Radiometal-Labeled Peptides in Cancer Diagnosis

Subjects: Oncology

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Radiolabeled biomolecules targeted at tumor-specific enzymes, receptors, and transporters in cancer cells represent an intensively investigated and promising class of molecular tools for the cancer diagnosis and therapy. High specificity of such biomolecules is a prerequisite for the treatment with a lower burden to normal cells and for the effective and targeted imaging and diagnosis. The most impressive outputs in categories of newly developed structures, as well as imaging and diagnosis approaches, and the most intensively studied oncological diseases in this context, are emphasized in order to show future perspectives of radiometal labeled amino acid-based compounds in nuclear medicine.

Amino acid peptide bifunctional chelating agent (BFCA) cancer receptor imaging

1. Introduction

The great emphasis in nuclear medicine is put on a synthesis and study of radiolabeled amino acid-derived biomolecules with a selective distribution and binding to target structures in living cells and tissues, i.e., enzymes, transporters, or peptide receptors. This allows targeted therapy and diagnostic evaluation of pathological changes in many fields, such as oncology, neurology, endocrinology, cardiology, and also investigation of inflammation processes or infection. Especially, malignant tumor diseases are of the biggest interest because of their increasing global incidence, and placing second in the causes of death.

Target-specific radiolabeled compounds, which bind with high affinity to specific protein structures (e.g., active places in enzymes or receptors), represent effective probes in a recognizing and visualizing tumor cells in their early stage. All types of malignant solid tumors often exhibit lower oxygenation levels than their original tissues resulting in a hypoxic state. Hence, there is an urgent need to enhance detection approaches for a monitoring of various tumor types, including hypoxic cancer lesions. In this field, amino acid-based target-specific radiopharmaceuticals have become significant tools in modern oncology allowing cancer imaging on molecular and cellular level.[1]

The aim of this entry is to summarize the most significant outputs related to the development of target-specific radiometal labeled biomolecules for imaging of severe tumor types and tumors with an increased incidence, including the most employed bifunctional chelating agents and peptide families and receptors such as somatostatin, cholecystokinin/gastrin, bombesin, integrins, and hypoxia endogenous markers, as well as inhibitors of prostate-specific membrane antigen and fibroblast activation protein.

2. Metal Radionuclides and Chelators Currently Used in Nuclear Medicine

Radiometallic compounds with targeted biodistribution and binding in the human body (i.e., target-specific) include in their structure: (i) biomolecules as a crucial biodistribution component (specific to receptor); (ii) a linker as a connecting component preserving specificity of biomolecule when attaching; (iii) a bifunctional chelating agent (BFCA); and (iv) metal radionuclides (see Figure 1).

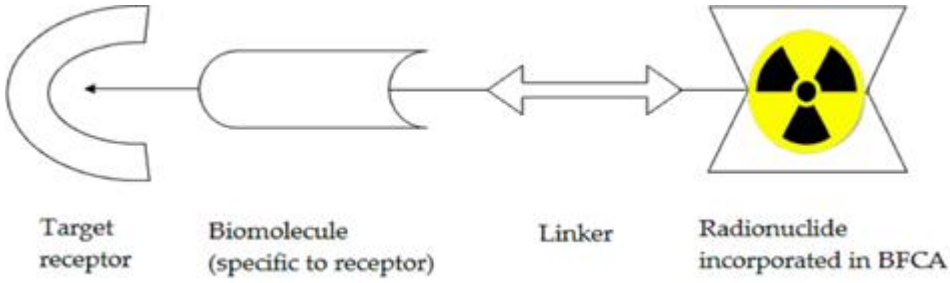

Figure 1. Basic scheme of a potential target-specific radiopharmaceutical.

2.1. Metal Radionuclides

Metal radionuclides belong to the most powerful and the most employed labels in nuclear medicine. Nuclear medicine research is currently focused on development of a highly potent target-specific biomolecule labeled with positron emitters, predominantly gallium-68, but also copper-64 and others. Apparently, other potential radionuclides such as zirconium-89, yttrium-86, and cobalt-55 have been included in recent studies. Anyway, there is still a leading position of technetium-99m in diagnostic clinical practice. In research, a prognosis for the development of Tc-radiopharmaceuticals is also quite positive due to novel modifications of BFCA and linkers continuously presented and developed for SPECT imaging. Basic parameters of the most common metallic radionuclides for diagnostic nuclear medicine are summarized in Table 1.

