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Radiometal-theranostics: the first 20 years*

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Abstract
This review describes the basic principles of radiometal-theranostics and its dawn based on the development of the positron-emitting ^{86}Y and ^{86}Y-labeled radiopharmaceuticals to quantify biodistribution and dosimetry of ^{90}Y-labeled analogue therapeutics. The nuclear and inorganic development of ^{86}Y (including nuclear and cross section data, irradiation, radiochemical separation and recovery) led to preclinical and clinical evaluation of ^{86}Y-labeled citrate and EDTMP complexes and yielded organ radiation doses in terms of mGy/MBq ^{90}Y. The approach was extended to [$^{86/90}$Y]Y-DOTA-TOC, yielding again yielded organ radiation doses in terms of mGy/MBq ^{90}Y. The review further discusses the consequences of this early development in terms of further radiometals that were used (^{68}Ga, ^{177}Lu etc.), more chelators that were developed, new biological targets that were addressed (SSTR, PSMA, FAP, etc.) and subsequent generations of radiometal-theranostics that resulted out of that.

Keywords Theranostics · Radiometals · Positron emission tomography (PET) · Radionuclide therapy (RNT) · Endoradiotherapy (ERT) · Peptide receptor radionuclide therapy (PRRT) · Radiopharmaceuticals · Radiotracers

Introduction

The term "theranostics" overlaps with terms such as "personalized medicine" or "precision oncology" insofar as medical decisions, procedures and/or products are tailored to the individual patient. This includes technologies to produce customized pharmaceutical products that contain individual dosages for one or more active ingredients. Diagnostic tests used to select appropriate therapies are referred to as "companion diagnostics".

In the context of radiopharmacy and molecular imaging, the concept is particularly succinct: the ultimate object is successful therapy with appropriate short-range particle emitters (α or β^-), crucially built on therapy-deciding and -accompanying diagnosis with photon emitters.

With the goal of patient-specific treatment, potent radiopharmaceuticals are used in a diagnostic (ideally using positron emitters for quantitative PET/CT) and a therapeutic variant. The diagnostic radiopharmaceutical is used to verify tumor indication and staging for an individual patient. Conversely, it verifies that the radiopharmaceutical at hand is a target-specific and selective molecule: the ideally suited for a specific patient. Precise diagnostic imaging also allows quantitative dosimetric information (expressed in terms of maximum radiation dose to the target tissue and tolerable dose to healthy organs) for the therapeutic variant of the theranostic agent. This is applied with optimal radioactivity of the appropriate radiopharmaceutical in the individual patient. Finally, post-therapeutic imaging with the diagnostic variant of the theranostic is part of the assessment of treatment success for the individual patient.

In the context of radiopharmacy and nuclear medicine, radiopharmaceuticals available in both a diagnostic (usually for PET/CT) and a therapeutic form are the central instruments. The transition from the diagnostic to the therapeutic derivative is made by substituting the diagnostic radionuclide by its therapeutic counterpart—where the oncological target should be identical and the pharmacological properties of the two variants should not differ. In cases where

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the theranostic pair is from nuclides of different elements ("mismatched pair", e.g. gallium-68 and lutetium-177) the properties are not identical but very similar so the in vivo behaviour should not differ significantly. Radiotheranostics, by definition, share the same physiology in that they address the same oncologic target. Figure 1 gives an overview over four typical molecular design options from a radiochemical/radiopharmaceutical perspective.

Option A (Fig. 1A) represents the specificity of individual radioisotopes to already have an oncologically relevant function in its ionic form. This includes, above all, the historically first implementation of the theranostic concept—it dates back more than 80 years. *SAUL HERTZ* realized the concept of thyroid diagnostics and therapy in the form of a single radionuclide, which offers both diagnostically and therapeutically relevant radiation: ^{131}I [1, 2].

Additional "chemistry" is not required—the physiological function of the isotope in the form of iodide [^{131}I]I^- is sufficient. Another example of option A is the use of the calcium mimetics ^{89}Sr or ^{223}Ra for the therapy of bone metastases; here, the cations Sr^{2+} or Ra^{2+} already have an effect due to their affinity for the hydroxyapatite structure of the bones too and are applied as chloride salts [^{89}Sr]$SrCl_2$ and [^{223}Ra]$RaCl_2$, respectively [3–5]. Diagnostic analogues such as ^{18}F as [^{18}F]F^-, ^{99m}Tc-bisphosphonates or modern ^{68} Ga-labeled bisphosphonates are all also effective "bone seekers" [6–11].

Option B (Fig. 1B) involves the rather rare clinically realized design of radiometallic-labeled complexes for therapy, where the physiological role is not from the metal but from a property of the ligand. Typical representatives are $^{186/188}$Re-HEDP complexes [12, 13].

Options C and D represent a paradigm shift. The transport function for the radioisotope to a concrete oncological target is taken over by a defined targeting vector (proteins such as antibodies, proteins as receptors, messenger analogues, inhibitors, amino acids, but also inorganic species). Now, neither the radioisotope nor the radiometallic ligand complex should have any physiological significance, but on the contrary should be physiologically inert to the greatest possible extent.

Option C applies to radiohalogens, especially ^{131}I. Clinically relevant cases are ^{131}I-MIBG and ^{131}I-labeled tyrosine derivatives for the therapy of glioblastoma and other diseases, respectively [14–17]. The radioiodine is introduced into the targeting vector in a covalent bond in such a way that the physiological role of guanidine or tyrosine is not diminished significantly. In the ideal concept of radiotheranostics, the substitution of ^{123}I or ^{124}I for the therapeutic isotope ^{131}I is sufficient to generate the potent diagnostic variant. Regardless of the type of iodine isotope, the pharmacokinetics of the theranostic remain absolutely identical.

Option D concerns radiometals. Unlike aliphatic or aromatic halogenation, the radiometal cannot be directly covalently coupled to a targeting vector, but requires a bifunctional chelating moiety. Docking such a relatively large chemical moiety to a small targeting vector can lead to major pharmacological interference (binding affinities, lipohilicity, etc.). Therefore, in terms of medicinal chemistry,

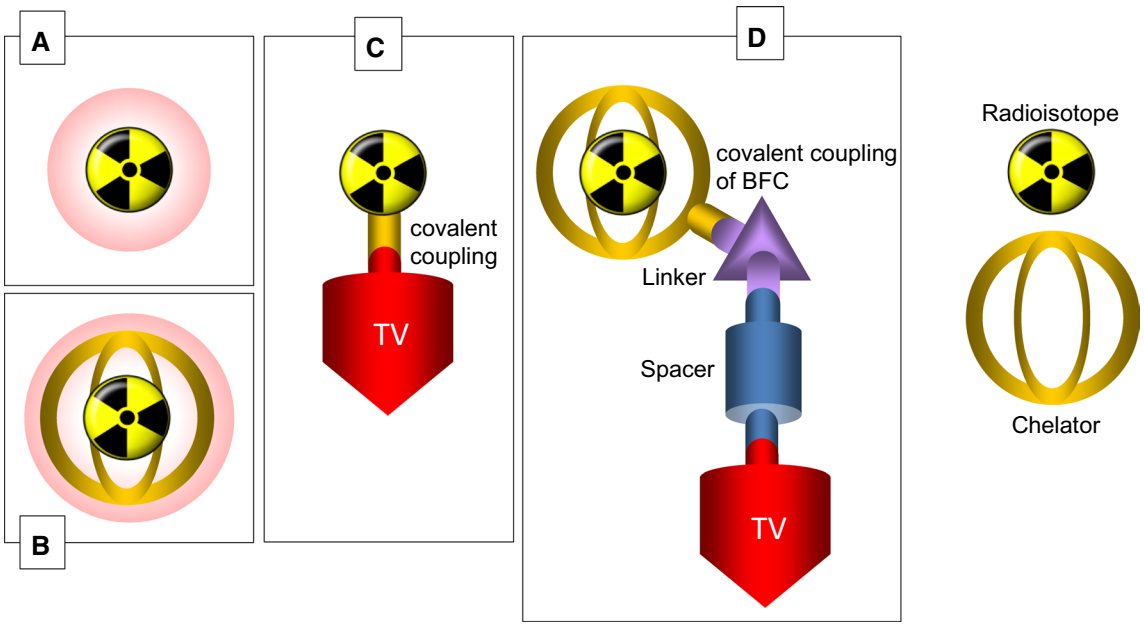

Fig. 1 Principal options of the molecular designs of Radiotheranostics. **A**: direct injection of radionuclide, **B**: injection of complexed radiometal, **C**: covalent coupling of a radionuclide to a targeting vector (red), **D**: radiometal complexed by bifunctional chelator (BFC) which is covalently bound by a linker to the targeting vector and a possible spacer

optimizations of the chelator, as well as in linker and spacer units, play a major role [18].

In nuclear medicine, the clinical routine of a theranostic application (its logical and logistical processes) can be represented in five stages.

Quantitative diagnostics (PET/CT) with the diagnostic derivative of the theranostic agent

First, disease and disease state are evaluated for an individual patient using an appropriate diagnostic radiopharmaceutical. Conversely, or simultaneously with this, it is verified that the radiopharmaceutical at hand is a target-specific molecule: the ideally suited for that individual patient.

Structural translation of the diagnostic into a therapeutic radiopharmaceutical

This central pillar of theranostics is the task of radiopharmaceutical chemistry. How to replace the positron emitter of the PET/CT form of the theranostic with a beta or alpha emitter without compromising the specificity of the radiopharmaceutical? This task is subdivided into sub-areas: (1) What is the appropriate combination of the diagnostic/therapeutic radionuclide? From this, (2) what are the chemical properties of the chosen theranostic radionuclide and how this must affect (3) the structure of the theranostic in terms of stable radiolabeling. Finally, (4) the appropriate structure must be characterized in vitro and in preclinical studies to demonstrate broad agreement in pharmacological properties with the diagnostic derivative of the theranostic.

