ACCOUNTS
of chemical research

Tumor Imaging and Therapy Using Radiolabeled Somatostatin Analogues

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RECEIVED ON AUGUST 30, 2008

CONSPECTUS

Molecular imaging plays an essential role in balancing the clinical benefits and risks of radionuclide-based cancer therapy. To effectively treat individual patients, careful assessment of biodistribution, dosimetry, and toxicity is essential. In this Account, we describe advances that combine features of molecular imaging and radionuclide therapy to provide new avenues toward individualized cancer treatment.

Selective receptor-targeting radiopeptides have emerged as an important class of radiopharmaceuticals for molecular imaging and therapy of tumors that overexpress peptide receptors on the cell membrane. After such peptides labeled with γ-emitting radionuclides bind to their receptors, they allow clinicians to visualize receptor-expressing tumors non-invasively. Peptides labeled with β-particle emitters could also eradicate receptor-expressing tumors.

The somatostatin receptors, which are overexpressed in a majority of neuroendocrine tumors, represent the first and best example of targets for radiopeptide-based imaging and radionuclide therapy. The somatostatin analogue ^{111}In-octreotide permits the localization and staging of neuroendocrine tumors that express the appropriate somatostatin receptors. Newer modified somatostatin analogues, including Tyr^3-octreotide and Tyr^3-octreotate, are successfully being used for tumor imaging and radionuclide therapy. Because there are few effective therapies for patients with inoperable or metastasized neuroendocrine tumors, this therapy is a promising novel treatment option for these patients.

Peptide receptor imaging and radionuclide therapy can be combined in a single probe, called a "theranostic". To select patients who are likely to benefit from this type of intervention, we first use a peptide analogue labeled with a diagnostic radionuclide to obtain a scan. Selected patients will be treated using the same or a similar peptide analogue labeled with a therapeutic radionuclide. The development of such theranostics could greatly advance the development of personalized treatments.

Apart from patient selection for radionuclide therapy, other imaging applications of targeted radiopeptides include localization of primary tumors, detection of metastatic disease (staging/restaging), dosimetry (prediction of response and radiotoxicity), monitoring effects of surgery, radio(nudide)therapy or chemotherapy, and detection of progression of disease or relapse (follow up).

For further evaluation of tumor receptor expression and to increase the value of cancer targeting using radiopeptides, researchers have introduced and evaluated different radiolabeled analogues of other peptide families, such as cholecystokinin (CCK), gastrin, bombesin, substance P, vasoactive intestinal peptide (VIP), and neuropeptide (NP)-Y analogues. We expect improvements in the development of new peptide analogues: such advances could reduce side effects and allow for the use of combination therapy (for example, combining radiopeptide analogues with chemotherapeutics).

1. Introduction to Molecular Imaging

Molecular imaging can be defined as the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems. It is performed using imaging agents visualized by imaging instrumentation. Studies can be 2D, 3D, or 4D and can include quantification over time.

Published on the Web 05/15/2009 www.pubs.acs.org
10.1021/ar800188e CCC: $71.50

Molecular imaging agents, also known as probes, may be radiopharmaceuticals, paramagnetic or fluorescent materials, or bubble-based agents. They are being used as physiological and molecular markers in a number of applications, such as cell trafficking, apoptosis, angiogenesis, cellular metabolism, and drug development studies. Probes may also be used for (the assessment of) therapeutic interventions.

Molecular imaging is carried out with instrumentation that enables signals from probes to be visualized and quantified in space and over time. Imaging techniques include radiotracer imaging [positron emission tomography (PET) and single-photon emission computed tomography (SPECT)], magnetic resonance imaging (MRI), MR spectroscopy (MRS), optical imaging, and ultrasound.

No single imaging modality currently provides the combination of sufficiently high sensitivity and high spatial and temporal resolution; the solution is consequently to combine modalities that offer different strengths. PET and SPECT, for example, are being used in combination with computed tomography (CT) and/or MRI. For the nuclear imaging techniques PET and SPECT radioactive tracers are used; they provide information in a sensitive, non-invasive, and quantitative manner.

