Candidates for Peptide Receptor Radiotherapy Today and in the Future

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Regulatory peptide receptors are overexpressed in numerous human cancers. These receptors have been used as molecular targets by which radiolabeled peptides can localize cancers in vivo and, more recently, to treat cancers with peptide receptor radiation therapy (PRRT). This review describes the candidate tumors eligible for such radiotherapy on the basis of their peptide receptor content and discusses factors in PRRT eligibility. At the present time, PRRT is performed primarily with somatostatin receptor- and cholecystokinin-2 (CCK2)-receptor-expressing neuroendocrine tumors with radiolabeled octreotide analogs or with radiolabeled CCK2-selective analogs. In the future, PRRT may be extended to many other tumor types, including breast, prostate, gut, pancreas, and brain tumors, that have recently been shown to overexpress several other peptide receptors, such as gastrin-releasing peptide-, neurotensin-, substance P-, glucagon-like peptide 1-, neuropeptide Y-, or corticotropin-releasing factor-receptors. A wide range of radiolabeled peptides is being developed for clinical use. Improved somatostatin or CCK_2 analogs as well as newly designed bombesin, neurotensin, substance P, neuropeptide Y, and glucagon-like peptide-1 analogs offer promise for future PRRT.

Key Words: tumor targeting; radiopeptides; receptors; peptide receptor radiation therapy; tumor selection

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In the past decade, there has been increasing evidence of peptide receptor expression on various human cancers (*1*). This observation has permitted the development of in vivo peptide receptor targeting of these tumors for diagnostic or therapeutic purposes (*2,3*). Because of the success of peptide receptor radiation therapy (PRRT) in somatostatin receptor-positive cancers, it is appropriate to review the various peptide receptors and corresponding tumors that are or may become candidates for PRRT and discuss eligibility criteria for patients with cancer. With the recent development of other "intelligent drug molecules" (e.g., imatinib, trastuzumab, and epidermal growth factor–receptor inhibitors) targeted to specific entities, it is increasingly important to select the right patient candidate for the right drug (*4*). If we do not systematically preselect PRRT patients on the basis of rational molecular biologic grounds, then clinical applications may yield poorly reproducible therapeutic results for these drugs and lead to false conclusions about the efficacy of targeted drug therapy in general (*4*).

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GENERAL CRITERIA FOR PRRT ELIGIBILITY

Two types of criteria should guide decisions on eligibility of cancer patients for PRRT: clinical and molecular biologic criteria (Table 1).

Clinical Criteria

Patients eligible for PRRT are those with cancer and multiple inoperable metastases. Most of these patients have been pretreated. Often, established adjuvant palliative therapies (chemotherapy, radiotherapy) have been tried in these patients with little or no success before PRRT (*3*). Patients with a single brain tumor are also eligible when a surgical approach or nonsurgical treatments (chemo- and radiotherapy) have failed (*5*).

Molecular Biologic Criteria

An absolute prerequisite for PRRT inclusion of a cancer patient from the categories cited in the previous paragraph is that the cancer expresses the corresponding peptide receptor in the primary tumor and in metastases. It is a further prerequisite that receptor density is high. Finally, knowing that peptide receptor expression in cancers may be heterogeneous (i.e., that some tumor areas can express a high receptor density whereas others lack the receptors), it is obvious that the more homogeneously a peptide receptor is expressed in a tumor, the better candidate target it is for PRRT (*1,6*).

Because many peptides act through multiple peptide receptor subtypes, it is crucial that the peptide receptor subtype expressed by a given tumor correspond to the subtype to which the radioligand used for PRRT binds with high affinity.

Although tumor location is in most cases not a crucial criterion for PRRT eligibility, it should be remembered that

TABLE 1
General Criteria for Peptide Receptor Radiation Therapy Eligibility

Clinical
Cancer with inoperable multiple metastases; single brain tumors.
No success with established therapies.
Molecular biological
Tumor expressing adequate peptide receptors.
Expressed subtype corresponds to affinity profile of radioligand.
Tumor expressing a high density of receptors.
Preferably homogenous distribution.
Tumor localization preferably outside the blood–brain barrier (alternative application for central nervous system tumors).
Preferably high radiosensitivity.

peptides usually cross the blood–brain barrier with difficulty. Therefore, brain tumors, including glioblastomas with partially perturbed blood–brain barrier, will be less accessible to intravenously injected peptides than are peripheral tumors. This does not mean that patients with brain tumors are ineligible for PRRT. Indeed, brachytherapy may be used as a PRRT alternative for brain tumor patients, based on the use of radiolabeled peptides applied locally to the tumor (*5*).

Although tumor size was shown to play an important role in the efficacy of PRRT in animal tumor models, similar studies have not been published for humans (*7*).

Tumor radiosensitivity is of clear importance in the success of targeted radiotherapy, but the radiosensitivity of a specific tumor ranks behind peptide receptor expression in eligibility criteria for PRRT. However, when 2 tumors have similar levels of peptide receptors, the one that is more radiosensitive is a better candidate for PRRT. It is not clear whether a radiosensitive tumor that usually has only a low density of somatostatin receptors (e.g., lymphomas) will be a good PRRT candidate.

TUMORS AND RECEPTORS ELIGIBLE FOR PRRT TODAY

The choice of the right tumor patients as PRRT candidates today is based on the following knowledge: (a) Previous information from in vitro receptor studies in cancer (*1*). These studies have provided data about incidence and receptor density in various human cancers. This allows the physician to make a first selection of types of tumors with high incidence of peptide receptor expression that may be eligible for PRRT. (b) Results of in vivo receptor scintigraphy with the relevant radioligand in the patient of interest. Such data should not only allow detection or confirmation of the site of the primary tumor and metastases but also permit evaluation of receptor density in the targeted tumor. To achieve the latter, the nuclear physician can calculate a tumor-to-liver ratio as a relative measure of receptor number (*3*). This ratio must be high for PRRT eligibility (*3*).

PRRT has been established for 2 peptide receptor systems: somatostatin receptors and, to a lesser extent, for cholecystokinin-2 (CCK2) receptors (Table 2). For both systems, clinical studies have reported efficacy in a significant number of patients (*8–11*).