Pretherapeutic dosimetry

Diagnostic imaging with the PET/CT form of the theranostic agent can be converted into quantitative dosimetric information in the form of time-activity correlations. In experimentally obtained time-activity correlations of the diagnostic derivative of the theranostic agent for healthy organs and lesions, the emission profile and physical half-life of the therapeutic radionuclide are now substituted. This is used to determine the optimal radioactivity (expressed in terms of maximum radiation dose to the target tissue and tolerable dose to healthy organs) of the appropriate radiotheranostic on the individual patient, cf. Figure 2.

Therapy

The therapeutic derivative of the theranostic is ideally applied at the activity level determined from the pretherapeutic dosimetry. This application can be repeated after appropriate times.

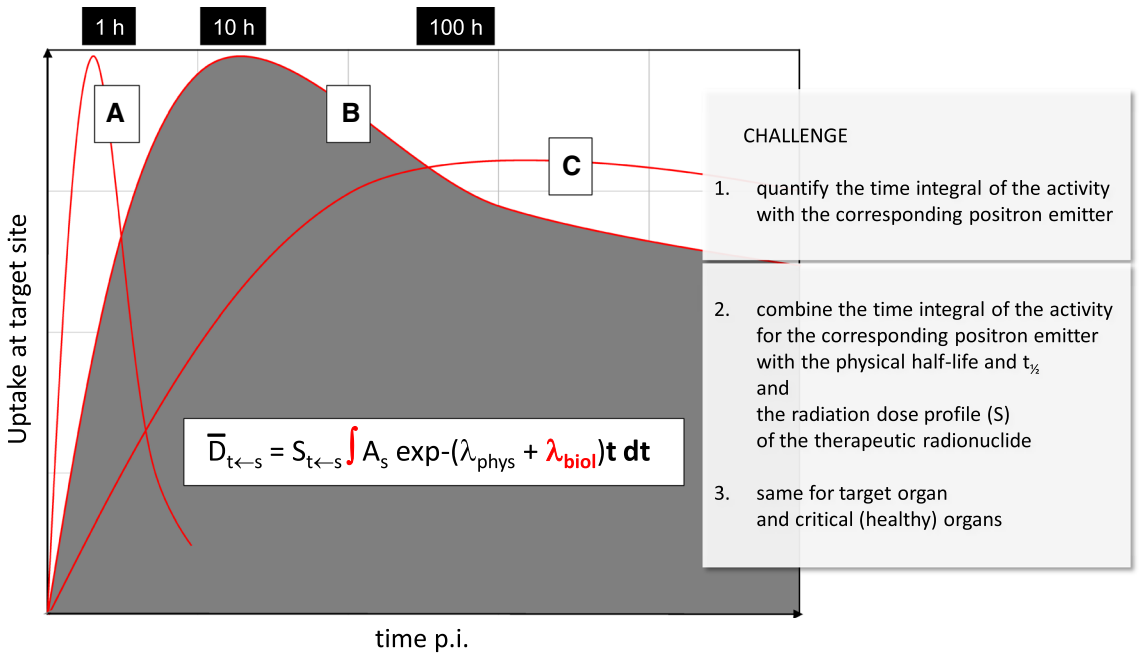

Fig. 2 Simplified illustration on the determination of radiation doses based on quantitative uptake kinetics obtained by the diagnostic PET tracer of the theranostic agent. **A**, **B** and **C** describe different pharmacology of the theranostic. The integral (e.g. the grey area for **B**) gives the cumulative radiation dose **D**, which is obtained from the kinetics, i.e. the biological and physical half-lives expressed by λ_{biol} and λ_{phys}, respectively. *S* is the S-factor representing transformation energies of a given radionuclides and *A* is the activity injected

Post-therapeutic monitoring

Usually, the outcome of therapy is followed by quantitative imaging with the diagnostic derivative of the theranostic agent. Ideally, lesion size and SUV values will have decreased compared to pre-therapy.

The 1990s: ^{86}Y/^{90}Y matched isotope pair and prototype of radiometal-based theranostics

Nuclear chemistry and physics know more than 3000 radioactive isotopes—in contrast, the number routinely used in the field of diagnostic as well as therapeutic nuclear medicine is small. This is due to the fact that important selection criteria such as type and energy of the emissions, physical half-life and, above all, availability have to be fulfilled together.

For PET, these would be the short-lived "organic" radionuclides ^{11}C, ^{13}N, ^{15}O, halogens such as ^{18}F, ^{124}I, and radiometals such as ^{82}Rb, ^{64}Cu, ^{68}Ga, ^{86}Y and others. In the field of therapeutics, ^{131}I, ^{89}Sr, ^{90}Y, ^{153}Sm, ^{177}Lu, ^{161}Tb, $^{186/188}$Re, ^{225}Ac and others are used. Realistically (i.e., if one does not want to speculate on further "exotic" nuclides whose transformation properties appear promising but whose availability for clinical routine is currently only wishful thinking) very few ideal combinations result from this selection.

Radioiodide [*I]I$^-$

Historically, the most important combination is, in fact, only one radionuclide—which offers both diagnostically and therapeutically relevant radiation. Radioiodine ^{131}I is one of the best-known radionuclides that can be used directly in its anionic form as iodide [^{131}I]I$^-$. Like nonradioactive iodide, it is accumulated in the thyroid gland. After administration, radioiodide is rapidly taken up by the thyroid via the sodium iodide symporter (NIS), and excess radioiodide is excreted renally. For administration, they are all formulated as sodium iodide in slightly basic aqueous solutions. They can be taken orally or administered by injection. Scintigraphic images of the thyroid gland allow identification of various diseases and dysfunctions of the organ, such as local foci of hyperthyroidism or hypothyroidism. Because of their long half-life, these iodine isotopes are usually provided by outside vendors for routine clinical use. For example, [^{131}I]NaI is usually supplied in capsule form with radioactivity already calibrated for specific patients. Several radioisotopes of iodine are suitable for molecular imaging and also enable PET (^{124}I) or SPECT (^{123}I, ^{131}I).

However, the spectrum of theranostically significant targeting vectors utilizing radioiodine is limited. A major challenge with radioiodinated compounds is the stability in vivo due to the weak C-I bond. Deiodination can be catalyzed by deiodinases, different enzymes like iodothyronine deiodinase (DIO1-3) for example, or proteolytic cleavage of peptides that contain iodine-substituted tyrosine units [19]. Cavina et al. gave an extensive review discussing the stability of radioiodinated pharmaceuticals depending on their molecular structures [20].

^{86}Y/^{90}Y

In the early 1990s, several laboratories began to consider using a SPECT radionuclide as a surrogate for a therapeutic radionuclide, e.g. ^{111}In ($t_{1/2}$ = 2.8 d), a trivalent metal, as a surrogate for ^{90}Y, another trivalent metal [21, 22]. The use of various other metallic radionuclides has also been discussed [21, 22].

While the β^--emitting therapeutic radionuclide ^{90}Y ($t_{1/2}$ = 2.7 d) had been available for a long time via the ^{90}Sr/^{90}Y generator system and was used for various therapies, there was no possibility of quantifiable imaging with ^{90}Y-labeled therapeutics at that time—the patient remained a “black box”. Therefore, the β^+-emitter ^{86}Y had to be first developed for medical use [23–25]. This included the evaluation and optimization of radionuclide production [23, 24], radiolabeling and its analytics as well as first pilot in vivo studies to learn about the in vivo quantification via PET [25]. With a half-life of $t_{1/2}$ = 14.7 h and a fraction of 32% positron emission it was suitable to reproduce the pharmacology of analogous ^{90}Y-pharmaceuticals well [26–32]. Rösch et al. [33] gives a retrospective overview of the various aspects of the radiochemical and nuclear development work including nuclear data, cyclotron irradiation, chemical processing, quality control, etc. of ^{86}Y and ^{86}Y-labeled pharmaceuticals, the methodology established to quantify the molecular imaging of ^{86}Y-labeled compounds in the form of multiple and long-term PET recordings, and finally, application examples that highlighted the ultimate goal of radiotheranostics, namely to determine the radiation dose of the ^{90}Y-labeled compound in mGy or mSv per MBq of ^{90}Y injected, based on the long-term PET measurements with ^{86}Y analogues (Fig. 3). Of historical note, in addition to the methodological aspect, is the specific demonstration of the approach for the case of [^{90}Y]Y-DOTA-TOC [29, 30]. Sandoz initially exercised the [^{86}Y]Y-DOTA-TOC program as a diagnostic arm of [^{90}Y]Y-DOTA-TOC before this entered the clinic. This was then realized first in baboons (Fig. 4) [29, 30] and later in patients (Fig. 5) [31, 34].