Table 1. Selected metallic radionuclides employed in diagnostic nuclear medicine.

Isotope	Radiation Type	E_{max} [keV] (Decay %)	Half-life	Production (Common Reaction)
^{99m}Tc	γ	141 (89.1%)	6.01 h	^{99}Mo/^{99m}Tc generator (cyclotron alternatively)
^{111}In		171.3 (90.2%)	2.83 d	cyclotron, ^{112}Cd(p, 2n)^{111}In

		245.4 (94%)		
^{67}Ga		93.3 (37%), 184.6 (20.4%), 300.2 (16.6%)	3.26 d	cyclotron, ^{68}Zn(p, 2n)^{67}Ga
^{64}Cu		653 (17.6%)	12.7 h	cyclotron, ^{64}Ni(p, n)^{64}Cu
^{68}Ga	β^+	836 (89%)	67.7 m	^{68}Ge/^{68}Ga generator (cyclotron alternatively)
^{89}Zr		395 (23%)	3.3 d	cyclotron, ^{89}Y(p, n)^{89}Zr

2.2. Bifunctional Chelating Agents (BFCA)

Since the metallic radionuclides themselves cannot be utilized in a direct radiolabeling of amino acid-based target-specific compounds (peptides, proteins), it is necessary to develop bifunctional chelating agents (BFCA) [2]. An appropriate BFCA can properly attach both a metallic radionuclide and a biomolecule. The double function of BFCA helps the biomolecule to retain its receptor specificity and to match metal properties with the intended utilization in the imaging / therapy of various diseases.

Various acyclic and cyclic BFCA have been introduced into (potential) radiopharmaceuticals. Traditional examples of acyclic and cyclic BFCA are discussed in this Section (for selected representatives see Figure 2), while the newer developed BFCA in Sections 3.1.-3.2.

From a group of acyclic BFCA, the polyaminopolycarboxylic acids-derived molecules, such as DTPA, EDDA, EDTA, as well as tripeptide MAG3, are the most commonly used acyclic BFCA containing hard donor atoms (N,O) in their molecule to form the coordination bond with metallic radionuclide. Another acyclic chelator, a siderophore-based desferrioxamine-B (DFO) has been utilized for effective radiolabeling of biomolecules with a metal. A significant advantage of the acyclic BFCA is faster metal binding kinetics, resulting in a faster radiolabeling procedure [3]. On the contrary, acyclic BFCA form less stable complexes than cyclic ones due to a higher interaction probability and more fixed geometry of donor atoms in the cyclic BFCA [4]. The cyclic BFCA are beneficial generally by providing more kinetically inert and thermodynamically stable complexes with metal radionuclides.

The cyclic BFCA containing macrocycle such as DOTA, NOTA, TETA, and their derivatives as well as various structurally related analogues are holding an important position in syntheses of radiolabeled peptide-based

compounds over a long period. Abrams and co-workers used 6-hydrazinopyridin-3-carboxylic acid, in short HYNIC, for radiolabeling of a polyclonal antibody with technetium-99m [5]. Ever since, HYNIC has become the most convenient chelator for ^{99m}Tc-labeled peptides and antibodies. Other chelators related to bisthiosemicarbazone [6][7], cyclam [8][9], and sarcophagine [10][11] have been increasingly studied to improve kinetic inertness and stability of complexes, especially those with copper isotopes. Several new next generation cyclic chelators or chelators derived from traditional ones with improved properties have been developed over past decade such as PCTA, AAZTA, TRAP, THP, and fusarinine C [12].

