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PERSPECTIVE

Generator-based PET radiopharmaceuticals for molecular imaging of tumours: on the way to THERANOSTICS

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Generator-derived radionuclides for PET/CT imaging are promising for optimizing targeted radiotherapy by an individual patient-based approach, applying pre-therapeutic evaluation, as well as dosimetric calculations, and for measuring treatment response after radionuclide therapy.

Introduction

Radionuclide generator systems provide an alternative route to access medically relevant radionuclides. However, the number of generator systems, providing radionuclides with decay parameters promising for various applications for imaging and treatment is limited. The ^{99}Mo/^{99m}Tc system, since decades being *the* prototype of a "medical" radionuclide generator, is still the basic source of diagnostic radiopharmaceuticals, today covering approximately 80% of all nuclear medical procedures worldwide.

In addition to the ^{99}Mo/^{99m}Tc generator, with its daughter nuclide emitting low energetic photon radiation dedicated to SPECT imaging and scintigraphy,[1] recent interest has focused on analogue generator systems with potential for molecular imaging using PET, such as the ^{68}Ge/^{68}Ga and ^{82}Sr/^{82}Rb generators. Finally, parent radionuclides generating particle-emitting daughters (α and β^- emitters) are increasingly relevant due to the growing number of radionuclide treatments and their novel indications, *e.g.* using radiolabelled peptides and antibodies.[2–4]

In turn, the increasing number of molecular targeted radiotherapies, *e.g.*, peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumours using ^{177}Lu and ^{90}Y labelled somatostatin analogues, is asking for a more precise pre-therapeutic quantification of the uptake kinetics and radiation doses delivered by particular radiopharmaceuticals in the case of an individual patient therapy.[5] In this context, some radionuclide generators which provide positron-emitting daughters may find particular application. For example, the ^{68}Ge/^{68}Ga generator is already in use in nuclear medicine departments as a routine source of positron emitting ^{68}Ga for PET/CT imaging before and after PRRT using DOTA-conjugated octreotide derivatives or other targeting vectors directed to G-protein coupled *trans*-membrane tumour receptors (GPCR). From a more chemical perspective, key advantages for the use of radionuclide generators and their daughters include the convenience of obtaining the desired radionuclide on demand, in high specific activity, *i.e.* no-carrier-added (nca) identity, and in chemical forms ready for instant radiopharmaceutical synthesis and/or direct, eventually on-line medical application. This paper is aimed to cover the particular features of state-of-the-art radionuclide generators providing positron-emitting daughters for molecular PET/CT imaging in oncology. It discusses the potential of these generator-based radionuclides for monitoring nuclear medical treatments.

Molecular imaging has reached a fascinating new level of diagnosing various diseases with very high specificity.[6,7] PET/CT, applying novel radiopharmaceuticals, is contributing significantly to this development, offering the advantage of very precise localization of tumours and metastases and quantification of the receptor status and metabolic pathways.[4]

However, tumour-type specific treatment is the ultimate goal. Recent developments reflect a clear trend towards a patient-based "individualized" approach of treating disease, including the precise planning and accurate control of a given therapeutic protocol for an individual patient.[4] In this context, dedicated radiopharmaceuticals (*e.g.*, ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE) may be used for PET/CT imaging.[8] In addition to ^{18}F- or ^{11}C-based PET tracers, positron emitters generated from radionuclide generator systems attract great attention. While "classical" PET tracers such as ^{18}F-FDG or ^{18}F-FLT monitor clinically relevant parameters such as tumour growth, cell proliferation or glucose metabolism *in vivo*, endoradiotherapeutic compounds need to be of different chemistry, mainly because most of the potent therapeutic radionuclides – except ^{131}I – are metals (^{90}Y, ^{153}Sm, ^{177}Lu, but also radioisotopes of radon, tin and others) or show – like ^{211}At – a more metallic character. For recent reviews on the selection, chemistry and dosimetry of those candidates see, for example refs. 9–12.

There are, interestingly, some molecular targeting vectors which could be used for both diagnoses (molecular imaging) and therapy (molecular targeted treatment), which is reflected in the acronym

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THERANOSTICS. In the context of generator-based positron-emitting radionuclides the concept of THERANOSTICS is:

(a) to achieve a quantitative molecular imaging diagnosis of a disease (soft tissue tumours such as neuroendocrine cancer – imaged *via* peptidic molecular targeting vectors, or bone diseases such as metastases – imaged *via* bisphosphonate-based targeting vectors),

(b) a follow up personalised treatment with a therapeutic analogue utilizing the same molecular imaging vectors (*i.e.* "just" substituting the generator-derived diagnostic trivalent radiometal by a therapeutic analogue),

(c) making use of patient-individual dosimetric considerations based on the diagnostic protocol, and

(d) finally applying post-therapeutic control procedures, again using the quantitative PET/CT opportunities provided by the generator-derived positron emitters.