The 2000s: ^{177}Lu/^{68}Ga

Biological targets

The most important radiotracer for nuclear medicine oncology imaging is 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]

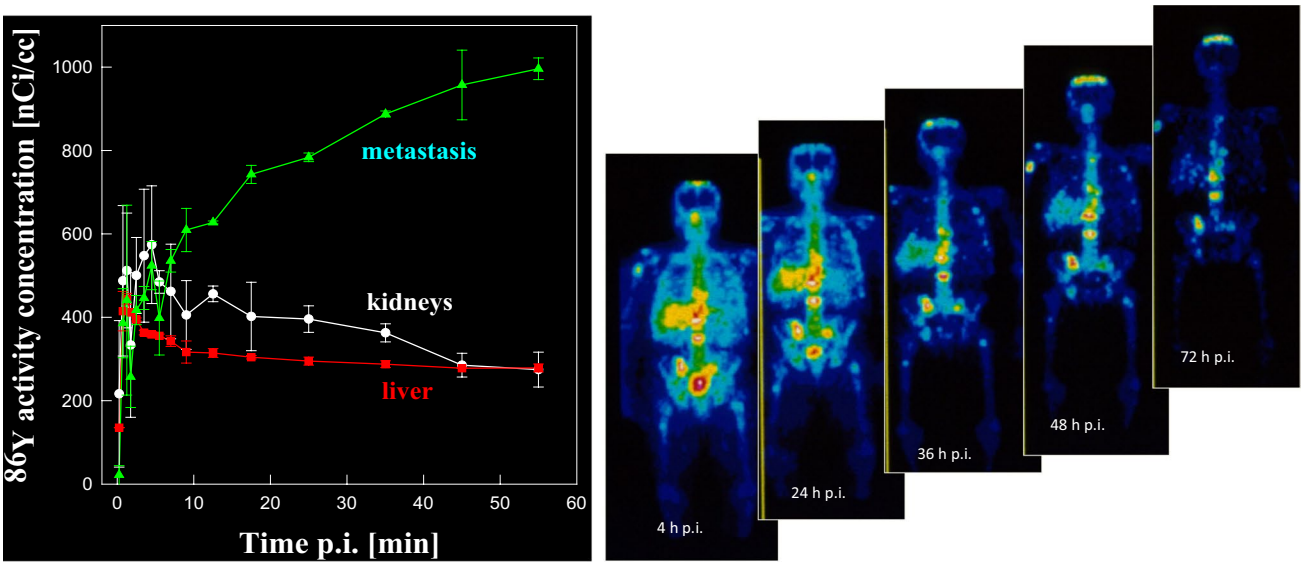

Fig. 3 [^{86}Y]Y-Citrate PET imaging in patient suffering from bone metastasis [26, 28]

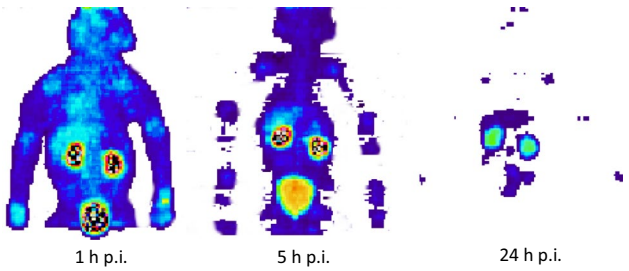

Fig. 4 [^{86}Y]Y-DOTA-TOC PET imaging in baboons [29, 30]

FDG). Cancer cells obtain their energy mainly through aerobic glycolysis which is very inefficient. To compensate for this, the glycolysis rate is upregulated as well as the oxidative phosphorylation (Warburg effect). [^{18}F]FDG is a glucose analogue which is likewise phosphorylated by the enzyme hexokinase. The [^{18}F]FDG-6-phosphate on the other hand cannot be metabolized further which results in an accumulation in the cancer cell (metabolic trapping) that can be visualized via PET. Consequently, this makes [^{18}F]FDG an almost universal oncological imaging tool. However,

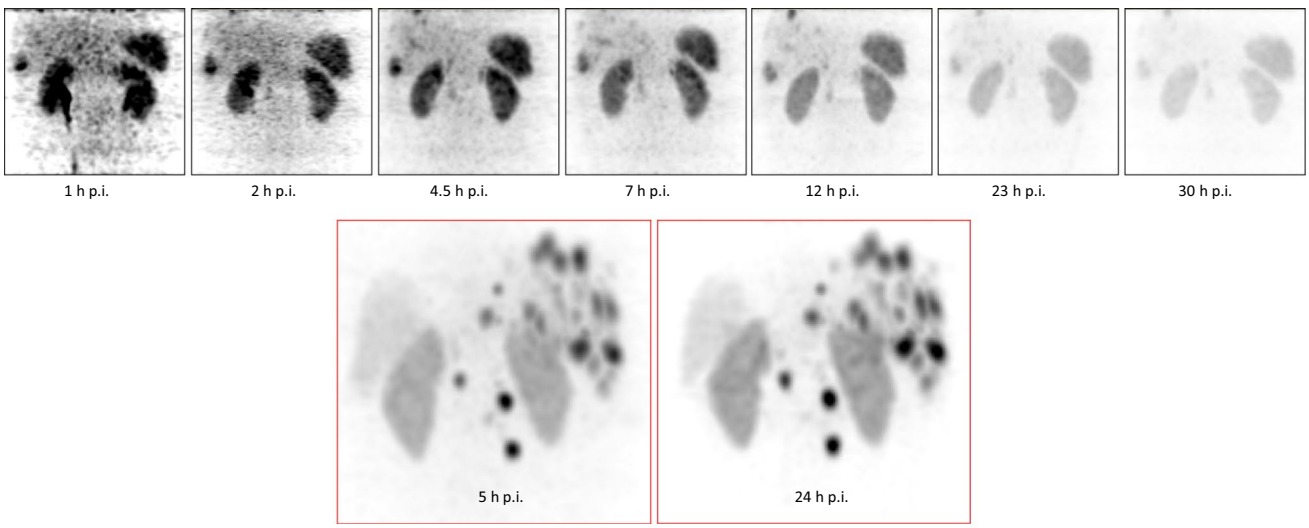

Fig. 5 [^{86}Y]Y-DOTA-TOC PET imaging in patients suffering from neuroendocrine cancer [31, 34]

radiopharmaceutical chemistry does not have a therapeutic counterpart of glycolysis metabolism. Therefore, for tumor therapy, alternative oncological targets need to be identified and the appropriate radiopharmaceuticals developed, ideally for both PET/CT imaging and therapeutics. Figure 6 provides a schematic overview of the relevant targets and classes of target vectors for this purpose.

Other targets are based on the increased metabolism and requirement of substances and building blocks for the high proliferation rate of tumor cells. Radiotracers as analogs of DNA and RNA building blocks are compounds such as 5-[^{18}F]fluorouracil, [^{11}C]thymidine, or 3′-deoxy-3′-[^{18}F] fluorothymidine, which allow determination of the proliferation status of tumor cells by PET imaging.

Another important mechanism for oncological targeting is enhanced amino acid transporter activity by tumor cells. *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET) and [^{11}C-methyl]-L-methionine are the most commonly used radiolabeled amino acid analogs. In the context of theranostics, iodinated analogs are another approach.

However, it appeared that the transmembrane receptors represent the most attractive target in radiotheranostics. Typically, the corresponding targeting vectors are radiometal-labeled tracers, which is in particular relevant for their therapeutic application. For diagnostic analogs, also ^{18}F-labeled modifications are being applied.

Radionuclides

The turn of the millennium saw a dramatic change in the theranostic isotopes utilized in the 1990s: The approach to produce carrier free ^{177}Lu and the appearance of the ^{68}Ge/^{68}Ga-radionuclide generator.

Although ^{90}Y was and still is an extremely important therapeutic isotope in theranostics and nuclear medicine in general, ^{177}Lu ($t_{1/2}$ = 6.65 d) became relevant because of the lower energy of the emitted β^- particles. The ^{176}Lu(n,γ) production pathway was easily established and gives good yields due to the high cross section, yet the content of ^{176}Lu carrier and the contamination with the long-lived isomer ^{177m}Lu appeared to be critical for theranostics targeting e.g. saturable oncological targets such as GPC receptors. The indirect ^{176}Yb(n,γ)^{177}Yb $\xrightarrow{\beta^-}$ ^{177}Lu production pathway suggested an alternative option [36]. It is now commercially realized at TBq scale and GMP levels [37].

With the start of the new millennium, the Obninsk team provided a ^{68}Ge/^{68}Ga-radionuclide generator providing the positron-emitting trivalent radiometal ^{68}Ga ($t_{1/2}$ = 68 min)

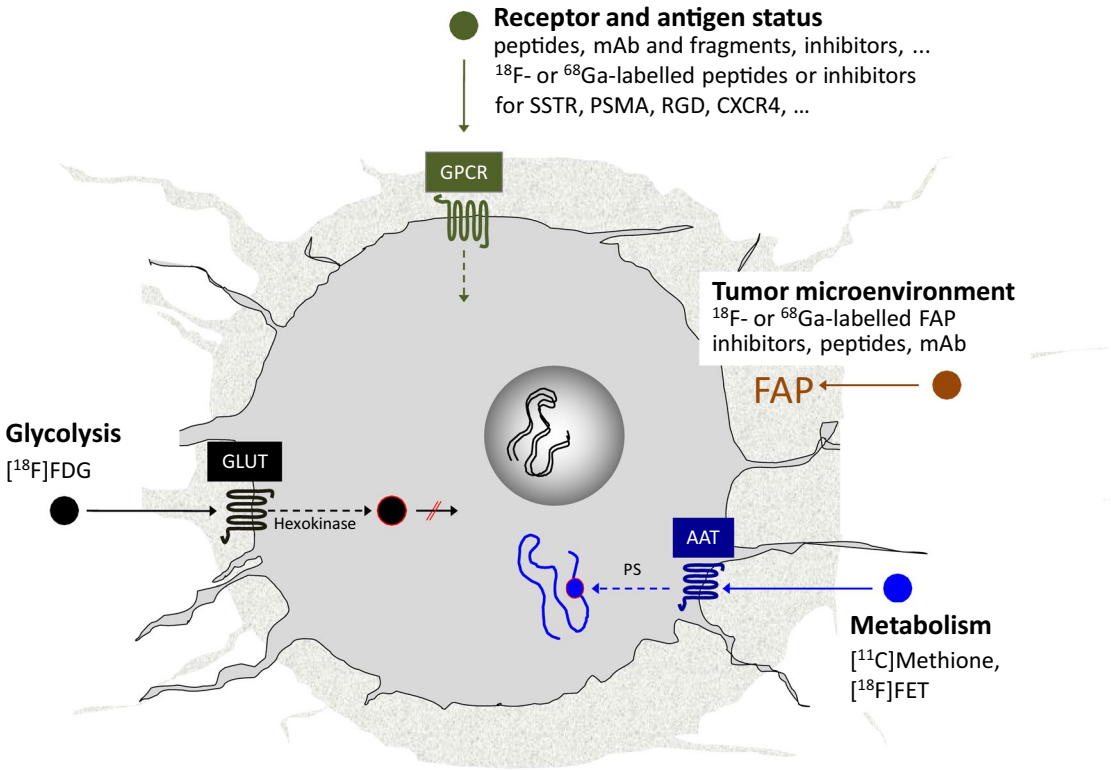

Fig. 6 Selected targets for PET imaging in oncology and corresponding radiotracers: 2-deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]FDG), *O*-(2-[^{18}F]fluoroethyl)-L-tyrosine ([^{18}F]FET). GLUT = glucose transporter, AAT = amino acid transporter, GPCR = G protein-coupled receptors, SST = somatostatin, mAb = monoclonal antibody, PSMA = prostate-specific membrane antigen, FAP = fibroblast activation protein, PS = protein synthesis [35]