TABLE 2
Current Tumor and Peptide Receptor Candidates for PRRT

Administration route	Tumors	In vitro evidence	In vivo evidence	
			Diagnostic	PRRT (ref.)
Intravenous	Somatostatin receptor sst2-expressing tumors			
	GEP NET*	+	+	+ (*3,8,10,11*)
	Paragangliomas*	+	+	+ (*43*)
	Pheochromocytomas*	+	+	+ (*43*)
	Small-cell lung cancer	+	+	
	Medullary thyroid cancer	+	+	+ (*43*)
	Breast cancer	+	+	
	Renal cell cancer	+	+	
	Thyroid cancer	+	+	+
	Malignant lymphomas	+	+	
	CCK2 receptor expressing tumors			
	Medullary thyroid cancer*	+	+	+ (*9*)
	GIST*	+		
	Small-cell lung cancer	+	+	
	GEP NET	+	+	
	Sex cord stromal ovarian tumor	+		
Topical	sst2-expressing central nervous system tumors			
	Medulloblastomas*	+	+	+
	Gliomas	+	+	+ (*5,12*)

*Most eligible for PRRT, on the basis of high incidence and density of receptors.

Somatostatin Receptors

Several groups have shown that cancers with a high somatostatin receptor density, in particular sst2 subtype (Table 2), are eligible for somatostatin receptor radiotherapy (*3,8,10,11*). This is predominantly the case for gastroenteropancreatic (GEP) neuroendocrine tumors (NETs), especially carcinoids and gastrinomas, which frequently have a high sst2 receptor density. Other NETs, such as pheochromocytomas, paragangliomas, and bronchial carcinoids, are also strong candidates (*1*). Small-cell lung cancers and medullary thyroid carcinomas, in selected cases, also have a receptor density sufficiently high to be included in this list. In practice, the pituitary adenomas (growth hormone, thyroid-stimulating hormone, and inactive adenomas) are not considered PRRT candidates, although they usually have very high sst2 density. The reason they are not considered for PRRT is the therapeutic success of established alternative methods. Finally, a small percentage of non-NETs at times may be selected for PRRT, including inoperable meningiomas, neuroblastomas, a subgroup of metastatic breast tumors characterized by high receptor density, metastatic renal cell carcinomas, and thyroid cancers (*1*).

All these tumors are usually reached adequately by intravenous application of the radioligand. However, as mentioned previously, a few tumor types, such as brain tumors, are less accessible by the intravenous route. These tumors (gliomas and medulloblastomas) may be targeted by a topical application of ^{90}Y- or ^{177}Lu-labeled octreotide derivatives. PRRT using octreotide derivatives has been shown to be successful for peripheral as well as central nervous system tumors (*3,5,12*).

CCK2 Receptors

Only a few reports have shown cancers with a high density of CCK2 receptors to be eligible for CCK2 receptor radiotherapy. On the basis of previous in vitro receptor studies, Behr et al. (*9*) selected as a first choice medullary thyroid carcinomas for in vivo targeting, because these express CCK_2 receptors in virtually all cases and have shown encouraging preliminary PRRT data (*13*). The main limiting problem for the development of PRRT using CCK2 receptors may be the high and therefore problematic kidney uptake with current CCK analogs (*9*). Fortunately, a new generation of CCK analogs has been designed with much less kidney uptake (*14*). CCK2 receptors have been shown to be overexpressed in several other cancers, including some GEP NETs, small-cell lung cancers, ovarian tumors, and, most interesting, also in gastrointestinal stromal tumors (GISTs), where they can be expressed in extremely high density (*13,15,16*).

Other Peptide Receptors

Proof of principle of in vivo targeting has been obtained recently with other peptide receptors. These include gastrin-releasing peptide (GRP) receptors, neurotensin (NT) receptors, and vasoactive intestinal peptide (VIP) receptors (*17–19*). However, no PRRT data on clinical use of these peptides are available, so these candidates will be discussed more thoroughly in the section on PRRT for the future.

In Vivo Versus In Vitro Receptor Evaluation

Extensive studies have been performed to assess the specificity of somatostatin receptor scintigraphy by comparing it directly with in vitro somatostatin receptor status (*20*). In most of the PRRT studies, however, patient eligibility was based only on ^{111}In-diethylenetriaminepentaacetic acid^0 (DTPA)-octreotide (Octreoscan; Mallinckrodt, Inc.) or CCK2 receptor scintigraphy in vivo rather than on an in vitro evaluation of receptor expression in surgically resected tumor samples. In vivo peptide receptor scanning is preferred because ^{111}In-DTPA-octreotide or CCK2 receptor scintigraphy has the advantage of being noninvasive with no requirement for tumor sampling. Moreover, these scanning methods can provide information about whole-body distribution of receptor-positive tumors and give a relative approximation of their density using the tumor-to-liver ratio. However, in vivo scintigraphy cannot give a clear assessment of the homogeneity or heterogeneity of receptor distribution within the tumors. This information and precise quantification can be obtained by in vitro receptor autoradiography, with the limitation that usually only a portion of the tumor is assessed. Figure 1 depicts homogeneously distributed somatostatin receptors in a GEP NET compared with heterogeneously distributed somatostatin receptors in a breast cancer, as measured by in vitro receptor autoradiography.