The most relevant and clinically successful type of those compounds today represents peptidic moieties recognizing GPCRs. If covalently conjugated to bifunctional chelators (such as derivatives of acyclic or cyclic polyamine polycarboxylates such as DTPA or DOTA) (Fig. 1), trivalent radionuclides can be applied to label these compounds.

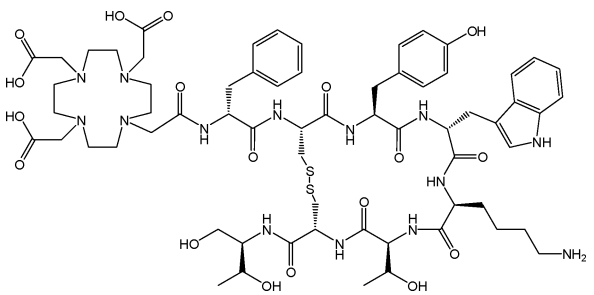

Fig. 1 DOTA-conjugated octreotide.

Consequently, the radiotherapeutic version creates radiopharmaceuticals labelled with a particle-emitting, "therapeutic" radionuclide, such as ^{90}Y, ^{153}Sm, ^{177}Lu *etc.* Analogously, molecular diagnostic imaging is achieved by introducing a positron-emitting, "PET" radionuclide, such as ^{68}Ga and ^{44}Sc or ^{86}Y. Treatment planning and monitoring can then be achieved by using the same pharmaceutical compound, just substituting the "therapeutic" radionuclide by a "diagnostic" one. Ideally, these "diagnostic" substituents decay by positron emission and are thus relevant for PET/CT in the context of quantitative imaging.

This radionuclide should ideally represent another isotope of the "therapeutic" radionuclide, which is the case for the pair ^{90}Y/^{86}Y. This was the rationale for developing nuclear production routes and radiochemical separation procedures towards the radionuclidic and chemically pure positron emitter ^{86}Y ($t_{1/2}$ = 14.74 h, β^+ branching 33%), see refs. 13–18.

Alternatively, another "diagnostic" radionuclide from a chemical element different to the "therapeutic" one may be used. In this case, however, pharmacological studies need to make sure that the analogy (rather than identity) in chemistry reflects a similarity in pharmacology for the two differently radiolabelled compounds.

Table 1 lists possible pairs of therapeutic radionuclides and diagnostic positron emitters. In fact, several radionuclide generators may be candidates for monitoring radionuclide and other therapies, namely ^{44}Ti/^{44}Sc, ^{68}Ge/^{68}Ga or ^{110m}Sn/^{110m}In.

Generator-produced positron emitters

A radionuclide generator is a concept defined as an effective radiochemical separation of decaying parent and daughter radionuclides such that the daughter is obtained in a pure radionuclidic and radiochemical form. Relevant developments have been reviewed in ref. 17. Among the generator pairs relevant for quantitative PET, all daughter nuclides are positron emitters and provide a significant positron branching, although in some cases the decay is accompanied by high-energy photons, which might require careful adoption of PET scanners. Parent nuclides are neutron deficient and are thus typically produced at accelerators.

Table 2 categorizes the most relevant "PET generators" according to the half-life of the daughter nuclide. As the short half-lives in the range of minutes do not allow radiochemical synthesis, these systems are relevant for perfusion imaging exclusively. In contrast, the longer-lived daughters may be used to synthesize labelled compounds, which are chemically, or physiologically analogous to the radiotherapeutic compounds used today for patient treatment. The longer-lived daughter nuclides, on the other hand, provide potential for the development of labelled radiopharmaceuticals matching the physical half-life of the therapeutic radionuclides.

Table 1 Diagnostic PET radionuclides matching relevant therapeutic radionuclides

Therapeutic nuclide		Diagnostic nuclide (positron emitter)			
Nuclide	Half-life $t_{1/2}$	Nuclide	Half-life $t_{1/2}$	β^+_{branch} (%)	Availability
Isotopic substituents					
^{131}I	8.04 d	^{124}I	4.18 d	23	Cyclotron
		^{122}I	3.62 min	77	Cyclotron, ^{122}Xe/^{122}I
^{67}Cu	2.58 d	^{62}Cu	9.74 min	97	Cyclotron, ^{62}Zn/^{62}Cu
^{90}Y	2.67 d	^{86}Y	14.74 h	33	Cyclotron
^{47}Sc	3.34 d	^{44}Sc	3.93 h	94	^{44}Ti/^{44}Sc
Non-isotopic substituents					
^{90}Y	2.67 d	^{68}Ga	67.7 min	89	^{68}Ge/^{68}Ga
^{153}Sm	1.95 d	^{44}Sc	3.93 h	94	^{44}Ti/^{44}Sc
^{177}Lu	6.71 d	^{110m}In	1.15 h	62	^{110m}Sn/^{110m}In
^{213}Bi	45.6 min				
^{225}Ac	10.0 d				