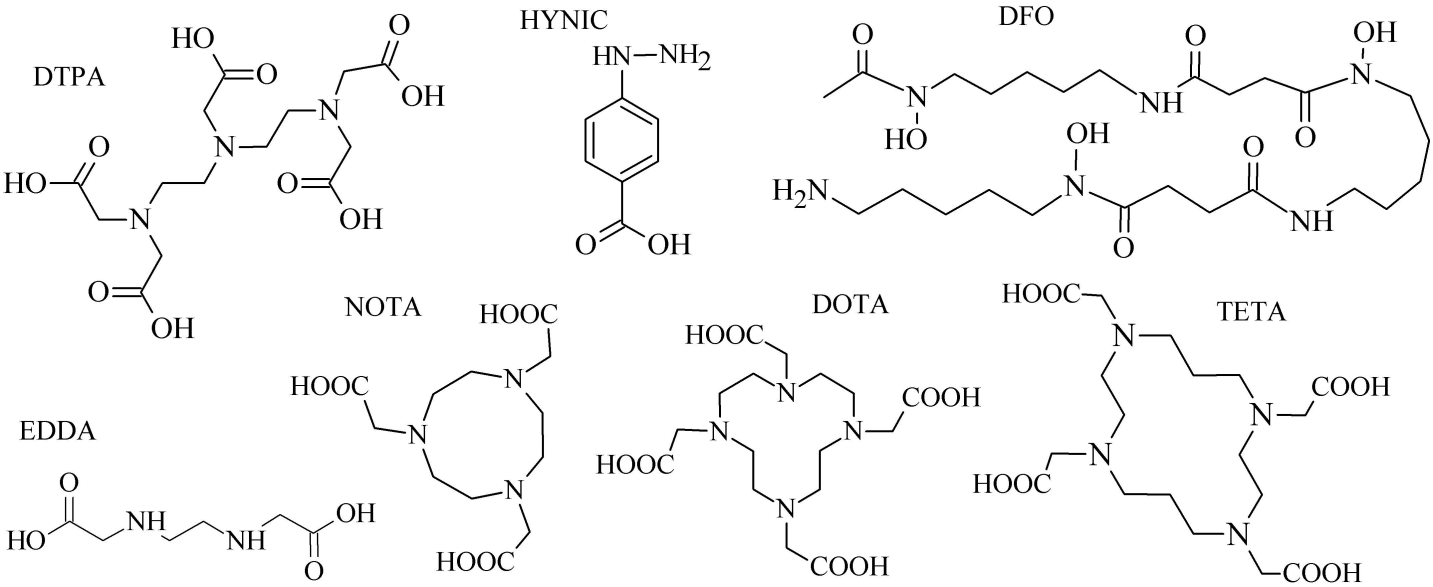

Figure 2. Chemical structures of the most common acyclic and cyclic chelators as a base of BFCA.

3. Radiolabeling Approaches for Target-Specific Peptide Molecules

Radiolabeled peptides as amino acid-based biomolecules are in the center of interest in the field of nuclear medicine and pharmacy because their biological action is mediated upon selective binding to specific peptide receptors and transporters overexpressed in numerous tumor cells. These receptors have shown potential as a molecular target for tumor imaging or targeted therapy with radiolabeled peptides (for the most important onco-specific peptide receptors and radiolabeled peptides see Section 4). The following Subsections (3.1.–3.3.) are dealing with current radiolabeling approaches used for peptides.

3.1. Conventional Radiolabeling Approaches of Peptides with Metallic Radionuclides

The choice of a radiolabeling approach depends on radionuclide nature and a bioactive molecule. Since a direct approach is more difficult to be used for a metal attachment to biomolecules and provides low site-specific and unstable products [13], an indirect labeling method with BFCA has become preferred for a metal-peptide linkage.

Indirect labeling approaches, such as pre-labeling (metal labeling before conjugation with biomolecule) or post-labeling (metal labeling after conjugation with biomolecule), are of the routine for ^{99m}Tc-coordination. The pre-labeling procedure is very useful in research to prove the concept and define the chemistry, contrary to a clinical use because of a long lasting radiosynthesis and hardly accomplished kit formulation [14]. In past few years, [^{99m}Tc]Tc-HYNIC, DTPA and MAG3 have been the most commonly used core for the conventional radiolabeling of bioactive peptides for tumor imaging.

For a ^{68}Ga-labeling procedure, nitrogen and oxygen donor groups of carboxylates, hydroxamates, amines are coordinated. Well-known representatives and the most frequently used BFCA are derived from 1,4,7-triazacyclononane and 1,4,7,10-tetraazacyclododecane, e.g., DOTA and NOTA, including their recently developed derivatives such as TRAP, PCTA, NOTP, and THP and DATA.

Indium-111 has several properties for coordination chemistry with gallium-68 in common. Softer donor groups can be offered to create seven or eight-coordinated complexes [49]. The DTPA- and DOTA-based chelators usually in *t*-butyl forms are generally the most employed for the ^{111}In-labeling [15].

The design of copper radiopharmaceuticals has put emphasis on polyaza-macrocycles derived BFCA such as cyclam, sarcophagines, tiosemicarbazones. Due to only moderate stability of [^{64}Cu]Cu-DOTA-labeled biomolecules under in vivo conditions and high liver accumulation, a number of cross-bridged cyclam derivatives were developed to form more stable ^{64}Cu-complexes [16].