TUMOR AND RECEPTOR PRRT CANDIDATES FOR THE FUTURE

Table 3 lists several peptide receptors and tumor types that may become eligible for PRRT in the near future. This list is based primarily on current in vitro receptor data from surgical samples. In vitro receptor data have been consid-

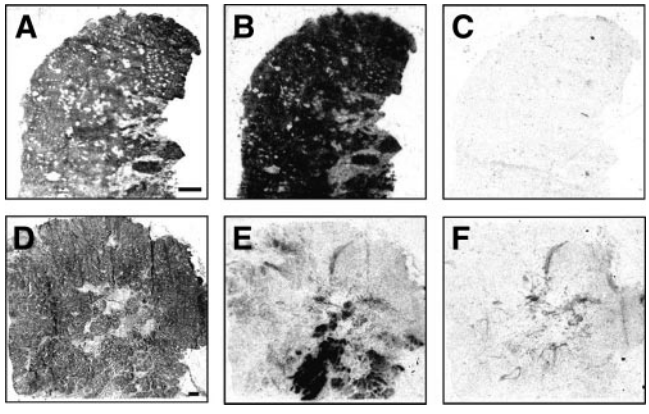

FIGURE 1. Homogeneous distribution of somatostatin receptors in a GEP NET (A–C) and nonhomogeneous distribution in a breast cancer (D–F). (A and D) Hematoxylin-eosin stained sections. Bars = 1 mm. (B and E) Total binding of ^{125}I-Tyr^3-octreotide with homogenous distribution in B but not in E. (C and F) Nonspecific binding.

TABLE 3
Tumor and Peptide Receptor Candidates for Peptide Receptor Radiation Therapy in Future

Administration route	Tumor	In vitro evidence	In vivo evidence	
			Diagnostic (ref)	PRRT
Intravenous	GRP-R-expressing tumors			
	Prostate cancer*	+	+ (*44*)	
	Breast cancer*	+	+ (*17*)	
	GIST*	+		
	Small-cell lung cancer	+		
	NT_1-R-expressing tumors			
	Exocrine pancreatic cancer*	+	+ (*18*)	
	Meningiomas	+		
	Ewing sarcomas	+		
	VIP-R-expressing tumors			
	$VPAC_1$†	+	+ (*19*)	
	$VPAC_2$: GIST*, other stromal tumors	+		
	NPY-R-expressing tumors			
	Y_1: breast Ca*	+		
	Y_1/Y_2: sex cord stromal ovarian tumors	+		
	Y_1/Y_2: adrenal tumors	+		
	GLP1-R-expressing tumors			
	Insulinomas*	+		
	Gastrinomas	+		
	CRF-R-expressing tumors			
	CRF_1: ACTH-prod. pituitary adenomas	+		
	paragangliomas	+		
	CRF_2: growth hormone-prod. pituitary adenomas	+		
	nonfunctioning pituitary adenomas	+		
	Tumors expressing multiple sst subtypes			
	Medullary thyroid cancer	+		
	Pituitary adenomas	+		
	Prostate cancers	+		
	Gastric cancers	+		
Topical	SP-R (NK1)-expressing central nervous system tumors			
	Gliomas*	+	+	+ (*31*)

*Most eligible for PRRT, on the basis of high incidence and density of receptors.
†Gastrointestinal cancers; many other $VPAC_1$-R-expressing tumors may be inadequate because of high $VPAC_1$ expression in normal tissues.

ered to be largely predictive for in vivo conditions, based on the excellent correlation between in vitro and in vivo receptor evaluation (*20*). The list is further supported by a limited number of reports on in vivo targeting for diagnostic purposes. PRRT studies are still largely absent in this group.

GRPs. Of great potential interest for PRRT are GRP receptors, because they are abundant in most breast and prostate cancers. Samples tested in vitro have originated only from surgically operable tumors. The investigated sample collection, therefore, has consisted predominantly of primaries rather than of metastatic tissues and rarely has contained advanced undifferentiated cancers or hormone-insensitive cancers (*21,22*). This means that the GRP receptor status of the latter tumor group remains largely unknown, having not been investigated for technical reasons. GRP receptor heterogeneity is frequent in breast cancer and could pose a potential problem for GRP receptor radiotherapy (*21*). One target that may be extremely attractive for PRRT is GISTs, because of the extraordinarily high GRP receptor density found in these tumors (*16*).

NT Receptors. A subgroup of ductal pancreatic carcinomas expresses a high density of NT receptors (*23*). A preliminary in vivo NT receptor scanning study visualized a faint signal from a tumor with a high density of these receptors (*18*). These tumors may be attractive for PRRT, despite the low cellularity of the type of cancer, often consisting of few but strongly receptor-positive neoplastic ducts embedded within a receptor-negative surrounding fibrosis (as in chronic pancreatitis) (*23*). This low cellularity may explain in part the weakness of the in vivo signal. Other tumors expressing NT receptors are meningiomas and Ewing sarcomas.

VIP Receptors. Although a majority of human cancers express VIP receptors of the VIP–pituitary adenylate cyclase-activating polypeptide 1 (VPAC1) subtype, the targeting of VPAC1-receptors for PRRT is unlikely to be have

great potential because of the ubiquitous distribution of VPAC1 in most organs (*24*). Conversely, VPAC2, which is only rarely expressed in normal tissues, may be a target for PRRT in VPAC2-expressing cancers. GISTs, with high VPAC2 receptor density, may be most attractive examples (*16*). In vivo data using ^{123}I-VIP as a universal ligand targeting VPAC1 and VPAC2 are available as proof of concept that VIP receptor-positive tumors, specifically gastrointestinal cancers, can be targeted in vivo in selected patients (*19,25*).

Neuropeptide-Y (NPY) Receptors. NPY receptors have been found to be highly expressed in breast cancer, predominantly as Y1 subtype, as well as in a subgroup of ovarian tumors (sex cord stromal tumors) and adrenal tumors (*26–28*). This is a new family of peptide receptors for which in vivo scanning studies in human tumors should be performed.

Glucagon-Like-Peptide 1 (GLP1) Receptors. A very high density of GLP1 receptors was reported in virtually all insulinomas and, at lower density, in gastrinomas, suggesting the use of GLP1 analogs for PRRT of these tumors (*15*). Whereas rat insulinomas were reported to be targeted in vivo by GLP1 analogs, such evidence is still missing for human insulinomas.

Corticotropin-Releasing Factor (CRF) Receptors. CRF receptors are expressed in selected human cancers (*29*). Those with a high density include adrenocorticotropic hormone-producing pituitary adenomas and paragangliomas (CRF1) as well as GH-producing and nonfunctioning pituitary adenomas (CRF2). These may be attractive PRRT candidates.