Table 2 Generator-produced positron emitters with potential for PET/CT imaging

Generator system	Parent $t_{1/2}$	Daughter $t_{1/2}$	β^+_{branch} (%)	$E_{\beta+}$/MeV	Option
$^{82}Sr/^{82}Rb$	25.6 d	1.27 min	95.0	1.41	Perfusion
$^{140}Nd/^{140}Pr$	3.37 d	3.39 min	51.0	0.544	Perfusion
$^{118}Te/^{118}Sb$	6.00 d	3.6 min	74.0	0.882	Perfusion
$^{122}Xe/^{122}I$	20.1 h	3.6 min	77.0	1.09	
$^{128}Ba/^{128}Cs$	2.43 d	3.62 min	69.0	0.869	Perfusion
$^{134}Ce/^{134}La$	3.16 d	6.4 min	63.0	0.756	Perfusion
$^{62}Zn/^{62}Cu$	9.26 h	9.74 min	97.0	1.28	Labelling, perfusion
$^{52}Fe/^{52m}Mn$	8.28 d	21.1 min	97.0	1.13	Perfusion
$^{68}Ge/^{68}Ga$	270.8 d	1.135 h	89.0	0.74	Labelling, perfusion
$^{110}Sn/^{110m}In$	4.1 h	1.15 h	62.0	0.623	Labelling
$^{44}Ti/^{44}Sc$	60.3 a	3.927 h	94.0	0.597	Labelling
$^{72}Se/^{72}As$	8.4 d	1.083 d	88.0	1.02	Labelling

Several generator pairs have been proposed decades ago and have continuously been improved radiochemically. However, only a few generators are in routine clinical use today, such as $^{62}Zn/^{62}Cu$, $^{68}Ge/^{68}Ga$ and $^{82}Sr/^{82}Rb$. Several others have been studied intensively concerning radiochemical parameters. Improved versions are described, for example, for $^{44}Ti/^{44}Sc$, $^{52}Fe/^{52}Mn$, $^{72}Se/^{72}As$ and $^{140}Nd/^{140}Pr$. In the context of quantitatively monitoring radiotherapeutic procedures, however, only a few of them are relevant due to specific reasons.

Isotopic matching

Ideally, the positron emitting generator daughter should be another isotope of the therapeutic radioisotope's chemical element. This is the case for *e.g.* ^{122}I *vs.* ^{131}I, and ^{62}Cu *vs.* ^{67}Cu. However, there is a significant discrepancy between the half-lives of the corresponding diagnostic and therapeutic isotope, *i.e.* 3.6 min (^{122}I) and 8.04 d (^{131}I) or 9.74 min (^{62}Cu) *vs.* 2.58 d (^{67}Cu), respectively.

Me(III) analogue chemistry

These generate trivalent radiometals, namely ^{68}Ga and ^{44}Sc and eventually ^{110m}In, to simulate radiotherapeutics based on trivalent particle emitters such as ^{90}Y, ^{153}Sm, ^{177}Lu (and other trivalent lanthanide radionuclides), ^{213}Bi, ^{225}Ac (and other trivalent actinide radionuclides). These therapeutic β^- or α-emitting radionuclides are usually attached to molecular tumour targeting vectors such as peptides or proteins (monoclonal antibodies or fragments thereof) *via* bifunctional chelators such as DTPA or macrocyclic versions such as DOTA. The concept in this case is to consider the coordination chemistry of the "original" trivalent therapeutic radionuclides as comparable to the coordination chemistry of the positron emitter. Whether the resulting biological parameters such as *e.g.* the *in vitro* binding affinities of the Me(III) analogue compounds still are reflecting sufficiently the parameters of the original therapeutics needs to be studied in each case. However, if there is a sufficient homology, the physical half-lives of 67.7 min, 1.15 h and 3.97 h, respectively, of ^{68}Ga, ^{110m}In and ^{44}Sc, may guaranty excellent PET imaging within a few hours post injection (^{68}Ga) or even one day (^{44}Sc).

In vivo generators

This concept involves labelling of molecular carriers (complexes, peptides, monoclonal antibodies and their fragments, *etc.*) with intermediate half-life generator parents, which generate much shorter half-life daughter radionuclides.[18] It may combine the longer physical (and biological) half-life of the parent nuclide with a short half-life of the positron emitting daughter nuclide.

The concept involves labelling of various molecular carriers with intermediate half-life generator *parents*, which - after accumulation in the desired tissue - generate much shorter half-life daughter radionuclides. These *in vivo* generated daughter radionuclides can act either as imaging agent (if decaying *via* single-photon or positron emission) or as therapeutic agent (if decaying *via* α, β^- or Auger electron emission). Several generator pairs could potentially be utilized as *in vivo* systems, presuming the parent nuclide offers the adequate chemical properties for synthesis of labelled compounds and a half-life suitable for the biochemical/physiological process the labelled compound is involved in. The two candidates applicable to the THERANOSTICS concept using PET are $^{134}Ce/^{134}La$ and $^{140}Nd/^{140}Pr$:

^{134}Ce ($t_{1/2}$ = 3.16 d)/^{134}La ($t_{1/2}$ = 6.4 min): ^{134}La was proposed as PET perfusion imaging agent,[19] but real practical applications have not yet been described.