Zirconium prefers anionic oxygen donor groups to create complexes with high coordination number [17]. In order to effectively utilize zirconium-89, various chelators have been employed such as DOTA, DTPA, as well as the most successful desferrioxamine B and 3-hydroxypyridin-2-one derivatives.

3.2. Radiolabeling Approaches of Peptides with Metallic Radionuclide Based on Click-Chemistry

There are two main characteristics making the click chemistry attractive, i.e., the bioorthogonality of reactions and mild reaction conditions (usually at room temperature and in aqueous media) [18]. Additional benefits include the selectivity, rapidity, and modularity of click ligations. Mindt et al. developed and extended the “click-to-chelate” methodology for radiometallic ligation [19][20].

The most commonly used term in click chemistry is copper-catalyzed azide-alkyne cycloaddition (CuAAC, Figure 3A). In recent years, several catalyst-free site-specific reactions have been investigated for effective radiolabeling of peptide biomolecules and nanomaterials including tetrazines and trans-alkenes for the inverse electron-demand Diels–Alder reaction (IEDDA), azide and cyclooctyne functionalities for the strain-promoted azide-alkyne cycloaddition (SPAAC), and functionalized phosphanes for the Staudinger ligation (Figure 3B–D) [21][22][23].

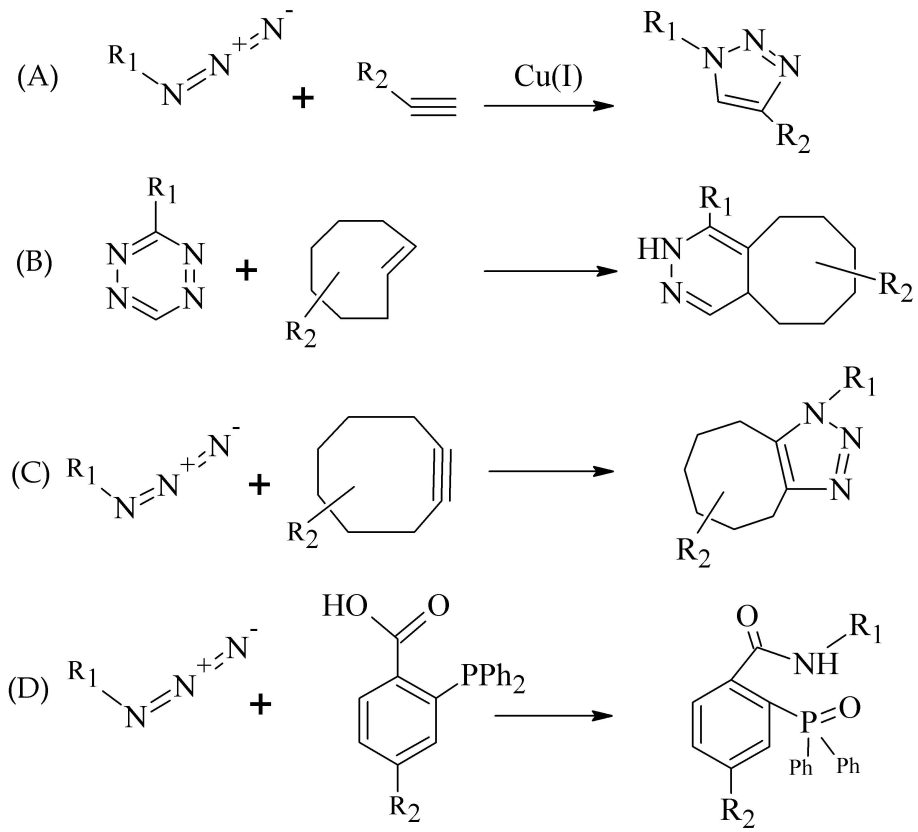

Figure 3. Selected click reactions for the preparation of intermediates used for metal chelating (R_1, R_2 - proper chelating and peptide moieties). (A) CuAAC, (B) IEDDA, (C) SPAAC, (D) Staudinger ligation.

Within the “click-to-chelate” methodology, the development of new clickable chelators is currently attracting a growing interest. New clickable chelators have been designed for ^{99m}Tc-labeled peptides, as well as for ^{68}Ga- and ^{64}Cu-labeled probes to obtain an increased hydrophilicity and decreased hepatobiliary retention (see examples in Figure 4).