Neurokinin 1 (NK1) receptors. Because gliomas have a density of NK1 receptors that is considerably higher than that of somatostatin receptors, the same topical approach as for somatostatin receptors has been proposed and a pilot study was started to evaluate the effect of PRRT in glioblastomas (*12,30*). The study is still in progress, but encouraging preliminary data have been reported (*31*).

MULTIRECEPTOR TARGETING

The presence of multiple peptide receptors in selected cancers may be the basis for multireceptor radiotherapy using 2 or more radiotracers concomitantly. This strategy would have 2 main advantages. First, 2 or more radioligands administered concomitantly could considerably increase the therapeutic dose to the tumor. Second, some of the problems related to receptor heterogeneity in tumors may be overcome, because it is likely that more tumor cells would be targeted with 2 or more radioligands than would be possible with only a single ligand. Figure 2 illustrates this with the example of CCK and somatostatin receptors. Most of the CCK receptors are distributed on the right part of the sample, whereas most of the somatostatin receptors are on the left. It is expected that PRRT with radiolabeled CCK and somatostatin analogs administered together would be more successful than PRRT using either tracer alone, because the tumor would be targeted much more homogeneously. Such multireceptor targeting could possibly prevent or reduce resistance or escape from radiotherapy. Tumors of interest for multireceptor targeting include breast cancers (expressing concomitantly GRP and NPY receptors) and GISTs (with GRP, CCK2, and VPAC2 receptors) (*16,32*).

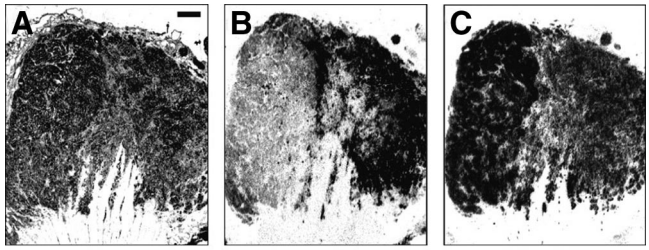

FIGURE 2. Concomitant but complementary distribution of CCK and somatostatin receptors in adjacent sections of GEP NET. (A) Hematoxylin-eosin stained section. Bar = 1 mm. (B) Autoradiograph showing CCK receptors predominantly expressed in right part of tumor. (C) Autoradiograph showing somatostatin receptors predominantly found in left part of tumor.

PEPTIDE RADIOLIGAND CANDIDATES

A prerequisite for successful PRRT is the availability of adequate peptide tracers. The best developed tracers at present are usually characterized by binding affinities in the low nanomolar range. So far, these small peptides have not been found to be immunogenic, unlike antibodies used in radiolabeled therapy. Peptide radioligands include those used for somatostatin receptor targeting, which are mostly derived from octreotide (*2*). Moreover, the development of adequate peptide radioligands for other receptors is also rapidly progressing (Table 4). Although many groups are working to develop GRP, CCK2, and NT radioligands, little information is available on adequate NPY, GLP-1, and VIP ligands to be used for PRRT (*1*).

Radioligands in Human Use Today

Somatostatin. Prototypical in targeted radiotherapy are radiopeptides based on somatostatin analogs. Four of these ligands are in clinical use. They are depicted in Figure 3. The oldest agent is ^{111}In-DTPA-octreotide. This peptide radioligand was designed for scintigraphy and, because of the Auger and conversion electrons emitted by ^{111}In, has been suggested to be useful for therapy as well. One of the drawbacks of this radiopeptide is its only moderate binding affinity to sst2 and almost negligible affinity to sst1, 3, 4, and 5. In addition, DTPA is not a suitable chelator for commercially available β-emitters such as ^{90}Y and ^{177}Lu. For these radiometals, it is better to use the macrocyclic chelator 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid (DOTA). It forms very stable (thermodynamically and kinetically) metal complexes. The DOTA-coupled

TABLE 4
Peptide Radioligands for In Vivo Targeting of Tumors Expressing Peptide Receptors

Peptide receptor	Radioligands in use in humans	Radioligands in development	Reference
Somatostatin			
sst2	DTPAOC DOTATOC DOTATATE	Carbohydrated derivatives and other biodistribution modifiers	*8,10,38,39,45*
sst2,5	DOTA-lanreotide		*46*
sst2,3,5		DOTANOC DOTABOC DOTANOCate DOTABOCate	*35,36*
sst1,2,3,4,5		KE 108 and derivatives	*37*
Bombesin			
GRP-R	Demobesin; RP527		*17,34*
NMB-R	—		
BB_3	—	—	
CCK			
CCK_2	Minigastrin; CCK analog	MG-11	*9,14,47*
Neurotensin			
NT-1	—	Neurotensin XI	*18*
NPY			
Y_2	—	Ac-[Ahx^{5-24},K^4($^{99m}Tc(Co)_3$)-PADA]-NPY	*41*
GLP1	—	Exendin-3 or -4	*42*
NK1	DOTAGA-substance P		*31*

somatostatin-based radiopeptides are ^{90}Y-DOTA^0-Tyr^3-octreotide (^{90}Y-DOTATOC, ^{90}Y-SMT-487), ^{90}Y-DOTA-lanreotide (MAURITIUS), and ^{177}Lu-DOTA-Tyr^3-The^8-octreotide (^{177}Lu-DOTATATE). They differ with regard to the sst receptor subtype affinity profile (*33*). The DOTATATE derivative has the highest sst2 receptor affinity, whereas DOTA-lanreotide has lower affinity to sst2 but shows sst5 affinity (*33*).

CCK/Gastrin. As indicated previously, CCK2 receptors may be attractive targets for internal radiotherapy. The ligand used for the first clinical trial was a DTPA-D-Glu chelator-modified minigastrin (Fig. 4) labeled with ^{90}Y. Because of kidney and hemotoxicity, the trial was stopped (*9*). New gastrin-derived ligands with much lower kidney toxicity but excellent target affinity are being developed (*14*). In these, 4 glutamic acid residues have been deleted from the minigastrin derivative. This truncated radiopeptide showed an improved binding affinity to the CCK2-receptor (0.2 vs. 1.0 nmol/L) and retained tumor uptake in the rat CA 20948 tumor model but showed a kidney uptake that was lower by a factor of 25 (*14*).