^{140}Nd ($t_{1/2}$ = 3.37 d)/^{140}Pr ($t_{1/2}$ = 3.39 min): The radiochemical principle of designing a generator is based on physical-chemical transitions of ^{140}Pr following the electron capture process. A significant separation effect was observed when the parent nuclide ^{140}Nd was coordinated to a DOTA-conjugated peptide or ethylamine, which were absorbed on resins. The thermodynamically and kinetically stable complex binds ^{140}Nd while the released ^{140}Pr is kinetically hindered to form similar complexes with the macrocyclic ligand. The ^{140}Nd-DOTA absorption on the solid phase remains stable within at least three half-lives of ^{140}Nd. ^{140}Pr is eluted in >93% yield if optimized eluent systems such 10^{-3} M DTPA are applied, with negligible levels of ^{140}Nd breakthrough. For 100 MBq of ^{140}Nd-DOTA-like activity and 0.5 h between two subsequent elutions (time enough for accumulation of 100% of ^{140}Pr activity), a breakthrough of only 25 kBq of ^{140}Nd (~0.025%) could be expected.[20]

In the context of monitoring the uptake of Me(III)-labelled radiotherapeutics, the generator mothers ^{134}Ce or ^{140}Nd may be used directly for synthesizing Me(III) analogue compounds. In this

case, their half-lives of 3.16 and 3.37 d almost perfectly match the half-lives of the relevant therapeutic nuclides such as ^{90}Y or ^{177}Lu. While it is obvious that the chemical similarity between *e.g.* ^{140}Nd-labelled and *e.g.* ^{177}Lu-labelled targeting vectors is rather high, and the biological behaviour of the two analogue tracers is comparable, the problem lies in the fate of the *in vivo* generated daughter nuclide. The concept implies that the chemical binding of the daughter nuclide is analogous to the parent one and the daughter radionuclide is thus not released from the original position of the label of the parent. If not, *i.e.* if released from the targeted tracer due to various factors (which are in part known from hot atom chemistry processes), the decay product will be bound in the near surrounding environment of the parent due to other chemical or biochemical binding (such as intracellular trapping effects) or is released and transported/migrated far away from the target site.

As investigated for the ^{140}Nd/^{140}Pr generator system, the daughter (^{140}Pr) may quantitatively be released from initial *e.g.* ^{140}Nd-DOTA-octreotide compounds despite the very high thermodynamic and kinetic stability of the trivalent lanthanide with the macrocyclic chelator.[20] This dramatic effect – different to the ^{166}Ho/^{166}Dy system – is explained by the different mode of radioactive decay. The electron capture transmission in ^{140}Nd → ^{140}Pr transformations ruptures the initial chemical bonds of the mother radionuclide and releases a daughter nucleus *in situ*, which is not able to form complexes with DOTA-like compounds, at least at room temperature. Thus, generator pairs of such decay and such ligands involved with kinetically determined complex formation characteristics appear not useful for *in vivo* generators.

Dosimetric considerations

Radiation doses to specific tissues can be determined using the MIRD approach,[5] see Fig. 2. The dosimetric properties are characteristic for each radionuclide according to their decay parameters such as half-life, type, abundance and energy of emissions, and represent tabulated values (S-factors). In contrast, the residence times of the labelled compounds should be measured experimentally. Adequate positron emitters, covering at least the relevant initial uptake kinetics, are ideally suited to determine these biological kinetic processes. For the calculation of radiation doses of specific radiotherapeutics, the biological residence data derived for the PET surrogate tracer may be used, while the S-factors of the therapeutic nuclide are taken.

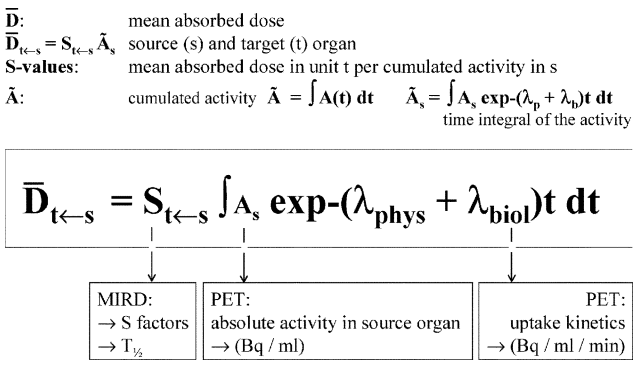

Fig. 2 Determination of radiation doses according to the MIRD scheme. Experimental input required is achieved by quantifying absolute activities and uptake kinetics providing biological residence data (λ_{biol}).