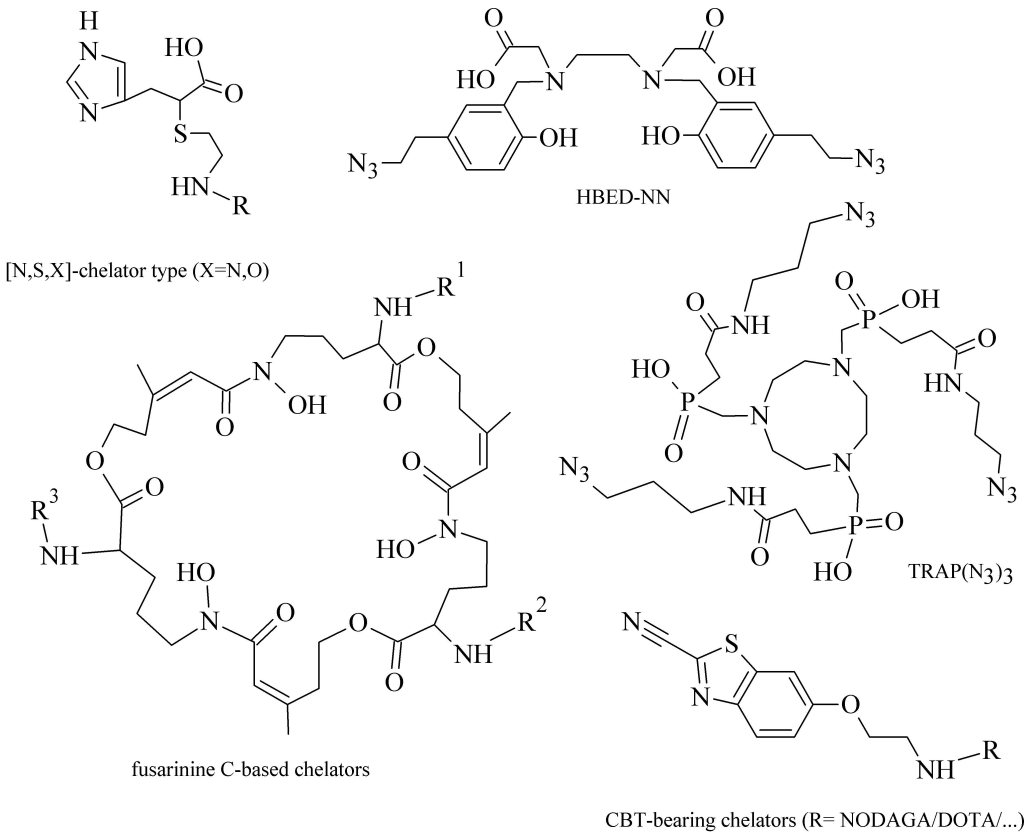

Figure 4. Examples of attractive clickable chelators for radiolabeling of biomolecules with metal radionuclides [24][25][26][27][28].

3.3. Radiolabeling Approaches of Peptides with Metallic Radionuclide Based on Nanoparticles

Over past 10 years, tens of articles have been focused on the metal-labeled nanoparticles (NP) conjugated to various peptides for SPECT and PET cancer imaging (see a representative image of radiolabeled nanoparticles using electron microscopy in Figure 5).

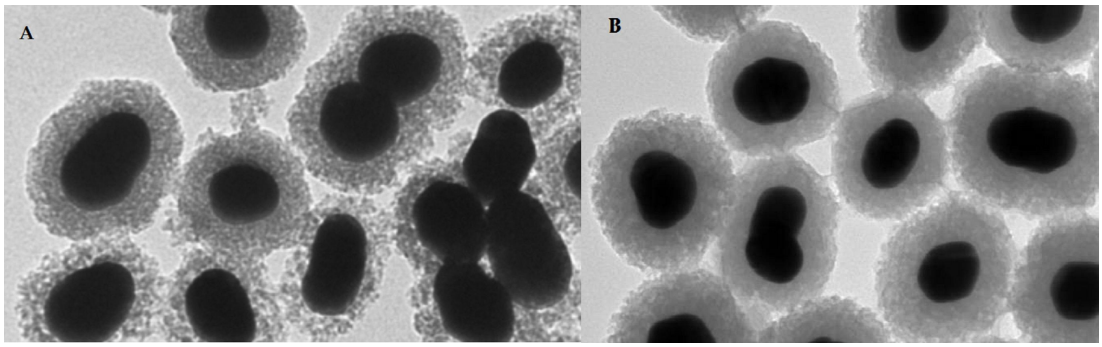

Figure 5. Representative image of PET-SERRS nanoparticles with non-optimized ^{68}Ga-labeling (A) with visible degradation of silica shells and after the optimization (B) with improved stability of the silica shells [29].

