020-0073-9

Sofou, S. (2008). Radionuclide carriers for targeting of cancer. *International Journal of Nanomedicine*, *3*(2), 181–199. https://doi.org/10.2147/ijn.s2736

Srirajaskanthan, R., Kayani, I., Quigley, A. M., Soh, J., Caplin, M. E., & Bomanji, J. (2010). The role of 68Ga-DOTATATE PET in patients with neuroendocrine tumors and negative or equivocal findings on 111In-DTPA-octreotide scintigraphy. *Journal of Nuclear Medicine*, *51*(6), 875–882. https://doi.org/10.2967/jnumed.109.066134

Sugiura, G., Kühn, H., Sauter, M., Haberkorn, U., & Mier, W. (2014). Radiolabeling strategies for tumor-targeting proteinaceous drugs. *Molecules*, *19*(2), 2135–2165. https://doi.org/10.3390/molecules19022135

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Teodoro, R., Faintuch, B. L., Núñez, E. G. F., & Queiróz, R. G. (2011). Neurotensin(8-13) analogue: Radiolabeling and biological evaluation using different chelators. *Nuclear Medicine and Biology*, *38*(1), 113–120. https://doi.org/10.1016/j.nucmedbio.2010.06.011

Thundimadathil, J. (2012). Cancer treatment using peptides: current therapies and future prospects. *Journal of Amino Acids*, *2012*, 1–13. https://doi.org/10.1155/2012/967347

Tsoli, M., Chatzellis, E., Koumarianou, A., Kolomodi, D., & Kaltsas, G. (2019). Current best practice in the management of neuroendocrine tumors. *Therapeutic Advances in*

Endocrinology and Metabolism, *10*, 1–18. https://doi.org/10.1177/https

Turner, J. H. (2018). An introduction to the clinical practice of theranostics in oncology. *British Journal of Radiology*, *91*(1091), 1–9. https://doi.org/10.1259/bjr.20180440

Turner, R., & Jones, T. (2003). Techniques for imaging neuroscience. *British Medical Bulletin*, *65*, 3–20. https://doi.org/10.1093/bmb/65.1.3

Valkema, R., De Jong, M., Bakker, W. H., Breeman, W. A. P., Kooij, P. P. M., Lugtenburg, P. J., De Jong, F. H., Christiansen, A., Kam, B. L. R., De Herder, W. W., Stridsberg, M., Lindemans, J., Ensing, G., & Krenning, E. P. (2002). Phase I study of peptide receptor radionuclide therapy with [111In-DTPA0]octreotide: The Rotterdam experience. *Seminars in Nuclear Medicine*, *32*(2), 110–122. https://doi.org/10.1053/snuc/2002.31025

Van Essen, M., Krenning, E. P., De Jong, M., Valkema, R., & Kwekkeboom, D. J. (2007). Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours. *Acta Oncologica*, *46*(6), 723–734. https://doi.org/10.1080/02841860701441848

Velikyan, I. (2014). Prospective of 68Ga-Radiopharmaceutical development. *Theranostics*, *4*(1), 47–80. https://doi.org/10.7150/thno.7447

Velikyan, I., Xu, H., Nair, M., & Hall, H. (2012). Robust labeling and comparative preclinical characterization of DOTA-TOC and DOTA-TATE. *Nuclear Medicine and Biology*, *39*(5), 628–639. https://doi.org/10.1016/j.nucmedbio.2011.12.010

Vogel, W. V, Van Der Marck, S. C., & Versleijen, M. W. J. (2021). Challenges and future options for the production of lutetium-177. *European Journal of Nuclear Medicine and Molecular Imaging*, *48*, 2329–2335.

Wang, L., Huang, X., Chai, Y., Zou, L., Chedrawe, M., & Ding, Y. (2017). Octreotide inhibits the proliferation of gastric cancer cells through P300-HAT activity and the interaction of ZAC and P300. *Oncology Reports*, *37*(4), 2041–2048. https://doi.org/10.3892/or.2017.5451

Wang, L., Lin, L., Wang, M., & Li, Y. (2020). The therapeutic efficacy of 177 Lu-DOTATATE/ DOTATOC in advanced neuroendocrine tumors. *Medicine*, *99*(10).