2. Molecular Imaging and Therapy Using Radiolabeled Peptides

In our department, we have ample experience with nuclear imaging and radionuclide therapy of tumors using radiolabeled peptides, especially somatostatin analogues.[1−3] Since the first studies, there has been exponential growth in the development and application of radiolabeled peptides for tumor imaging and therapy because peptides have fast clearance, rapid tissue penetration and target accessibility, and low antigenicity and can be produced easily. The specific receptor-binding properties of the peptide ligand can be exploited using a radiolabeled ligand to guide the radioactivity to the tumors expressing a particular receptor. The high affinity of the ligand for the receptor facilitates retention of the radiolabel in the tumor, while its relative small size facilitates rapid clearance from the blood. In Table 1, characteristics of radionuclides commonly used for imaging and therapy are shown. Receptor-binding peptides labeled with γ-radiation emitters for SPECT (indium-111 and technetium-99m) or positron emitters for PET (gallium-68 and fluorine-18) enable visualization of receptor-expressing tissues non-invasively: a technique referred to as peptide receptor imaging (PRI). In addition, peptides labeled with β-particle emitters (yttrium-90 and lutetium-177) have the potential to eradicate receptor-expressing tissues: an approach referred to as peptide receptor radionuclide therapy (PRRT).

TABLE 1. Characteristics of Several Radionuclides Applied in Imaging and Radionuclide Therapy

radionuclide	radiation	energy (keV)	half-life
^{99m}Tc	γ radiation	140	6.01 h
^{111}In	γ (+Auger electrons)	172 and 247 (+25 (maximum) for Auger)	2.8 days
^{68}Ga	positrons	1920 (maximum)	68 min
^{18}F	positrons	635 (maximum)	110 min
^{90}Y	β particles	2281 (maximum)	2.7 days
^{177}Lu	β particles (+γ radiation)	430 (maximum) (+113 and 208 for γ)	6.7 days

Using such receptor targeting peptides, we can perform diagnosis and radionuclide therapy using a single or similar compound (Figure 1). A peptide analogue labeled with a diagnostic radionuclide is used for imaging to select patients who will benefit from radionuclide therapy; this selection is based on high tumor uptake and favorable target/nontarget ratios. Radionuclide therapy is performed using the same or a similar peptide analogue labeled with a therapeutic radionuclide.

The concept of targeting receptor-expressing tumor cells *in vivo* with radiolabeled receptor binding ligands has proven its validity and value using radiolabeled somatostatin analogues, the first and most widely used peptides applied for imaging and radionuclide therapy. The aim of this Account is therefore to describe molecular imaging and therapy applications of radiolabeled somatostatin analogues.

3. Somatostatin Analogues Applied for Molecular Imaging and/or Therapy

The metabolically stable somatostatin analogue ^{111}In-DTPA-octreotide (OctreoScan, DTPA = diethylenetriaminepentaacetic acid) (Figure 2) was approved by the Food and Drug Administration (FDA) on June 2, 1994 for imaging of patients with neuroendocrine tumors. In the intervening period, it has been proven that this radiopeptide permits the localization and staging of tumors that express the appropriate somatostatin receptors. The most important of these is receptor subtype 2 (sst_2), as octreotide has the highest affinity for this subtype receptor.[2,4] The utility of the bifunctional DTPA chelate covalently coupled to peptides is well-known, because it enables high specific activity complexation of ^{111}In, which can be applied for SPECT imaging. ^{111}In-DTPA-octreotide is currently the most commonly used tracer for imaging of neuroendocrine tumors.

The next generation of modified somatostatin analogues (Figure 2) included DOTA,Tyr^3-octreotide (DOTATOC, DOTA =