An indirect method has been much more preferred for the radiolabeling of NP with metals. In the indirect method, BFCA is necessary to allow a stable linkage between radionuclide and NP [30]. Gold NPs have been conjugated to peptides with [^{99m}Tc]Tc-HYNIC for integrin-positive glioma imaging [31], with [^{99m}Tc]Tc-DTPA for breast cancer

imaging [32], for gastrin releasing peptide receptor imaging [33][34] and somatostatin receptor-positive neuroendocrine tumor imaging [35]. The ^{64}Cu- and ^{68}Ga-labeled NPs functionalized with a peptide were reported in several papers too. The multifunctional gold nanorod nanocarriers were bound with doxorubicin and conjugated to [^{64}Cu]Cu-NOTA-RGD [36]; [^{64}Cu]Cu-sulphide NPs conjugated to the pegylated bombesin [37]; [^{68}Ga]Ga-DOTA-somatostatin and neurotensin analogues to gold NPs [38]; [^{68}Ga]Ga-NODAGA-bombesin to the polyethylene glycol-coated ultra-small superparamagnetic iron-oxide nanoparticles [39]; and [^{68}Ga]Ga-DOTA-bombesin analogue conjugated to the *N,N,N*-trimethyl chitosan-coated magnetic nanoparticles [40].

4. Onco-receptors and Their Radiometal Labeled Peptides for Tumor Imaging

In this Section, the most commonly studied onco-receptors are summarized, showing significant radiometal labeled peptide ligands and inhibitors of tumor-related proteins in clinical trials for tumor imaging. An illustrative example of a study [41] of radiolabeled [^{68}Ga]Ga-OPS202 and [^{68}Ga]Ga-DOTATOC biomolecules for neuroendocrine tumors imaging is in Figure 6.

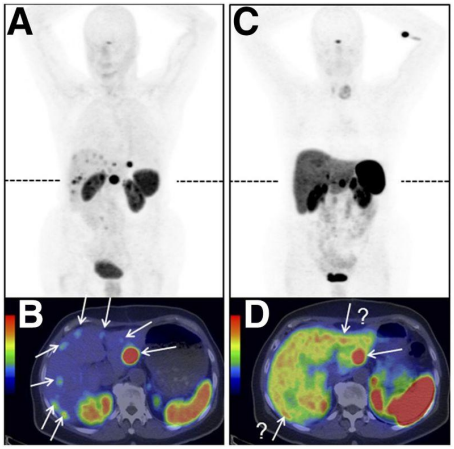

Figure 6. PET/CT images of a patient with ileal neuroendocrine tumors showing bilobar liver metastases (marked with arrows) after application of [^{68}Ga]Ga-OPS202 (A) and its transaxial fusion image (B) and [^{68}Ga]Ga-DOTATOC (C) and its transaxial fusion image (D) (adapted from [41]).

Many peptide compounds with high affinity to their receptors as molecular targets have been investigated over years including somatostatin and its analogues for somatostatin receptors (SSTR) imaging, bombesin (BBN) and its analogues for gastrin-releasing peptide receptor (GRPR) imaging, cholecystokinin and its analogues for cholecystokinin receptor (CCKR) imaging, exendin analogues for glucagon-like peptide 1 (GLP-1) receptor imaging, RGD analogues for $\alpha_v\beta_3$ integrins imaging, and other important peptide analogues, i.e. neurotensin, α-melanocyte stimulating hormone (α-MSH), substance P, and vasoactive intestinal peptide analogues.

Table 2. The amino acid sequences of the most commonly studied peptide ligands for onco-receptors.