If the positron emitter and the therapeutic nuclide are representing isotopes of the same element, the equation in Fig. 2 is correct. However, if the PET nuclide represents a nuclide of another chemical element, the biological parameters of the two pharmaceuticals may differ to a specific degree. In this case, a lump factor may be introduced considering these deviations, as routinely established for example for ^{18}F-FDG mimicking glucose consumption rates *in vivo*.

Relevant generators for isotopic matching

^{62}Zn ($t_{1/2}$ = 9.26 h)/^{62}Cu ($t_{1/2}$ = 9.74 min): The ^{62}Cu was chelated to human serum albumin (HSA)[21] and benzyl-TETA-HSA[22] and used for blood pool imaging.[23] Several hypoxia and perfusion ^{62}Cu-complexes have been developed and applied for PET studies such as [^{62}Cu]ATSM (diacetyl-bis(N^4-methylthiosemicarbazone)) and [^{62}Cu]PTSM (pyruvaldehyde bis(N^4-methylthiosemicarbazone), see, *e.g.* refs. 24–27. Human biodistribution and dosimetry studies of the perfusion agent [^{62}Cu]PTSM were investigated and this tracer was recommended for repeated studies of myocardial imaging in the same patient as well as for quantification of the cerebral blood flow.[28–30] The compound was also applied for the assessment of angiotensin II-induced blood flow changes in patients with colorectal liver metastases.[31] However, until now there was no intention to use the generator–derived ^{62}Cu as a PET-surrogate to therapeutic ^{67}Cu.

Relevant generators for Me(III) analogue chemistry

^{110}Sn ($t_{1/2}$ = 4.1 h)/^{110m}In ($t_{1/2}$ = 1.15 h): Positron-emitting ^{110m}In could be a choice for quantitative imaging.[32,33] Isotopically pure ^{110m}In is prepared *via* the generator system ^{110}Sn/^{110m}In.[32]

^{68}Ge ($t_{1/2}$ = 270.8 d)/^{68}Ga ($t_{1/2}$ = 68 min): This generator system has found widespread application, mainly for the synthesis of DOTA- or NOTA-conjugated octreotide derivatives. A first compilation of the data relevant to ^{68}Ge/^{68}Ga generator systems was published in 1996.[34] The IAEA has recently initiated a comprehensive review of the production of several generator mother nuclides including a chapter on ^{68}Ge.[35] In 2010, a review entitled "The renaissance of ^{68}Ge/^{68}Ga generators stimulates new developments in ^{68}Ga radiopharmaceutical chemistry" in detail covers aspects of parent nuclide production, design of generators and post-processing of generator eluates, as well as chelator chemistry for Ga(III).[36]

Today, Me(IV) oxide-based matrices are preferred for commercial generator productions. A modified TiO_2 phase was used at Cyclotron Ltd., Obninsk, Russian Federation, since about 2000. A similar generator is available as 'IGG 100' providing improved elution characteristics. These generators are eluted with 0.1 M HCl and show initial ^{68}Ga elution yields of about 80% with ^{68}Ge breakthrough of about $<10^{-3}$ %. Another system is produced at iThemba Laboratories, Republic of South Africa, using a SnO_2-based solid phase. Optimum ^{68}Ge elution efficacy is reported at 0.6 M HCl, decreasing at lower HCl concentration. Systematic research continues to develop new ^{68}Ga radiopharmaceuticals.

Significant potential has been developed since about 2000 for imaging neuroendocrine tumours using [^{68}Ga]DOTA-DPhe^1-Tyr^3-octreotide ([^{68}Ga]DOTA-TOC) and PET). This diagnosis, in particular if carried out using PET/CT imaging, is superior to any