in a chemical environment easily to label radiopharmaceuticals by its diluted hydrochloric acid eluent system and its low contamination levels of long-lived parent isotope ^{68}Ge ($t_{1/2}$ = 271 d) [38]. The post-processing chemistry introduced by Zhernosekov et al. [39] and Asti et al. [40] translated this generator to nuclear medicine. This was crucial to the increasing success of ^{68}Ga and its routine applications in PET diagnosis. This has been discussed in several reviews in detail, e.g. by Rösch and Riss [41] as well as Rösch and Baum [42], or different reports and book chapters [43, 44].

The 2000s: ^{177}Lu/^{68}Ga and theranostic octreotides for NET

A look at the surface proteins expressed by tumor cells reveals an astonishing number and variety of potential targets. The metabolism and other cellular functions of tumor cells appear to be completely unregulated. As a result, the expression of surface proteins is dramatically increased on tumor cells, which can easily reach a million-fold overexpression compared to normal cells. Moreover, several tumor entities (over)express (specific) transmembrane proteins that are hardly or only very restrictedly expressed in healthy tissues. Transmembrane receptors are large protein structures located in the cell membrane. These receptors have three main domains: the transmembrane, extracellular, and intracellular domains. The extracellular domain is the part of the cell surface that is recognized by specific ligands. In contrast, the intracellular domain is the part that generates a signal inside the cell by activating (effector) proteins or enzymes.

One prominent family is the G protein-coupled receptors (GPCRs), in which the intracellular domain is coupled to the so-called G protein, which is responsible for further signal transduction in the cell. Some GPCRs undergo endocytosis after ligand binding, which is a major advantage because it effectively traps the radiotracer inside the tumor cell.

Clearly, these surface structures are generally potential targets for tumor diagnosis and therapy. The most important transmembrane receptor class of the last decade in nuclear medicine is the human somatostatin receptor (hSSTR) family. Out of the five subtypes, hSSTR2 is the most important subtype, and to a much lesser extent hSSTR1, 3, and 5. hSSTRs are highly overexpressed in neuroendocrine tumors and some other human tumor types. Expression of hSSTR2 on tumor cells can reach 2.5-million-fold overexpression. Physiological expression of hSSTR2 in healthy tissues is very limited and is mainly found in the spleen. Therefore, hSSTR2 offers ideal properties as a target for tumor imaging (and therapy). In addition, the hSSTR family undergoes endocytosis after ligand binding, resulting in very efficient trapping of the ligand in the addressed cell.

The native ligand, somatostatin, is a peptide hormone of 14 or 28 amino acids (two isoforms). Somatostatin has a plasma half-life of only 2 min and is therefore unsuitable for molecular imaging. The truncated derivative octreotide, a much smaller cyclic peptide, has been developed as a somatostatin analog for the treatment of acromegaly and for the treatment of neuroendocrine tumors. In an initial approach, octreotide was conjugated to DTPA as a chelating system for radiolabeling with indium-111. ^{111}In-labeled DTPA-octreotide is available as Octreoscan© for SPECT imaging [45, 46]. Further developments led to the corresponding derivative, [DOTA^{o}-D-Phe^{1}-Tyr^{3}]-octreotide (DOTA-TOC), with the chelating agent DOTA for radiolabeling with various radiometals and a strongly enhanced affinity for hSSTR2 [47–50]. The theranostic pair ^{86}Y/^{90}Y was used for research and development as described in the previous chapter. [29–31, 34] Later on, for clinical routine application the theranostic pair was changed to ^{68}Ga/^{177}Lu due to the better availability of these radionuclides. Together with another variant, DOTA-TATE, DOTA-TOC is the major precursor for radiolabeled somatostatin analogs [51]. [^{68}Ga]Ga-DOTA-TOC/TATE are the most commonly used tracers in routine clinical practice for PET imaging of hSSTR2-positive tumors and metastases (cf. Figure 7).

Lessons to learn for the design of theranostic monomers

The key component is the system oncological target/specific targeting vector. The chelator is covalently attached either directly to the targeting vector (amid coupling is the preferred method usually utilizing a -COOH group at the chelator and an amine at the targeting vector).

A first lesson to learn was that for therapeutic application macrocyclic chelators are much better suited because of the thermodynamic and kinetic stability of the chelates, cf. ^{111}In-labeled DTPA-octreotide for SPECT imaging vs. ^{90}Y-, ^{177}Lu or ^{225}Ac-labeled DOTA-TOC/-TATE therapeutics [51]. Pioneering work by H. Mäcke and others revealed, that the chelate is influencing the pharmacology of the theranostic compound [52, 53]. Accordingly, careful tailoring of the chelator and the radiometal belong to the challenges in radiopharmaceutical chemistry. Figure 8 depicts some of the non-macrocyclic and cyclic chelators and some bifunctional derivatives introduced around the turn of the millennium.

The proof-of-principle peptidic radiometal theranostics: ^{90}Y-, ^{177}Lu-, ^{225}Ac-labeled DOTA-TOC/-TATE to treat neuroendocrine tumors: ^{90}Y-DOTA-TOC therapies of neuroendocrine started in the last years of the last millennium, and

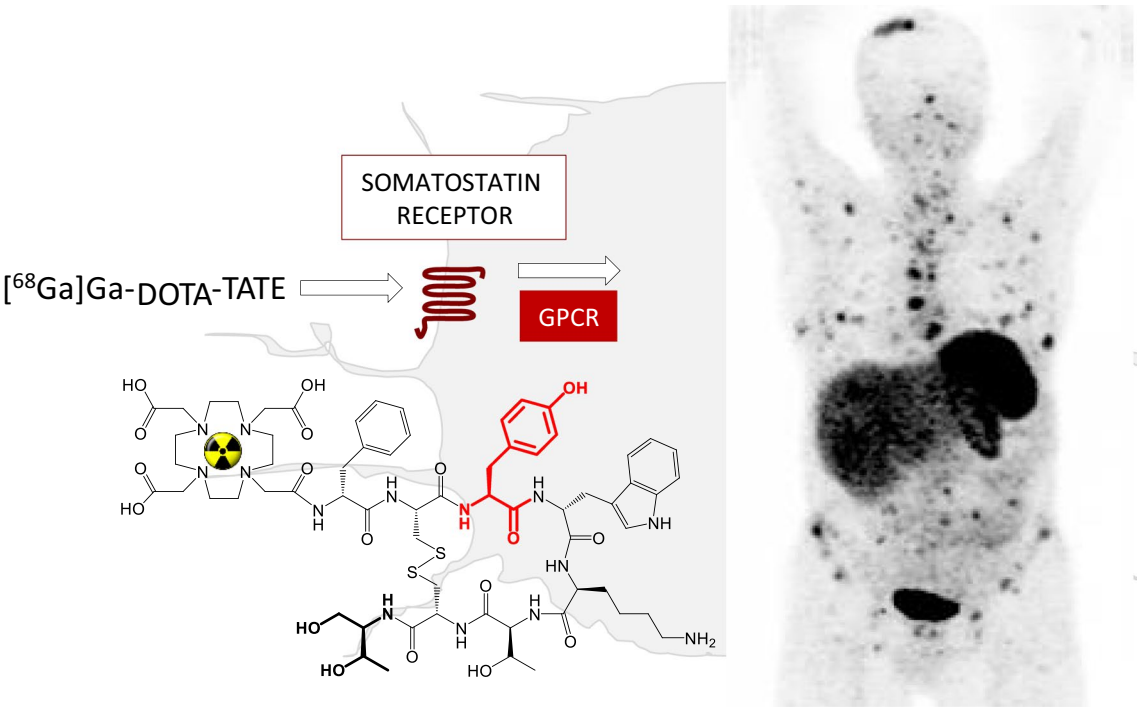

Fig. 7 PET imaging with [^{68}Ga]Ga-DOTA-TATE in patients suffering from neuroendocrine cancer [35]