Substance P. Another peptide candidate used in PRRT for brain tumors is ^{90}Y-DOTAGA-substance P, shown in Figure 5. This tracer is given as brachytherapy intratumorally or into the tumor cavity (*31*). It is directed against the NK1 receptor, overexpressed in human glioblastoma (*30*). The peptide is metabolically unstable, and the efficacy of PRRT in glioblastoma (targeting the NK1 receptors) could probably be increased if radiopeptides resistant to proteases were introduced into the clinic.

Bombesin. Two ^{99m}Tc-based bombesin ligands with high affinity for GRP receptors are being used clinically. One is called demobesin, a tetraamine-derivatized bombesin antagonist [D-Phe^6,Leu-NHEt^{13},desMet^{14}] bombesin (6–14) (*34*). Preliminary results show good tumor delineation in prostate cancer patients.

The other ^{99m}Tc-based ligand is a N_3S chelator coupled to bombesin (7–14) via a gly-5-aminovaleric acid spacer. It can be labeled with high specific activity and radiochemical yield and has been shown to identify breast and prostate primary cancer and metastases (*17*). This agent should also be suitable for labeling with ^{188}Re, the therapeutic congener of ^{99m}Tc.

NT. Little activity has been reported on the development of NT-based radioligands. Buchegger et al. (*18*) published a study of 4 patients using a metabolically stabilized (8–13) neurotensin analog, (NT-XI) modified with *N*-carboxymethyl-histidine for labeling with a $Tc(CO)_3^+$ unit. Research is being pursued by this group using the carbonyl approach, with the therapeutic goal of labeling with the β-emitter ^{188}Re.

Radioligands in Development

Somatostatin. There are still potential improvements in the field of somatostatin receptor targeting. One step being pursued is the development of somatostatin-based radioligands with a broader receptor subtype affinity profile. This may not only extend the range of targeted cancer candidates but also increase the tumor uptake, because of the presence of several receptor subtypes on the same tumor cell.

Several new compounds have been developed that show high affinity to sst2, 3, and 5 (*35,36*). These were modified at position 3 of the octapeptide. The best radiopeptides were

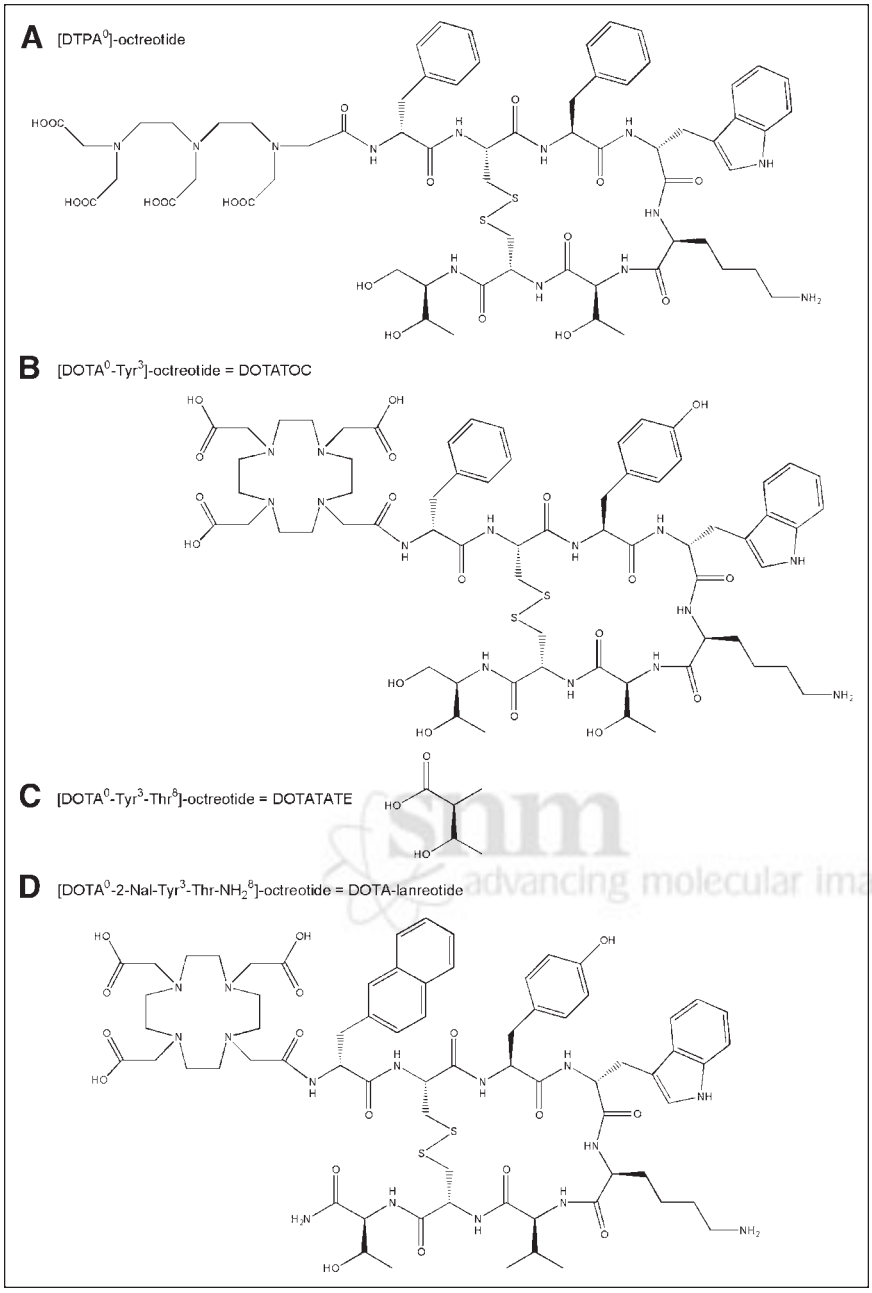

FIGURE 3. Chemical structures of DTPA- and DOTA-modified somatostatin-based peptides for targeted radiotherapy. (A) DTPA^0-octreotide. (B) DOTA^0-Tyr^3-octreotide (DOTATOC). (C) DOTA^0-Tyr^3-Thr^8-octreotide (DOTATATE). (D) DOTA^0-2-Nal-Tyr^3-Thr-NH$_2^8$-octreotide (DOTA-lanreotide).

those with unnatural amino acids 1-naphtyl-alanine (1-Nal) and benzothienyl-alanine (BzThi).