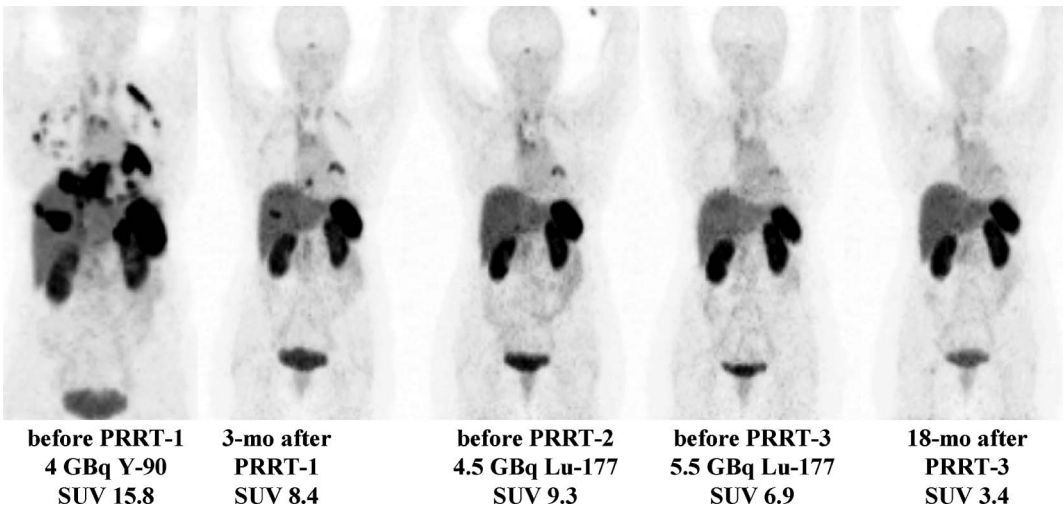

Fig. 3 Persisting complete remission of disseminated metastases arising from a neuroendocrine tumour in the mediastinum after four cycles of peptide receptor mediated radionuclide therapy (PRRNT) using ^{90}Y-DOTA-TATE as illustrated by serial ^{68}Ga-DOTA-TATE receptor PET imaging.

other imaging approach. ^{68}Ga-labelled compounds may be used as surrogates for analogue ^{90}Y- or ^{177}Lu-radiotherapeuticals prior to treatment. In this case, the scale of the SUV_{max} values quantified by ^{68}Ga-PET indicates whether a response to the treatment could be expected. In fact, there are significant correlations for DOTA-octreotides for neuroendocrine tumours between ^{68}Ga-SUV_{max} values and the success of treatment in terms of partial and minimal response (PR + MR), stable disease (SD) and progressive disease (PD), see Fig. 3. In the course of those treatments, the periodical progress of the disease can be monitored (PET/CT imaging) and quantified (SUV_{max} values again of relevant ^{68}Ga-analogue compounds), see Table 3 and Fig. 4.

New directions concern the relation between PET/CT of disseminated bone metastases or other osteoblastic bone diseases using ^{68}Ga-labelled DOTA-bisphosphonates[37] and the follow-up therapy using corresponding ^{177}Lu-compounds (Figs. 5–7).

Like for the pairing of diagnostic and therapeutic tracers in the case of DOTA-conjugated octreotide analogues applied to neuroendocrine tumours also bone diseases can be both diagnosed and treated using the same compound (*i.e.* ^{68}Ga *vs.* ^{177}Lu or ^{90}Y).

Table 3 Standardized uptake values (SUV_{max}) of ^{68}Ga-DOTA-TATE prior and post peptide receptor mediated radionuclide therapy (PRRNT) indicating a significant correlation between the diagnostic SUV_{max} as determined by PET/CT and the success of treatment in terms of partial and minor response (PR + MR), stable disease (SD) and progressive disease (PD) using ^{90}Y-DOTA-TATE for treating neuroendocrine tumours

		SUV_{max} (^{68}Ga)		
	n	prior-PRRT	post-PRRT	*p*
PR + MR	45	27.2 ± 14.8	16.4 ± 9.6	<0.0001
SD	22	17.6 ± 9.9	16.4 ± 9.5	—
PD	10	12.9 ± 5.6	19.9 ± 7.5	0.002

Fig. 7 illustrates scintigraphic images of a patient treated with ^{177}Lu-BPAMD for disseminated bone metastases. The generator-derived ^{68}Ga thus allows pre-therapeutic imaging, in particular because of the relatively fast uptake of the Me(III)-BPAMD compounds.

^{44}Ti ($t_{1/2}$ = 60 a)/^{44}Sc ($t_{1/2}$ = 3.927 h): Compared to the chemically similar system ^{68}Ge/^{68}Ga, this generator provides a much

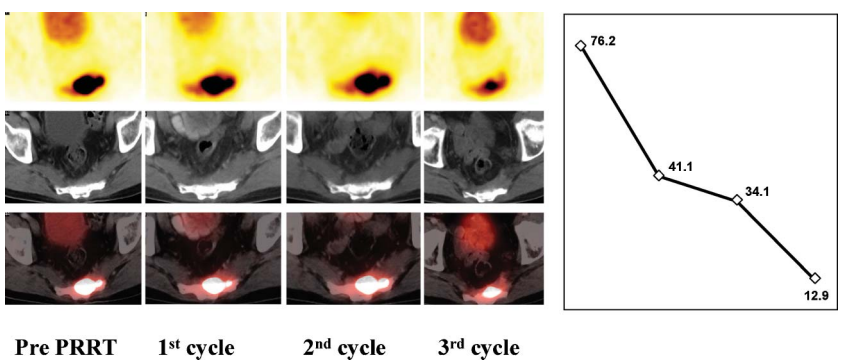

Fig. 4 Paraganglioma with sacral invasion and bone, liver and lymph node metastases responding to PRRNT (three cycles using ^{177}Lu- and ^{90}Y-DOTA-TATE; total administered activity 13.3 GBq): time course of SUV_{max} demonstrating clearly success of therapy already after the first cycle, whereas by visual analysis of the PET images treatment response can only be seen after several therapy courses. Morphology-based imaging as demonstrated by CT scan does not exhibit any significant change over time. This case is a typical example for the frequent observation that molecular and functional response precedes morphological alterations.