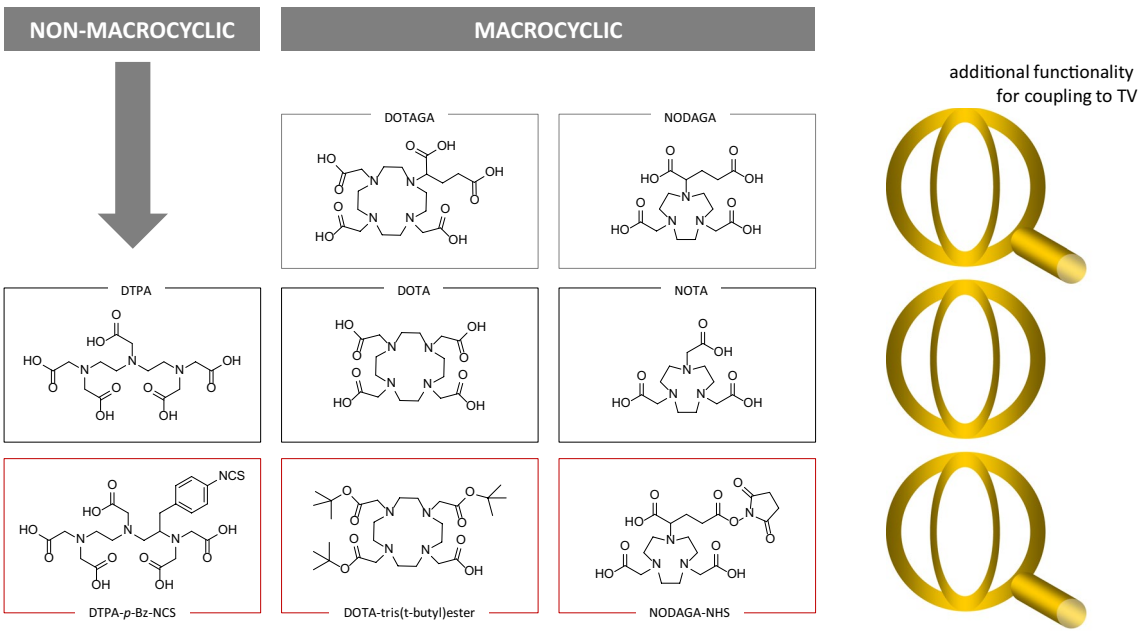

Fig. 8 Some of the non-macrocyclic and cyclic chelators and some bifunctional derivatives introduced around the turn of the millennium

systematic experiences were obtained in the 2000s [47, 48, 54–56]. Figure 9 gives a representative illustration of such applications. Obviously, the theranostic concept became a great success, and many patients benefited from this treatment. However, only decades later, this was validated by a systematic and successful clinical phase III study [57].

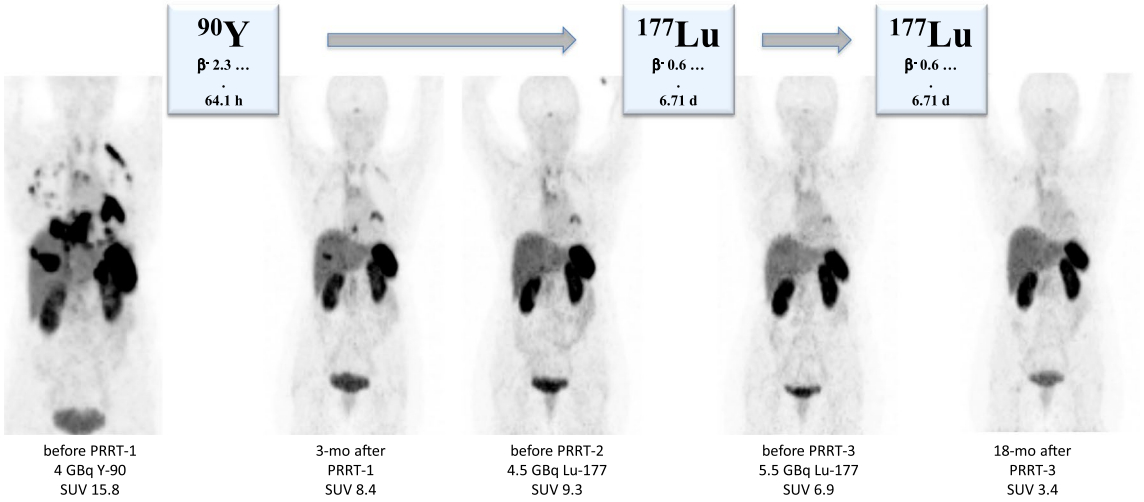

Fig. 9 ^{90}Y-DOTA-TOC therapies of neuroendocrine cancer; PRRT = peptide receptor radiation therapy. [^{68}Ga]Ga-DOTA-TOC PET images prior (left) treatment and after / between successive applications of first [^{90}Y]Y-DOTA-TOC followed by two cycles of [^{177}Lu]Lu-DOTA-TOC (Courtesy by R. P. Baum) [58]

The 2010s: more oncological vectors

In addition to the key/lock systems SSTR/octreotide derivatives for neuroendocrine tumors and PSMA/PSMA inhibitors for prostate cancer (PCa), there are other examples that have been validated for the diagnosis of other cancers in nuclear medicine. The chemical design is exactly the one of option D in Fig. 1. The key component is the system oncological target / specific targeting vector, while the chelator remains a common chelate.

PSMA/PSMA inhibitor

The prostate-specific membrane antigen (PSMA) has been identified as a suitable target for prostate cancer diagnosis and therapy. The corresponding binding motif is a PSMA inhibitor. Over time the very small peptidomimetic structure of Glu-urea-Lys (KuE) has established itself as the by far most commonly used PSMA-targeting vector. Several radiolabeled derivatives have been developed for molecular imaging with ^{18}F, ^{68}Ga and other radionuclides. The most successful and clinically used diagnostic ligand is the ^{68}Ga-labeled ligand from DKFZ Heidelberg, which uses an HBED chelate: PSMA-11 ((EuK)-Ahx-HBED-CC, see Fig. 11A) [59, 60]. A comparative study with [^{18}F]fluoromethylcholine showed a much higher contrast which enabled the visualization of small metastases despite low PSA levels [61]. Figure 10 shows PET imaging of prostate cancer with [^{68}Ga]Ga-PSMA-11.

Figure 11 shows three of the most common KuE-based radiopharmaceuticals routinely used for the diagnosis of prostate cancer by PET/CT.

PSMA-617 (Fig. 11 B) has a DOTA chelator which enables theranostic application in contrast to PSMA-11 which can only be labeled with ^{68}Ga for diagnostic PET. Unlike with [^{177}Lu]Lu-DOTA-TATE, where over 15 years have passed between the first application and the approval [51], the approval process [^{177}Lu]Lu-PSMA-617 is going a lot faster. Between the original unleashing in 2015 by Benesova et al. [62] and the start of the phase III clinical VISION trial in 2018 only 3 years and only 7 years until its recent approval passed [63]. Several big studies were published quickly in the early years which helped to accelerate the process [64, 65].

Besides that, efforts were made to establish ^{18}F-labeled PSMA-inhibitors where [^{18}F]F-DCFPyL was investigated heavily which lead to two phase III studies that resulted in a recent FDA approval [66, 67]. [^{18}F]F-PSMA-1007 (Fig. 11 C) has also increasingly found its way into clinical routine over the last few years [68–70].

Hydroxyapatite in bone metastases/ Bisphosphonates

Malignant tumors of the prostate, breast and other organs often lead to the formation of painful bone metastases in advanced stages. The disease is related to the activity of osteoblasts and osteoclasts, which are the active components of bone growth. The inorganic bone matrix itself consists mainly of calcium hydroxyapatite. Conventional drugs and diagnostic and therapeutic radiopharmaceuticals all share a high binding affinity to the inorganic matrix and/or the enzymes that regulate bone growth. Drugs for the treatment of osteoporosis are often used as bisphosphonate

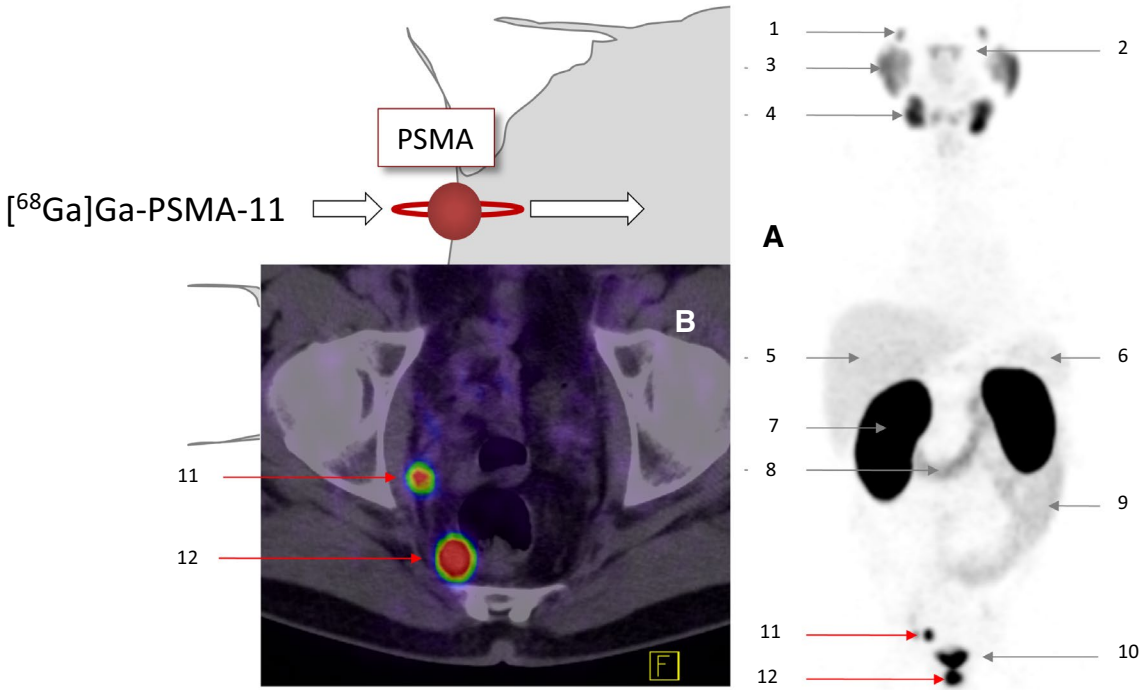

Fig. 10 [^{68}Ga]Ga-PSMA-11 PET imaging in patients suffering from prostate cancer [58]. **a** Maximum Intensity Projection (MIP) of a PET/CT at 1 h p.i. **b** Fusion PET/CT image. The primary prostate cancer tumor (12) as well as the lymph node metastases (11) can be visualized with a very high contrast (Courtesy of Afshar-Oromieh, DKFZ, Heidelberg, Germany) [35]