Attempts are also being made to develop pansomatostatin radioligands. Data on the first peptide, KE 108, which has higher potency than somatostatin-28 to all receptor subtypes and can be radioiodinated, were published recently (*37*). This peptide was also modified by coupling DOTA to the *N*-terminus (Fig. 6). It was still able to bind with high

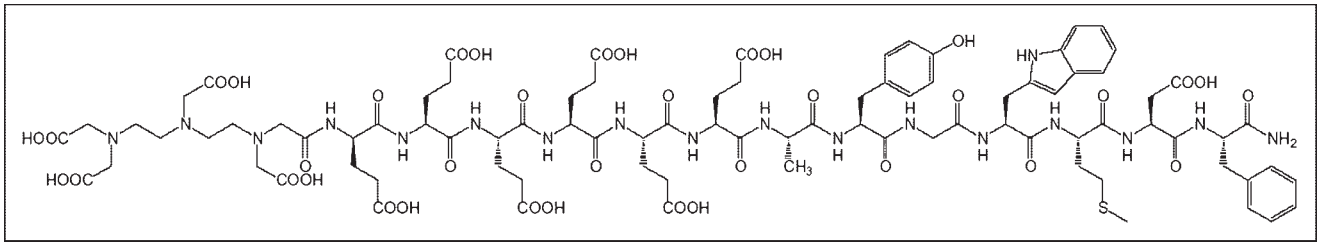

FIGURE 4. Structural formula of the CCK2-selective analog DTPA-D-Glu-Glu$_5$-Ala-Tyr-Gly-Trp-Met-Asp-PheNH$_2$ (minigastrin).

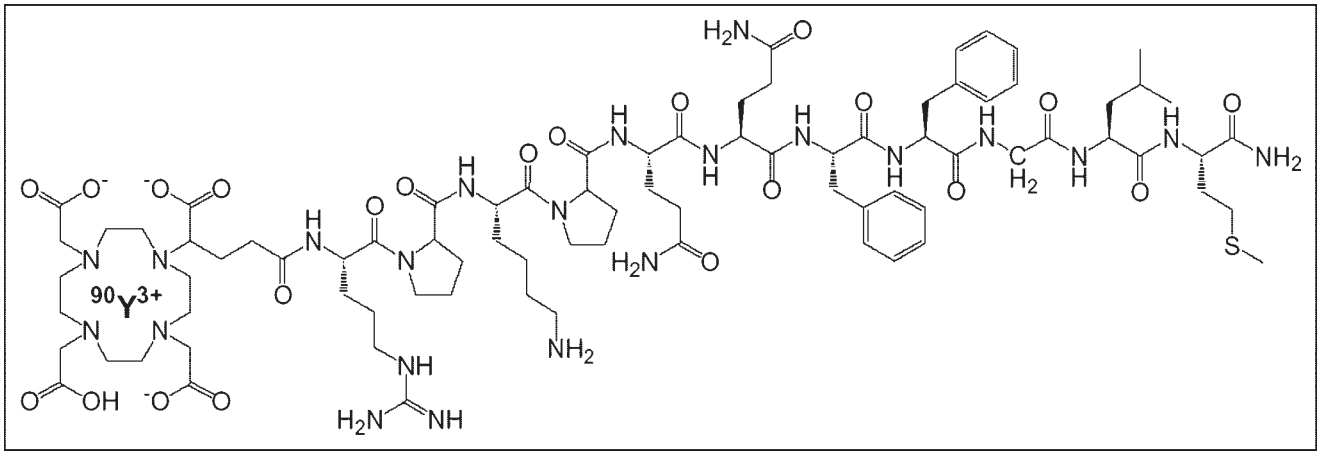

FIGURE 5. Structural formula of ^{90}Y-DOTAGA-substance P.

affinity to all 5 somatostatin receptor subtypes (Reubi and Mäcke, unpublished data).

Another recent strategy has been to couple octreotide or octreotate derivatives to carbohydrates to improve tracer pharmacokinetics (*38,39*).

Bombesin. A promising group of peptides was developed by Hoffman et al. (*40*) for targeted radiotherapy of GRP receptor-positive tumors. These are based on the bombesin (7–14) sequence and coupled to DOTA via aminocarboxyalkyl spacer groups. These peptides were successfully labeled with ^{177}Lu, ^{166}Ho, and other radiolanthanides. They are especially promising candidates for PRRT of prostate and breast cancer patients.

NPY. A new radioligand was described by Langer et al. (*41*). This research group has used the $Tc(CO)_3^+$ approach and developed a highly selective high-affinity Y_2-receptor ligand Ac-[Ahx$^{5-24}$,K^4 (^{99m}Tc(CO)$_3$-2-picolylamine *N,N*-diacetic acid) (PADA)]-NPY. This radioligand has about 1.5 nmol/L Y_2-affinity if complexed to cold $Re(CO)_3^+$. Another NPY radioligand in development is the Y_1/Y_2-selective [K^4(^{nat}Re(CO)$_3$-PADA, A^{26}]-NPY derivative, found to bind with 16 nmol/L affinity to Y_1 and 8.5 nmol/L to Y_2 (*41*).

GLP-1. GLP-1 is an intestinal hormone that stimulates insulin secretion. Its action is mediated by a receptor expressed in islet cells. These receptors are massively overexpressed in insulinoma (*15*). Therefore, radiolabeled versions of GLP-1 and its metabolically more stable congener exendin 3 or 4 have been developed and studied in mouse models. ^{111}In was coupled to these peptides via DTPA-complexation, and ^{123}I labeling was performed via the IODO-GEN method (*42*).