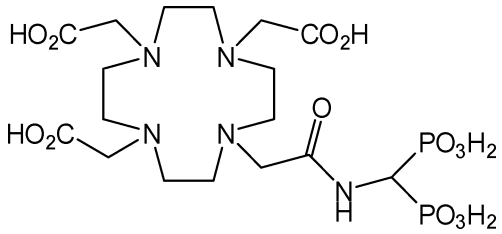

Fig. 5 Structure of DOTA-conjugated bisphosphonate BPAMD.

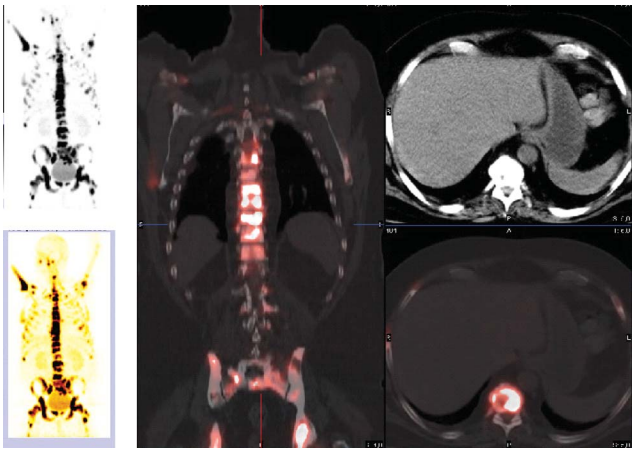

Fig. 6 ^{68}Ga-BPAMD PET, CT and PET/CT for imaging of bone metastases (first in human use) in a patient with prostate cancer.[37]

longer-lived daughter for extended PET/CT measurements. The first high activity level (185 MBq) and thus clinically relevant generator was described recently.[38] The system achieved elution of 180 MBq ^{44}Sc in 20 mL of eluate solution. To allow efficient ^{44}Sc labelling, a post-elution processing of initial ^{44}Sc generator eluates was investigated in order to reduce its volume, its HCl concentration and to remove oxalate anions.[39] The post-processing requires only 10 min. The overall yield of the post-processing reached 90% referred to the ^{44}Sc obtained from the ^{44}Ti/^{44}Sc generator. The generator finally provides 150 MBq of ^{44}Sc containing <10 Bq of ^{44}Ti ready for radiolabelling chemistry.

As a trivalent metal cation, ^{44}Sc may be used to synthesize radiopharmaceuticals analogously to currently used radionuclides in diagnosis and therapy, such as ^{68}Ga and ^{111}In or ^{90}Y and ^{177}Lu, as well as for non-radioactive Gd(III). Using 21 nmol of DOTA-TOC in 2 mL of a processed ^{44}Sc eluate in ammonium acetate buffer pH = 4.0 provided >98% labelling yields within 25 min of heating in an oil-bath at 95 °C. This time can be reduced to only 3 min by applying microwave-supported heating. The ^{44}Sc-DOTA-TOC was found to be stable in ethanolic solution, 0.9% NaCl, phosphate buffer with sodium chloride (PBS pH = 7.4), and also in the presence of metal cations (Fe^{3+}, Ca^{2+}, Cu^{2+}, Mg^{2+}), as well as other ligand competitors, such as EDTA and DTPA. This study for the first time experimentally verified that nca ^{44}Sc forms stable complexes with macrocylic ligands containing nitrogen and oxygen donor atoms. The developed method guarantees high yields and safe preparation of injectable ^{44}Sc-labelled radiopharmaceuticals for routine application and it is easy to automate. This may allow follow-up research on labelling and radiopharmaceutical chemistry of the positron emitter ^{44}Sc(III) and molecular imaging of ^{44}Sc-labelled tracers using PET/CT taking advantage of the 3.97 h half-life of this positron emitter.

As a proof-of-principle, ^{44}Sc-DOTA-TOC was synthesized and somatostatin GPCR localization was verified in patient studies,[40] see Fig. 8. High quality PET/CT images have been recorded even 18 h post injection. The indention is to measure the uptake kinetics of *e.g.* ^{44}Sc-DOTA-TOC in metastatic neuroendocrine tumours in order to estimate the optimum radiation dose the individual patient will receive in a subsequent therapeutic application of