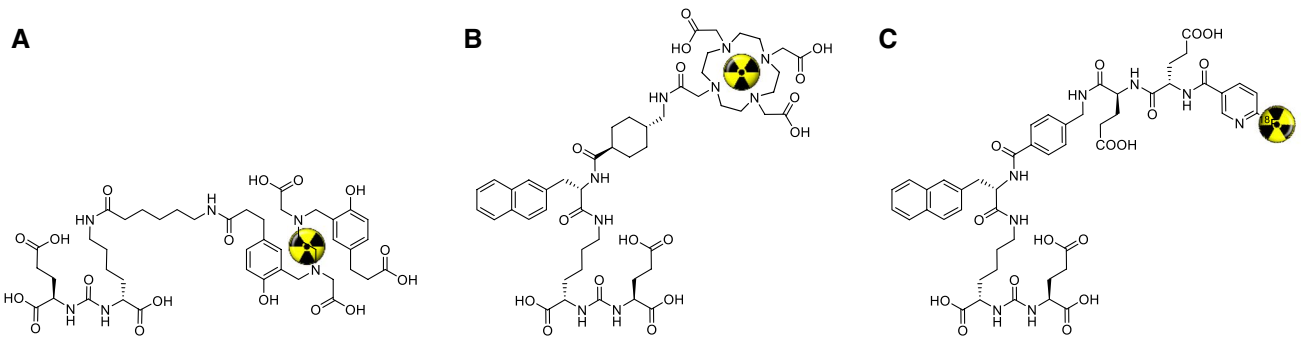

Fig. 11 Representative theranostic PSMA inhibitors: PSMA-11 labeled with ^{68}Ga (**A**), PSMA-617 labeled with ^{68}Ga, ^{177}Lu, ^{225}Ac and others (**B**), PSMA-1007 labeled with ^{18}F (**C**)

components. Bisphosphonates resemble pyrophosphate but are metabolically stable due to the replacement of the central oxygen atom with a carbon atom. In addition, this carbon atom allows the attachment of two functional groups. By using a hydroxy group as a substituent, the affinity for hydroxyapatite can be increased.

Utilizing bisphosphonates as a targeting vector, a series of theranostic tracers were developed with high binding potency to bone metastases. The first generation of bisphosphonates were the DOTA-conjugated precursors BPAMD, BPAPD and BPPED that were investigated as ^{68}Ga-labeled derivatives in PET diagnosis [7–9]. Further the precursor were labeled with the therapeutic nuclides ^{177}Lu- and ^{225}Ac and have been successfully applied in patient studies [11, 71–73]. Figure 12 shows the structure of BPAMD and its PET- and ERT-application in vivo.

CAFs / FAP inhibitors

In contrast to specific molecular tumor targets such as the somatostatin receptor in neuroendocrine tumors and the prostate-specific membrane antigen in prostate cancer, the

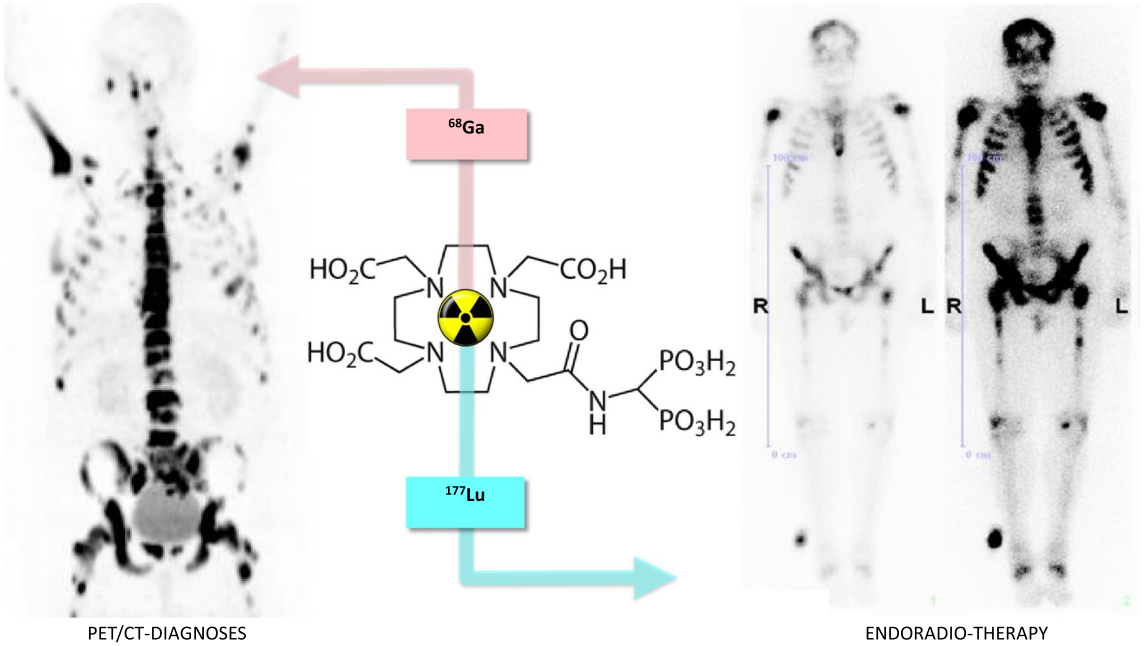

Fig. 12 BPAMD, a DOTA-conjugated first-generation bisphosphonate labeled with ^{68}Ga or ^{177}Lu and its use in theranostics of disseminated bone metastases [35]

tumor microenvironment has recently been identified as a suitable target for cancer diagnosis and therapy. Cancer is a heterogeneous disease that arises in an extremely complex microenvironment. Malignant tumors are composed not only of cancer cells but also of a large majority of endogenous host stromal cells (e.g., fibroblasts, vascular and immune cells) and extracellular matrix (ECM) components, collectively referred to as the tumor microenvironment (TME) [74]. The stromal cells within the tumor (tumor stroma) comprise the majority of the total tumor mass (up to 90%) and are connected by a desmoplastic reaction [75]. Among all cells within the TME matrix, fibroblasts are considered dominant cells whose biological functions play a strong role in all stages of cancer progression and metastasis. Cancer-associated fibroblasts (CAFs) are thought to have potent tumor-modulating effects and are found in most solid tumors. In general, CAFs account for up to 80% of all fibroblasts in TME. CAFs are identified by the expression of several specific biomarkers on their surface, such as SMA (Smooth Muscle Actin), S100A4 or FSP-1 (Fibroblast-Specific Protein 1), PDGFR/ (Platelet-Derived Growth Factor Receptors), and FAP (Fibroblast Activation Protein). Fibroblast Activation Protein alpha (FAPα or FAP), also known as Seprase, is a type II membrane-bound serine protease associated with fibrosis, tissue repair, inflammation, and ECM degradation. FAP contains two types of enzymatic activity: dipeptidyl peptidase and endopeptidase. Endopeptidase enables FAP to mediate proteolytic processing of collagen I cleaved by matrix metalloproteinase, leading to prevention of morphogenesis, tissue remodeling and repair [76–78].

FAP appears to be a promising target in oncology because it is not expressed in normal fibroblasts and in the stroma of benign epithelial tumors, whereas it is significantly increased in the stromal compartments of various malignant tumors. The challenge for radiopharmaceutical chemistry is to develop molecular targeting vectors with high affinity for FAP and high selectivity towards related proteases. Recently, molecular antibodies, small peptides, and inhibitors have been transformed into molecular imaging probes, with inhibitors utilizing the (4-quinolinoyl)-glycyl-2-cyanopyrrolidine scaffold representing the most exciting class [79, 80]. The inhibitor structure UAMC1110 showed nanomolar affinity and the best selectivity towards the concurring enzymes prolyl endopeptidase (PREP) and dipeptidyl peptidases DPPIV, DPPVIII and DPPIX [80].

Radiopharmaceutical chemists at the German Cancer Research Center in Heidelberg pioneered the translation of this inhibitor into effective diagnostic radiopharmaceuticals by coupling chelators to the amine of the quinoline moiety of the inhibitor and introducing a series of linker and spacer motifs [81, 82]. At the University in Mainz (Germany) a linker based on squaric acid (SA), which links several bifunctional chelators (DATA^{5m}, DOTA, etc.) to the inhibitor was used [83, 84]. Currently, ^{68}Ga-labeled derivatives such as FAPI-04, FAPI-46, DATA^{5m}.SA.FAPi and DOTA.SA.FAPi (cf. Figure 13) are being investigated in vivo.

These first generation of FAPi-radiotracers show promising value in the diagnosis of many different tumor types and provide new information, also in comparison with established oncologic tracers such as [^{18}F]FDG [85, 86]. Figure 14 shows an exemplary PET image of of a thyroid cancer patient visualized with [^{68}Ga]Ga-DOTA.SA.FAPi.