Conclusion. In general one may conclude that those peptides that will perform adequately in diagnostic imaging eventually will be coupled to DOTA and DOTAGA for labeling with the β-emitters suitable for PRRT or with technology enabling ^{188}Re labeling. Research in this direction is ongoing in academia and industry.

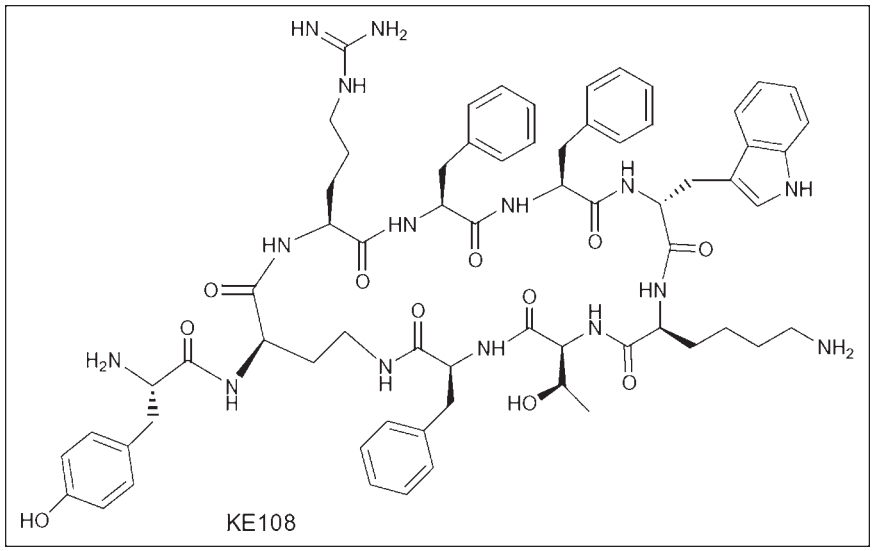

FIGURE 6. Structural formula of KE 108 (pan-somatostatin).