Peptide	Amino acid sequence

somatostatin	Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys (3-14) disulfid
bombesin	Glp-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2
cholecystokinin	Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH_2
glucagon-like peptide 1	His-Asp-Glu-Phe-Glu-Arg-His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-NH_2
RGD	Arg-Gly-Asp
neurotensin	Glp-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-NH_2
α-MSH	Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2
substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2
vasoactive intestinal peptide	His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2

The peptide receptors regulate various endocrine and exocrine secretion throughout a human body. Under pathological conditions, peptide receptors are overexpressed in many tumor types such as SSTR in GEP-NET, pituitary adenomas, breast cancer, small-cell lung cancer, melanoma [42][43][44][45][46]; GRPR in breast, lung, pancreas, colon, and prostate [47][48][49]; CCK2R in small cell lung cancers and medullary thyroid carcinomas [50]; GLP-1R in insulinomas, gastrinoma, pulmonary NET, and medullary thyroid cancer [51][52]; and $\alpha_v\beta_3$ integrins associated with angiogenesis, tumor growth, invasion, and metastasis in breast, non-small cell lung, pancreatic, ovarian, and prostate cancer, oral squamous cell carcinoma, or glioma [53]. Another common feature for tumor development and progression is hypoxia, a phenomenon when a level of oxygen is below its demands. Hypoxia is a key component in cellular expression, tumor blood vessel formation, cancer progression, metastasis, often

leading to cell death. Many studies have been comprised of radiolabeled small nitroimidazole derivatives [54][55][56][57], small sulfonamide- and peptide-based biomolecules [58][59][60] and monoclonal antibodies [61][62], resulting in a development of new agents capable of accessing to overexpressed proteins under hypoxic state (i.e., hypoxia inducible factor HIF-1 regulated genes for carbonic anhydrase CA IX, vascular endothelial growth factor, angiopoietin-2, etc. [63]). A specific CA-binding of various 1,3,5-triazinyl-sulfonamide derivatives with amino-acid substituents has been demonstrated in our several recent works [64].

In recent years, inhibitors of cancer-related proteins based on small peptide biomolecules are widely developed and investigated such as prostate-specific membrane antigen (PSMA) and fibroblast activation protein (FAP) inhibitors. The PSMA is primarily expressed in benign and malignant prostatic tissue [65], but also in other tumor types including breast, gastric, and colorectal cancer, lung and renal carcinoma, and brain tumors [66][67][68][69][70][71]. The FAP overexpression has been observed in various malignancies, e.g., pancreatic, hepatocellular, lung, breast, colorectal, or ovarian [72][73][74][75][76][77]. Various radiolabeled small peptide-based inhibitors containing Glu-C(O)-Lys (EuK) sequence (Figure 7A) for PSMA targeting and FAP-inhibitors (FAPI) based on 2-cyanopyrrolidin-quinoline carboxamide (Figure 7B) have been recently developed to effectively localize and treat related tumors.

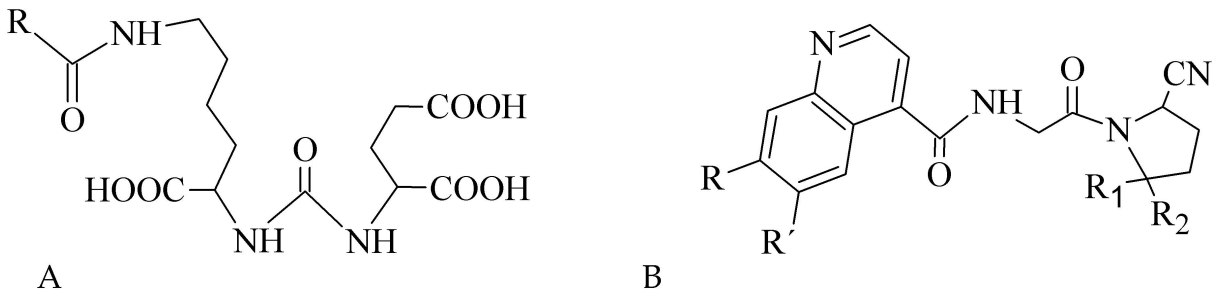

Figure 7. Structural motifs of small peptide inhibitors of proteins. (A) EuK motif as a base for PSMA inhibitors, (B) 2-cyanopyrrolidin-quinoline carboxamides as a base for FAP inhibitors.

Table 3. Summary of the most significant radiolabeled peptide analogues in recent clinical trials for receptor-positive tumor imaging.