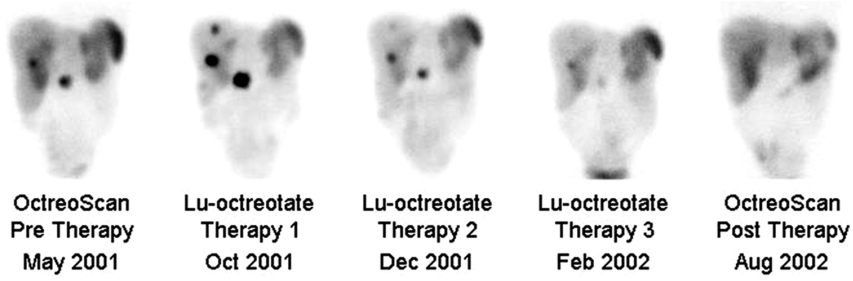

FIGURE 1. Illustration of how similar peptides labeled with different radionuclides can be applied for diagnosis and therapy in the same patients. Anterior views of diagnostic somatostatin receptor imaging using OctreoScan ([^{111}In-DTPA^0]octreotide, left and right images) and images after subsequent therapies with [^{177}Lu-DOTA^0,Tyr^3]octreotate (each with 7400 MBq) in a patient with a neuroendocrine pancreatic tumor (middle abdomen) with liver metastases. Notice the higher tumor uptake on the image after the first therapy because of the higher affinity of [^{177}Lu-DOTA^0,Tyr^3]octreotate if compared to [^{111}In-DTPA^0]octreotide. Also, note the decreasing uptake in the tumor sites after each therapy cycle, which is predictive of tumor shrinkage on CT scanning. The patient had a partial remission (a tumor size decrease of more than 50%) on CT after therapy and had no discernible tumor uptake on the post-therapy diagnostic OctreoScan planar image (utmost right image).

octreotide	D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr (ol)
[Tyr^3]octreotide	D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr (ol)
[Tyr^3]octreotate	D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr

FIGURE 2. Structures of the somatostatin analogues octreotide, Tyr^3-octreotide, and Tyr^3-octreotate.

1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid). This peptide analogue has a higher affinity for sst_2[4] and has the chelator DOTA instead of DTPA, which forms thermodynamically and kinetically stable complexes with a variety of radiometals for PRI as well as PRRT: ^{111}In for SPECT,^{68}Ga for PET, and ^{90}Y and ^{177}Lu for PRRT. On the other hand, DOTA in comparison to DTPA requires a heating step during radiolabeling.

DOTA,Tyr^3-octreotate (DOTATATE) is a third-generation somatostatin analogue for PRI and PRRT (Figure 2). It differs from DOTATOC in that the C-terminal threoninol has been replaced with threonine. In comparison to DOTATOC, it shows considerable improvement in binding to sst_2-positive tumors.[4]

^{99m}Tc-labeled somatostatin analogues, such as ^{99m}Tc-hydrazino pyridine-3-carboxylic acid (HYNIC), Tyr^3-octreotide/octreotate, and ^{99m}Tc-N4, Tyr^3-octreotate were designed for high specific activity labeling with ^{99m}Tc; they are growing in importance because of the cost-effectiveness and wide availability of ^{99m}Tc.[5−8] PET scanning with ^{68}Ga- and ^{18}F-labeled somatostatin analogues will be increasingly applied for detection and follow up of patients with neuroendocrine tumors because of the higher sensitivity of this technique and the reduced time needed for investigation in comparison to SPECT.[9−12]

3.1. Nuclear Imaging, Including the Role of Imaging in Therapy Studies. Somatostatin analogues bind to their receptors on, e.g., gastroenteropancreatic (GEP) neuroendocrine tumors (NETs); radiolabeled somatostatin analogues are being successfully applied for PRI and PRRT of GEP NETs. Radiopeptide molecular imaging can visualize primary tumors and possible metastatic lesions and can offer insight into the variability of receptor expression in tumor lesions within a patient. *In vitro* receptor techniques are usually hampered by the fact that they provide information only about a restricted part of the tumor rather than about the whole tumor and all metastases. The advantage of nuclear medicine is that it can visualize the whole primary lesion and potential metastases by virtue of studying a variety of molecular processes with high sensitivity in the body. Mapping of these results with those of anatomic imaging may give individualized information about heterogeneity between metastases as well.

The receptor status of all tumors in a patient is an important issue, because, e.g., somatostatin receptor-negative lesions may be poorly differentiated and characterized by aggressive growth and poor prognosis, with consequences for the choice of therapy.

The increasing use of molecular imaging changes the basic approach to treatment planning for radionuclide therapy, also because it is possible to take into account the specific biokinetics of the tracer in each patient to determine how the treatment could be tailored. Images obtained after administration can be used to monitor where the radiation is taken up within a patient and can be used to perform dosimetry to estimate radiation doses and predict therapeutic efficiency on tumor lesions as well as effects on normal organs. High tumor uptake on somatostatin receptor scintigraphy and limited amount of liver metastases were predictive factors for tumor remission after ^{177}Lu-DOTATATE therapy.[13]

After therapy, imaging can be applied to detect the progression of disease or relapse.