Wang, L., Tang, K., Zhang, Q., Li, H., Wen, Z., Zhang, H., & Zhang, H. (2013). Somatostatin receptor-based molecular imaging and therapy for neuroendocrine tumors. *BioMed Research International*, *2013*. https://doi.org/10.1155/2013/102819

Wängberg, B., Nilsson, O., Johanson, V., Kölby, L., Forssell-Aronsson, E., Andersson, P., Fjälling, M., Tisell, L. -E., & Ahlman, H. (1997). Somatostatin receptors in the diagnosis and therapy of neuroendocrine tumors. *The Oncologist*, *2*, 50–58. https://doi.org/10.1634/theoncologist.2-1-50

Widyastuti, W., Roseliana, A., Taufik, C., & Aguswarini, S. (2007). Preparasi 99mTc-HYNIC-TOC dan pencitraan pada pasien tumor. *Prosiding PPI-PDIPTN, Pustek Akselerator Dan Proses Bahan - BATAN*, 89–94.

Wild, D., Bomanji, J. B., Benkert, P., Maecke, H., Ell, P. J., Reubi, J. C., & Caplin, M. E. (2013). Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. *Jornal of Nuclear Medicine*, *54*(3), 364–372. https://doi.org/10.2967/jnumed.112.111724

Wild, D., Fani, M., Behe, M., Brink, I., Rivier, J. E. F., Reubi, J. C., Maecke, H. R., & Weber, W. A. (2011). First clinical evidence that imaging with somatostatin receptor antagonists is feasible. *Journal of Nuclear Medicine*, *52*(9), 1412–1417. https://doi.org/10.2967/jnumed.111.088922

Wild, D., Fani, M., Fischer, R., Pozzo, L. Del, Kaul, F., Krebs, S., Rivier, J. E. F., Reubi, J. C., Maecke, H. R., & Weber, W. A. (2014). Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: A pilot study. *Journal of Nuclear Medicine*, *55*(8), 1248–1252. https://doi.org/10.2967/jnumed.114.138834

World Health Organization. (2019). Global health estimates: Leading causes of death. Cause specific mortality 2000-2019. *World Health Organization*, https://www.who.int/data/gho/data/themes/mortality.

Worm, D. J., Els-Heindl, S., & Beck-Sickinger, A. G.

(2020). Targeting of peptide-binding receptors on cancer cells with peptide-drug conjugates. *Peptide Science*, *112*, e24171. https://doi.org/10.1002/pep2.24171

Wright, C. L., Zhang, J., Tweedle, M. F., Knopp, M. V., & Hall, N. C. (2015). Theranostic imaging of yttrium-90. *BioMed Research International*, *2015*, 481279,. https://doi.org/10.1155/2015/481279

Wuest, F. (2005). Aspects of positron emission tomography radiochemistry as relevant for food chemistry. *Amino Acids*, *29*, 323–339. https://doi.org/10.1007/s00726-005-0201-1

Yeole, M. P., Dhole, S. N., & Kulkarni, N. S. (2013). Peptide nanomedicine in cancer treatment. *Asian Journal of Pharmaceutical and Clinical Research*, *6*(Suppl 2), 28–32.

Zhang, C., Lin, K. S., & Bénard, F. (2017). Molecular Imaging and Radionuclide Therapy of Melanoma Targeting the Melanocortin 1 Receptor. *Molecular Imaging*, *16*, 1–15. https://doi.org/10.1177/1536012117737919

Zhang, H., Moroz, M. A., Serganova, I., Ku, T., Huang, R., Vider, J., Maecke, H. R., Larson, S. M., Blasberg, R., & Smith-Jones, P. M. (2011). Imaging expression of the human somatostatin receptor subtype-2 reporter gene with 68Ga-DOTATOC. *Journal of Nuclear Medicine*, *52*(1), 123–131. https://doi.org/10.2967/jnumed.110.079004