Outlook: more oncological vectors and new radioisotopes

Radioisotopes

In radiotherapy, it is the desired action of particle-induced ionization of α or β^- emitters on tumor DNA. It requires the identification of the most successful radionuclide candidates which offer adequate nuclear parameters, specific activities and effective production routes including yield, purity, and cost. Routine clinical availability is the key issue. As of today, the number of such therapeutic isotopes is relatively low, yet important carrier-free β^- emitters such as ^{90}Y and ^{177}Lu are available even at a GMP level. Availability of ^{225}Ac, in contrast, is limited.

However, there is a substantial risk that the supply chain of those radionuclides cannot satisfy the demand of e.g. radiolabeled PSMA inhibitors. The growing number of registered theranostic radiopharmaceuticals and their dramatically growing demand even for the well-established radionuclides ask for upscaling production capacities. Interestingly, the use of nuclear reactors dedicated to nuclear energy also

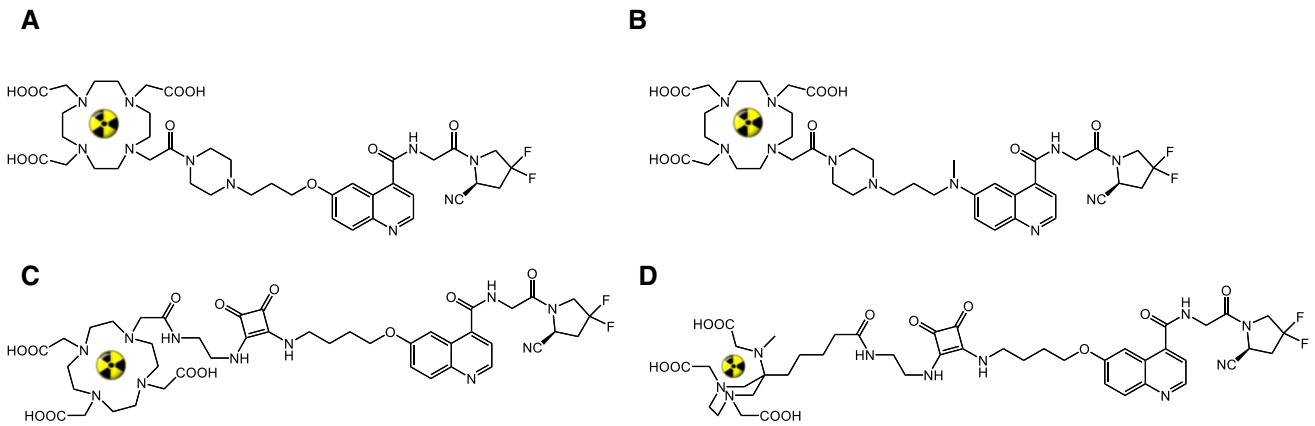

Fig. 13 Representative FAP inhibitor-based precursor for potential theranostic application: FAPI-04 (**A**), FAPI-46 (**B**), DOTA.SA.FAPi (**C**), DATA^{5m}.SA.FAPi (**D**)

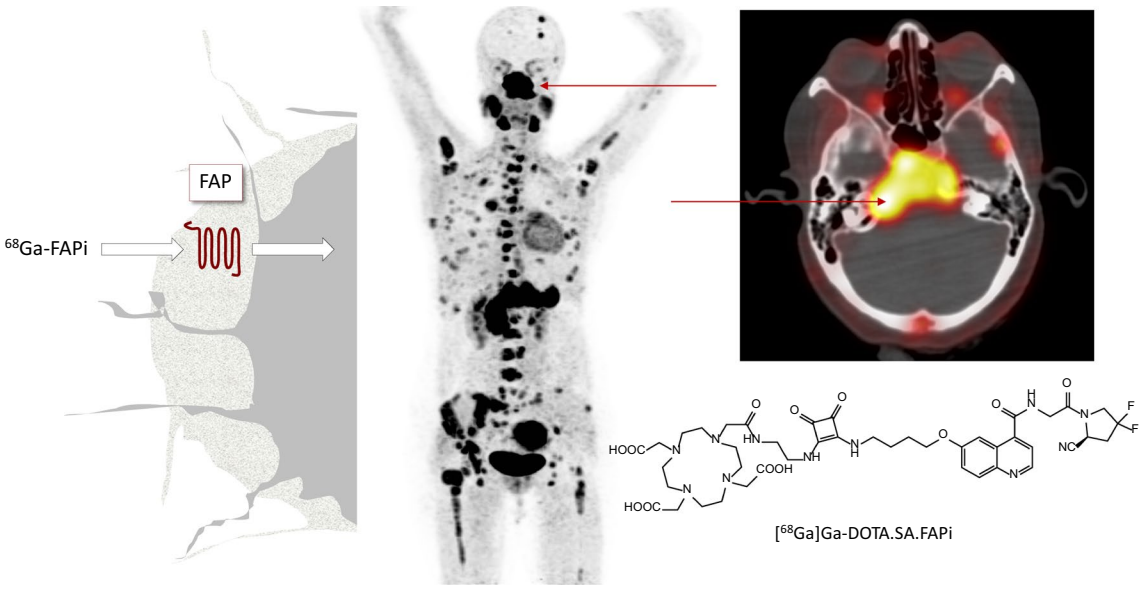

Fig. 14 [^{68}Ga]Ga-DOTA.SA.FAPi PET imaging in patients suffering from thyroid cancer (Courtesy by C. S. Bal)

for isotope production is a fascinating avenue. In parallel, alternative production routes such as the potential of photonuclear reactions are being investigated-asking for dedicated facilities. Finally, research and development towards new radionuclides must continue-with ^{161}Tb representing an important example (cf. Figure 15). Other candidates are still pending routine commercial availability on larger activities such as ^{211}At or ^{212}Pb.

New oncological targets and new design of targeting vectors

The dominant systems of target/targeting vectors are Somatostatin receptors (NET patients)/octreotides and PSMA (prostate cancer patients)/PSMA inhibitors-both quantified in successful clinical phase III trials and being registered drugs. In addition, in the last decade new systems have been translated from bench to bedside such as the TME / FAP inhibitors or peptides as mentioned, as well as the inorganic vectors for the system Hydroxyapatite (bone metastases) / bisphosphonates. Yet there are many more examples, just to mention bombesine-based targeting vectors targeting Gastrin-releasing protein receptor (GRPR) also known as bombesin type-2 receptor for use in prostate cancer [87, 88], the chemokine receptor CXCR4 ligands [89] and RGD-containing cyclic peptides targeting $\alpha_v\beta_3$ and other integrines [90–92] for different types of cancer, new SSTR antagonists for NET [93–95] etc. This is an ongoing progress.

However, there are also some new developments in radiopharmaceutical chemistry. One example to mention is the creation of homo- and hetero-multimers. The principal designs are illustrated in Fig. 16 with a bifunctional chelator as the central unit which has at least two functional groups for the coupling with the linker and the targeting vector. Furthermore, additional spacer units may be required.

The effect of multivalency on affinity, avidity and selectivity of receptor-ligand interactions is known for several

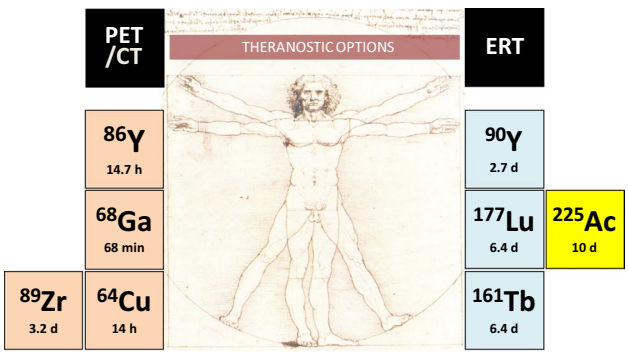

Fig. 15 Selected positron emitters (left) and α or β^- emitters (right) with established theranostic application with ^{161}Tb being about to enter the clinics

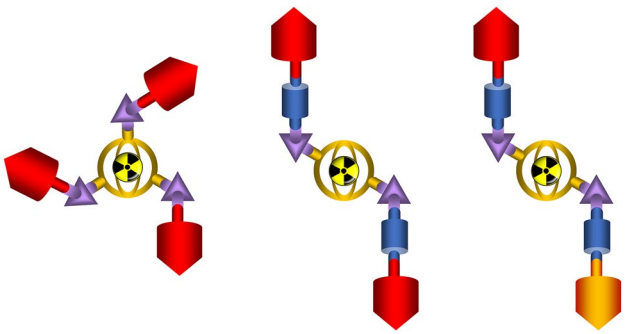

Fig. 16 Schematic designs of chelator-based multimeric radiopharmaceuticals

decades [96, 97]. Based on this, multimeric designs found its way into radiopharmaceuticals in the 2000s mainly targeting the integrin $\alpha_v\beta_3$ with RGD-containing cyclic peptides such as c[RGDfK] as targeting vectors [98–100] but also with aptamers targeting MUC_1 [101]. A ^{64}Cu-labeled RGD-tetramer (^{64}Cu-DOTA-E{E[c(RDGfK)]$_2$}$_2$) showed first promising results indicating a prolonged tumor retention time while tumor uptake and blood clearance were rapid [100].

Notni et al. developed a new bifunctional chelator TRAP (triazacyclononane-triphosphinate) which showed superior ^{68}Ga-labeling properties compared to DOTA and NOTA (milder reaction conditions, broader pH range during labeling, higher specific activities while retaining high complex stability) and simultaneously allowed the conjugation of three targeting vectors [102]. A following study with ^{68}Ga-TRAP(RGD)$_3$ ("^{68}Ga-Avebtrin", Fig. 17) could demonstrate the superiority of the RGD trimer compared to RGD monomers [103].