REFERENCES

1. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. *Endocr Rev.* 2003;24:389–427.
2. Heppeler A, Froidevaux S, Eberle AN, Maecke HR. Receptor targeting for tumor localisation and therapy with radiopeptides. *Curr Med Chem.* 2000;7:971–994.
3. Kwekkeboom DJ, Krenning EP, de Jong M. Peptide receptor imaging and therapy. *J Nucl Med.* 2000;41:1704–1713.
4. Tofilon PJ, Saxman S, Coleman CN. Molecular targets for radiation therapy: bringing preclinical data into clinical trials. *Clin Cancer Res.* 2003;9:3518–3520.
5. Merlo A, Hausmann O, Wasner M, et al. Locoregional regulatory peptide receptor targeting with the diffusible somatostatin analogue ^{90}Y-labeled DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC): a pilot study in human gliomas. *Clin Cancer Res.* 1999;5:1025–1033.
6. Reubi JC, Waser B, Foekens JA, Klijn JGM, Lamberts SWJ, Laissue J. Somatostatin receptor incidence and distribution in breast cancer using receptor autoradiography: relationship to EGF receptors. *Int J Cancer.* 1990;46:416–420.
7. de Jong M, Breeman WA, Bernard BF, et al. Tumor response after [(90)Y-DOTA(0),Tyr(3)]octreotide radionuclide therapy in a transplantable rat tumor model is dependent on tumor size. *J Nucl Med.* 2001;42:1841–1846.
8. Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. *Eur J Nucl Med.* 2003;30:417–422.
9. Behr TM, Behe MP. Cholecystokinin-B/Gastrin receptor-targeting peptides for staging and therapy of medullary thyroid cancer and other cholecystokinin-B receptor-expressing malignancies. *Semin Nucl Med.* 2002;32:97–109.
10. Waldherr C, Pless M, Maecke HR, Haldemann A, Mueller-Brand J. The clinical value of [^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide (^{90}Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Ann Oncol.* 2001;12:941–945.
11. Paganelli G, Zoboli S, Cremonesi M, et al. Receptor-mediated radiotherapy with ^{90}Y-DOTA-D-Phe1-Tyr3-octreotide. *Eur J Nucl Med.* 2001;28:426–434.
12. Schumacher T, Hofer S, Eichhorn K, et al. Local injection of the (90)Y-labelled peptidic vector DOTATOC to control gliomas of WHO grades II and III: an extended pilot study. *Eur J Nucl Med.* 2002;29:486–493.
13. Reubi JC, Schaer JC, Waser B. Cholecystokinin(CCK)-A and CCK-B/gastrin receptors in human tumors. *Cancer Res.* 1997;57:1377–1386.
14. Bernard BF, Béhé M, Breeman WAP, et al. Preclinical evaluation of minigastrin analogs for CCK-B receptor targeting. *Cancer Biother & Radiopharm.* 2003;18:281.
15. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumors as molecular basis for in vivo multireceptor tumor targeting. *Eur J Nucl Med.* 2003;30:781–793.
16. Reubi JC, Korner M, Waser B, Mazzucchelli L, Guillou L. High expression of peptide receptors as a novel target in gastrointestinal stromal tumours. *Eur J Nucl Med Mol Imaging.* 2004;31:803–810.
17. Van de Wiele C, Dumont F, Vanden Broecke R, et al. Technetium-99m RP527, a GRP analogue for visualisation of GRP receptor-expressing malignancies: a feasibility study. *Eur J Nucl Med.* 2000;27:1694–1699.
18. Buchegger F, Bonvin F, Kosinski M, et al. Radiolabeled neurotensin analog, ^{99m}Tc-NT-XI, evaluated in ductal pancreatic adenocarcinoma patients. *J Nucl Med.* 2003;44:1649–1654.
19. Virgolini I, Raderer M, Kurtaran A, et al. 123-I-vasoactive intestinal peptide (VIP) receptor scanning: update of imaging results in patients with adenocarcinomas and endocrine tumors of the gastrointestinal tract. *Nucl Med Biol.* 1996;23:685–692.
20. Krenning EP, Kwekkeboom DJ, Pauwels S, Kvols LK, Reubi JC. *Somatostatin Receptor Scintigraphy.* New York, NY: Raven Press; 1995:1–50.
21. Gugger M, Reubi JC. GRP receptors in non-neplastic and neoplastic human breast. *Am J Pathol.* 1999;155:2067–2076.
22. Markwalder R, Reubi JC. Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. *Cancer Res.* 1999;59:1152–1159.
23. Reubi JC, Waser B, Friess H, Büchler MW, Laissue JA. Neurotensin receptors: a new marker for human ductal pancreatic adenocarcinoma. *Gut.* 1998;42:546–550.
24. Reubi JC, Läderach U, Waser B, Gebbers J-O, Robberecht P, Laissue JA. Vasoactive intestinal peptide/pituitary adenylate cyclase-activating peptide receptor subtypes in human tumors and their tissues of origin. *Cancer Res.* 2000;60:3105–3112.
25. Hessenius C, Bäder M, Meinhold H, et al. Vasoactive intestinal peptide receptor scintigraphy in patients with pancreatic adenocarcinomas or neuroendocrine tumors. *Eur J Nucl Med.* 2000;27:1684–1693.
26. Reubi JC, Gugger M, Waser B, Schaer JC. Y1-mediated effect of neuropeptide Y in cancer: breast carcinomas as targets. *Cancer Res.* 2001;61:4636–4641.
27. Korner M, Waser B, Reubi JC. Neuropeptide Y receptor expression in human primary ovarian neoplasms. *Lab Invest.* 2004;84:71–80.
28. Körner M, Waser B, Reubi JC. High expression of NPY receptors in tumors of the human adrenal gland and extraadrenal paraganglia. *Clin Cancer Res.* 2004;in press.
29. Reubi JC, Waser B, Vale W, Rivier J. Expression of CRF1 and CRF2 receptors in human cancers. *J Clin Endocrinol Metab.* 2003;88:3312–3320.
30. Hennig IM, Laissue JA, Horisberger U, Reubi JC. Substance P receptors in human primary neoplasms: tumoural and vascular localisation. *Int J Cancer.* 1995;61:786–792.
31. Schumacher T, Eichhorn K, Hofer S, et al. Diffusible brachytherapy (DBT) with radiolabelled substance P in high grade gliomas: first observations [abstract]. *Eur J Nucl Med.* 2001;28:1040.
32. Reubi JC, Gugger M, Waser B. Coexpressed peptide receptors in breast cancers as molecular basis for in vivo multireceptor tumor targeting. *Eur J Nucl Med.* 2002;29:855–862.
33. Reubi JC, Schaer JC, Waser B, et al. Affinity profiles for human somatostatin receptor sst1-sst5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. *Eur J Nucl Med.* 2000;27:273–282.
34. Nock B, Nikolopoulou A, Chiotellis E, et al. [^{99m}Tc]demobesin 1, a novel potent bombesin analogue for GRP receptor-targeted tumour imaging. *Eur J Nucl Med.* 2003;30:247–258.
35. Wild D, Schmitt JS, Ginj M, et al. DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. *Eur J Nucl Med Mol Imaging.* 2003;30:1338–1347.
36. Ginj M, Chen J, Reubi JC, Maecke HR. Preclinical evaluation of new and highly potent analogs of octreotide for targeted radiotherapy [abstract]. *Eur J Nucl Med Mol Imaging.* 2003;30(suppl 2):S198–S199.
37. Reubi JC, Eisenwiener KP, Rink H, Waser B, Macke HR. A new peptidic somatostatin agonist with high affinity to all five somatostatin receptors. *Eur J Pharmacol.* 2002;456:45–49.
38. Wester HJ, Schottelius M, Scheidhauer K, Reubi JC, Wolf I, Schwaiger M. Comparison of radioiodinated TOC, TOCA and Mtr-TOCA: the effect of carbohydration on the pharmacokinetics. *Eur J Nucl Med.* 2002;29:28–38.
39. Schottelius M, Wester HJ, Reubi JC, Senekowitsch-Schmidtke R, Schwaiger M. Improvement of pharmacokinetics of radioiodinated tyr(3)-octreotide by conjugation with carbohydrates. *Bioconjug Chem.* 2002;13:1021–1030.
40. Hoffman TJ, Gali H, Smith CJ, et al. Novel series of ^{111}In-labeled bombesin analogs as potential radiopharmaceuticals for specific targeting of gastrin-releasing peptide receptors expressed on human prostate cancer cells. *J Nucl Med.* 2003;44:823–831.
41. Langer M, La Bella R, Garcia-Garayoa E, Beck-Sickinger AG. ^{99m}Tc-labeled neuropeptide Y analogues as potential tumor imaging agents. *Bioconjug Chem.* 2001;12:1028–1034.
42. Behe M, Behr TM, Schmalor W, Herbst B, Gotthardt M. Indium-111 labelled GLP-1 for in vivo diagnostic of insulinomas [abstract]. *J Nucl Med.* 2002;43(suppl):92P.
43. Valkema R, De Jong M, Bakker WH, et al. Phase I study of peptide receptor radionuclide therapy with [In-DTPA]octreotide: the Rotterdam experience. *Semin Nucl Med.* 2000;32:110–122.
44. Scopinaro F, De Vincentis G, Varvarigou AD, et al. ^{99m}Tc-bombesin detects prostate cancer and invasion of pelvic lymph nodes. *Eur J Nucl Med Mol Imaging.* 2003;30:1378–1382.
45. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe^{1}]- and [^{123}I-Tyr^{3}]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med.* 1993;20:716–731.
46. Smith-Jones P, Bischof C, Leimer D, et al. "Mauritius" a novel somatostatin analog for tumor diagnosis and therapy [abstract]. *J Nucl Med.* 1998;39(suppl):223P.
47. Kwekkeboom DJ, Bakker WH, Kooij PP, et al. Cholecystokinin receptor imaging using an octapeptide DTPA-CCK analogue in patients with medullary thyroid carcinoma. *Eur J Nucl Med.* 2000;27:1312–1317.