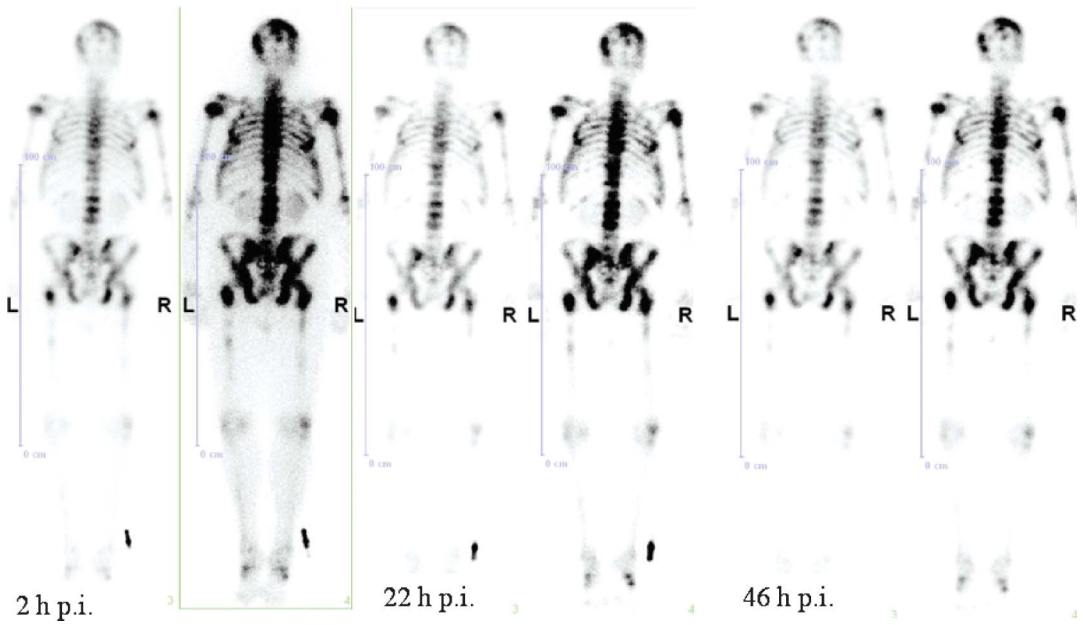

Fig. 7 ^{177}Lu-BPAMD for treatment of a patient with osteoblastic, painful bone metastases arising from prostate cancer (posterior and anterior views). Note long residence time of the labelled BPAMD in the osteoblastic metastases (first in human use).

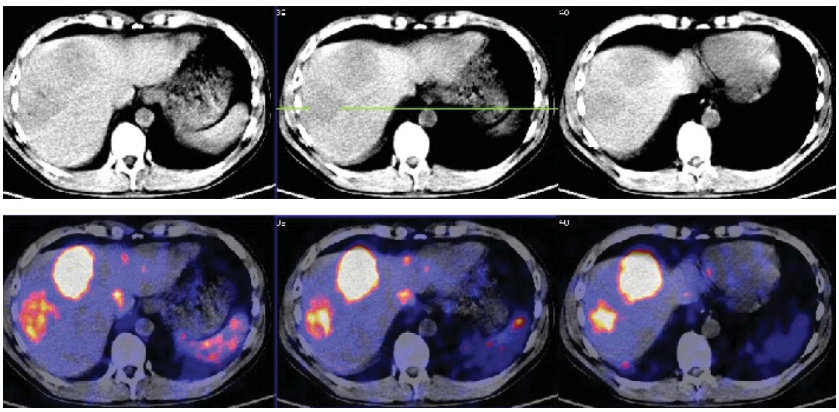

Fig. 8 PET/CT imaging of somatostatin receptor positive liver metastases 18 h after administration of 37 MBq of ^{44}Sc-DOTA-TOC (first in human use).

biologically and chemically analogous compounds, *e.g.* ^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TOC, *cf.* Fig. 2. As illustrated in Fig. 2, all the necessary quantitative "biological" information needed for radiation dosimetry according to the MIRD scheme can be deduced from the PET data.

Conclusion

Currently a few radionuclide generator systems for PET are available – either as rather scientific tools, limited to a restricted number of nuclear chemical or medical departments (^{44}Ti/^{44}Sc, ^{62}Zn/^{62}Cu, ^{140}Nd/^{140}Pr), or as already routinely, commercially available products (mainly ^{68}Ge/^{68}Ga and ^{82}Sr/^{82}Rb). However, those systems delivering trivalent radionuclides show not only promise as valuable diagnostic tools, but are increasingly considered and applied as systems for bridging quantitative PET with a more personalized treatment strategy. ^{68}Ga-based compounds or ^{44}Sc analogues (if uptake kinetics of several hours need to be covered) provide quantitative data on uptake parameters (SUV, uptake kinetics in tumour and healthy organs) of the corresponding oncologic targeting vectors in a particular patient, which can be related to the calculation of the optimum therapeutic dose of the corresponding ^{177}Lu or ^{90}Y labelled radiotherapeutic compounds. Those generator-derived, chemically analogue systems thus perfectly illustrate the approach towards THERANOSTICS medical strategies.

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