The concept was expanded to tetraazacyclododecane scaffold which resulted in the chelator DOTPI [104]. This allowed for the synthesis of tetramers and the radiolabeling with a broader range of radiometals such as ^{177}Lu which enables therapeutic applications. As a proof-of-concept DOTPI was conjugated with the PSMA-targeting vector KuE via Cu^{I}-catalyzed alkyne-aide cycloaddition (CuAAC, Huisgen-reaction) and copper-free strain-promoted alkyne-aide cycloaddition (SPAAC) with DBCO (dibenzyocyclooctyne) and investigated [105].

The chelator sarcophagine (Sar) is especially suited to form stable and kinetically inert complexes with Cu^{II}. Figure 18A shows the PSMA dimer SarbisPSMA which was labeled with ^{64}Cu. In vivo-investigation in comparison to the monomer SarPSMA showed far superior tumor uptake, tumor-to-background ratio and longer tumor retention of the dimer [106].

Besides PSMA also Gastrin-releasing peptide receptors (GRPRs) are interesting targets and strongly expressed in

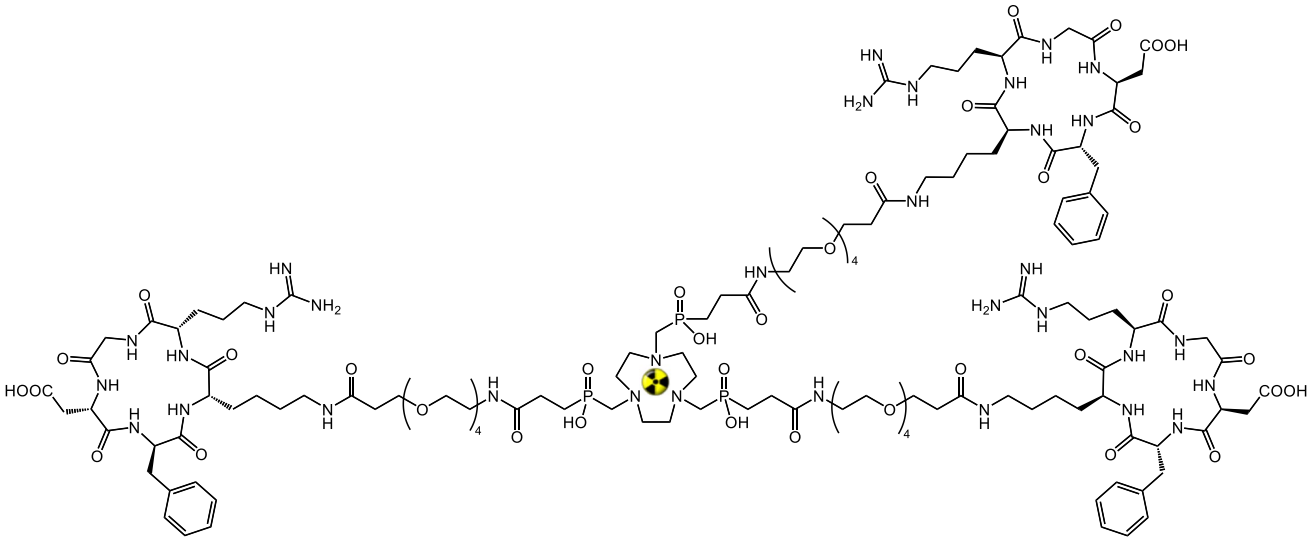

Fig. 17 Structure of TRAP(RGD)$_3$ which can be labeled with ^{68}Ga [103]

several types of cancer such as prostate cancer which can be targeted with bombesin (BBN)-derived peptides. Here, also several attempts were made to investigate homodimeric bombesin radiotracers [88, 108, 109].

Recently the dimeric concept was translated to FAP inhibitor-based radiopharmaceuticals since the first-generation of FAPIs like FAPI-04 and FAPI-46 and other monomers (cf. Figure 13) suffer from short tumor retention time limiting its translation towards therapy using radionuclides with longer half-lives such as ^{177}Lu or ^{225}Ac. Figure 18B shows the structure of DOTAGA.(SA.FAPi)$_2$ which was labeled with ^{68}Ga and ^{177}Lu [107]. In comparison with [^{177}Lu]Lu-DOTA.SA.FAPi, [^{177}Lu]Lu-DOTAGA.(SA.FAPi)$_2$ showed higher tumor uptake, faster clearance and longer tumor retention time. Even after 7 days p.i. the tumor lesions could still be visualized via whole-body scintigraphy [110]. The slighty higher uptakes in colon and kidneys were tolerated well by the patients.

Other groups also published FAPi dimers such as [^{177}Lu]Lu-BiOncoFAP [111] and [^{68}Ga]Ga-DOTA-2P(FAPI)$_2$ [112] recently and showed similar results in murine in vivo studies regarding the biodistribution and pharmacokinetics.

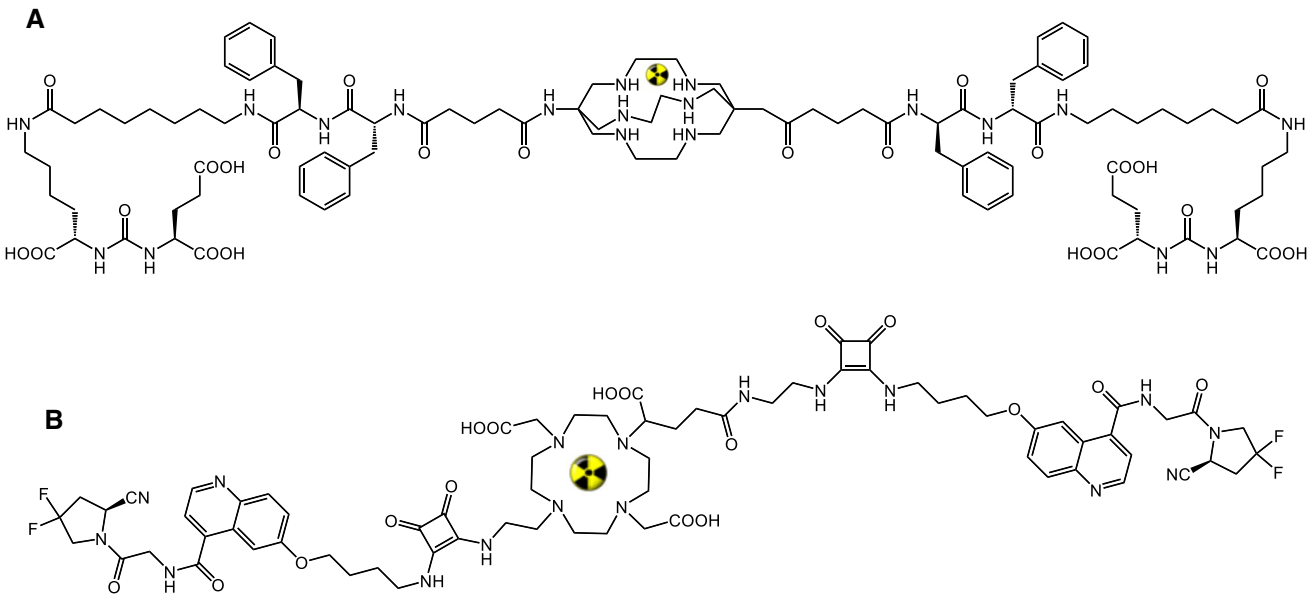

Fig. 18 Structure of SarbisPSMA (**A**) and DOTAGA.(SA.FAPI)$_2$ (**B**) [106, 107]

Heterodimers also appeared in recent years having a similar molecular design than the homodimers but with two different targeting vectors. Most of the combinations try to simultaneously target GRPRs and integrins with a bombesin derivative and a cyclic RGD peptide [113–115]. PSMA-BBN [116, 117] and recently the first PSMA-FAP heterodimer [118] have also been published. Some PCa patients are PSMA-negative so they do not overexpress PSMA. This means that cannot be visualized via a monomeric PSMA radiotracer. A heterodimer could therefore be interesting to improve the rate of successful diagnosis or therapy. It has also been reported that the enzymes are both overexpressed in different malignant tumors at the same time [119, 120].

Besides that, a combination of one of an established oncological targeting vector and a human serume albumin (HSA) binding moiety emerged in radiopharmaceuticals. In most cases 4-(*p*-iodophenyl)butyric acid oder Evans Blue (EB) are used as a HSA binding moiety [121]. These moietites bind reversibly to albumin which results in a prolonged circulation in the blood and therefore a delayed renal clearance. This results in a prolonged tumor retention also which is why a higher accumulated radiation dose can be deposited in the tumor region. This approach has been investigated for SSTR and PSMA in humans. This could be confirmed e.g. with ^{177}Lu-EB-TATE and ^{177}Lu-EB-PSMA-617 with a 7.9- and 5.7-fold higher dose to the tumor compared to the monomeric derivatives, respectively [121–123]. But the drawbacks were also observed since the radiation dose is increased in healthy tissue as well which can result in overall lower tumor-to-background ratios. Much higher uptake was also observed in the kidneys (3.2- and sixfold) and especially the bone marrow (18.2- and sixfold) which can be critical. Even when lower initial activities are needed to treat a patient (particularly interesting for ^{225}Ac) the uptake in healthy tissue increases roughly in the same order of magnitude than in the tumor [121–123].

Conclusion

Since the 1990s huge progress was made in radiometal-based theranostics in every field concerning radiopharmaceuticals. This includes new methods to produce radionuclides (improved production routes of established radionuclides as well as making new radionuclides available for routine use), improved labeling chemistry (acyclic vs. macrocyclic chelators), new oncologic targets (SSTR, PSMA, FAP, …) combined with new targeting vectors (TOC/TATE, PSMA and FAP inhibitors, …), sophisticated linker and spacer chemistry. The development in this field still is ongoing with new molecular designs (dimers and multimers with multiple targeting vectors) and most importantly the ever-increasing interaction of diagnosis and therapy.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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