Composition of Studied Compounds - Metal Radionuclide - BFCA - Linker	Results and Findings - Patients in Clinical Trials - Onco-receptor / Cancer Type Studied - Imaging Technique Used - Benefits/Limitations/Conclusion	Reference

- Peptide		
- ^{68}Ga - DOTA, NODAGA - x - JR11, TOC	- 12 patients - somatostatin rec. / GEP-NET - PET/CT - very high TBR and image contrast of liver lesions for [^{68}Ga]Ga-NODAGA-JR11; studies in larger patient group proven	[41]
- ^{68}Ga - DATA - x - TOC	- 53 patients - somatostatin rec. / GEP-NET - PET/CT - comparable imaging profile of [^{68}Ga]Ga-DATA-TOC with DOTA-NOC; DATA-conjugate useful for instant kit labeling	[78]
- ^{68}Ga - DOTA -4-amino-1-carboxymethylpiperidine - RM2	- 16 patients - gastrin-releasing peptide rec. / prostate - PET/CT, multiparametric MRI - fusion of MRI and PET/CT improved detection of a primary disease, but expression of GRPR and PSMA was not correlated	[79]
- ^{111}In - DOTA - x	- 16 patients - cholecystokinin rec. / advanced medullary thyroid - SPECT/CT	[80]

- (D-Glu$^{1-6}$)minigastrin	- high uptake in lesions and favorable dosimetry confirmed, but increased calcitonin concentrations in blood; initiation of ^{177}Lu-analogue assessment	
- ^{99m}Tc - HYNIC, tricine, TPPTS - x - RGD2	- 20 patients - $\alpha_v\beta_3$ integrins / breast - gamma camera - good uptake in breast lesions and also metastatic sites in lymph nodes visible in 2 patients - useful easily available kit for further clinical studies	[81]
- ^{68}Ga - THP - Ahx - EuK motif	- 118 patients - PSMA / prostate - PET/CT - PET/CT impacts on management decisions in high-risk prostate cancer prior to radical therapy and biochemical recurrence	[82]
- ^{68}Ga, ^{177}Lu - DOTA - piperazine - FAPI-02,-04	- 23 patients together - fibroblast activation protein / fibrosarcoma, pancreatic, breast, lung, colon, thyroid, head and neck - microPET, PET/CT - [^{68}Ga]Ga-FAPI-02 with TBR equal to or even better than [^{18}F]FDG, PET/CT with ^{68}Ga-probes can be performed without fasting and resting time	[83][84][85]
- ^{68}Ga - DOTA	- 80 patients - fibroblast activation protein / 28 different tumor entities	[86]

- piperazine - FAPI-04	- PET/CT - the highest uptake in breast, esophagus, lung, pancreatic, head-neck, and colorectal cancer; FAPI limitations similar to those of FDG for renal and thyroid cancer	
- ^{68}Ga - DOTA - piperazine - FAPI-04	- 68/75 patients - fibroblast activation protein / different tumor types - PET/CT - higher TBR of FAPI compared to FDG for brain metastases, FAPI identified more lesions for hepatic and peritoneal tumor manifestations, and had higher sensitivity in a detection of lymphonodal, osseous and visceral metastases	[87][88]

5. Concluding Remarks and Future Perspectives

In this entry, recent advances in the radiolabeling process of amino-acid based biomolecules, the most commonly used metal radionuclides, their chemistry and BFCA, as well as the most important peptide receptor families (including currently the most perspective field of PSMA and FAP ligands), were discussed. Continual efforts in proposing new structures with improved pharmacokinetic properties for selective targeting of cancer cells and effective utilization in imaging techniques should be guaranteed. The disease imaging on a molecular level, as well as radionuclide availability on-site, lower radiation burden, detection of early stage problem, and monitoring of a response to treatment in the combination with targeted therapy for a personalized approach to a patient, have a great potential to bring additional valuable outputs in the field of nuclear medicine in future.

Over the past years, great progress in a radiolabeling with metallic radionuclides has been demonstrated. Optimized structures of some of the newly developed radiolabeled biomolecules should provide enhanced affinity and selectivity to the onco-receptors, lower radiation dosage for patient, decreased interactions with other drugs or physiological proteins, without misrepresenting results, and, by that, a more favorable utilization in diagnostic nuclear medicine over other imaging techniques (e.g., MRI, CT). Current research is directed towards peptide radiolabeled agents that are aimed at proteins overexpressed in pancreatic, colorectal, prostate, and brain tumors. These types belong to the most frequently diagnosed and the most severe cancers. The integrin $\alpha_v\beta_3$ receptors from traditional receptor families and PSMA, as well as FAP ligands are very attractive and perspective probes due

to their intense association and overexpression within a variety of cancer cells and new vasculature in general, and so tumor growth, proliferation, and metastasis.

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