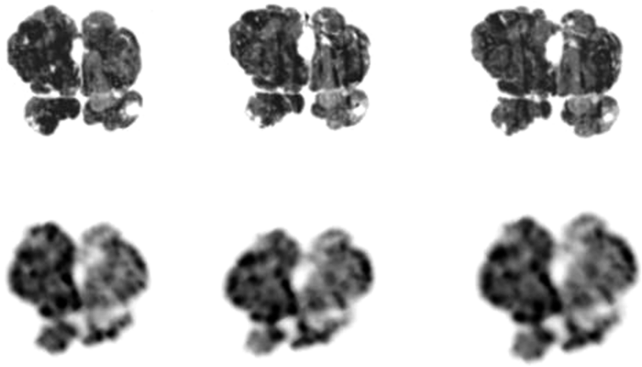

FIGURE 3. Uptake of ^{111}In-DTPA-octreotide in a CA20948 rat pancreatic tumor expressing somatostatin receptors. (Upper row) *In vivo* SPECT images of a CA20948 tumor in a rat. (Lower row) Corresponding *ex vivo* autoradiograms of the same tumor tissue after excision. Note the agreement in configuration as well as intensity of uptake of the radiopeptide using both techniques.

Our experiences emphasized that anatomic imaging alone in the follow up of GEP NETs can indicate that tumors respond to therapy from stabilization to partial regression, but these techniques are not specific to indicate the proportion or even absence of viable cancer cells inside these tumors. In the case of incomplete responses, tumor volumes on CT or MR imaging may overestimate the actual viable cancer cell volume. When tumors can still be seen by CT or MR imaging, the presence of viable cancer cells in such tumors can be demonstrated non-invasively by PRI.

Although the spatial resolution of nuclear molecular imaging is increasing, *in vivo* information about intratumoral heterogeneity of cancer cells cannot be obtained using the current clinical systems, underlining the need for the integrated functional/anatomical systems (e.g., PET/CT or SPECT/CT).

In conclusion, there is a a growing role for image guidance for patient selection, for monitoring, for dosimetry, and for optimizing targeting and therapy.

3.2. Preclinical Imaging. Until recently, PET and SPECT scintigraphy was mainly applied in the clinical setting because the use of PET and SPECT in small animals was hampered by the relatively low resolution of the available systems. Special animal cameras (the so-called microcameras) with good spatial resolution (Figure 3) and sensitivity have been developed since, allowing quantitative studies in (small) experimental animals.[14−17] SPECT and PET can therefore be employed for animal imaging as well as for human imaging, making the techniques highly valuable in translational research.

Preclinical imaging applications include non-invasive imaging of, e.g., (1) pharmacokinetics of (newly developed) tracers by determining the location, duration, and magnitude of radioactivity retention *in vivo* over time in a single animal, (2) tumor development and receptor expression *in vivo* in animal models over time, (3) therapeutic efficiency of PRRT, and (4) normal organ function after PRRT (Figure 4). In addition, data can be coupled to structural changes in follow-up studies in one animal.

3.3. Somatostatin Receptor Radionuclide Therapy. Therapeutic studies in animal models showed the great promise of PRRT using somatostatin analogues.[18−20] Since then, several clinical studies have been started using different analogues labeled with different radionuclides. Because there are only a few effective therapies for patients with inoperable or metastasized neuroendocrine tumors, PRRT with radiolabeled somatostatin analogues is a promising new treatment option for these patients, provided that pretherapy somatostatin receptor scintigraphy is positive. Treatment with any of the various ^{111}In-, ^{90}Y-, or ^{177}Lu-labeled somatostatin analogues that have been used can result in symptomatic improvement. Tumor size reduction was however seldom achieved with ^{111}In-labeled somatostatin analogues, because of the short particle range and lack of crossfire of the Auger electrons emitted by ^{111}In.[3,21] Therefore, somatostatin analogues radiolabeled with ^{90}Y (Table 1), emitting β particles with high energy and long particle ranges, have been applied. Antitumor effects of ^{90}Y-DOTATOC between various studies ranged considerably: objective response (OR) was achieved in 9−33%.[3,22−24]

DOTATATE labeled with the β particles and γ-rays emitting radionuclide ^{177}Lu (Table 1) has been used in our hospital since 2000. ^{177}Lu β particles have a lower energy and shorter particle ranges than those emitted by ^{90}Y, leading to a better energy absorption in smaller tumors. In addition, ^{177}Lu is not a pure β emitter but also emits low-energy γ-rays (10% abundance), and this directly allows post-therapy imaging and dosimetry. With ^{177}Lu-DOTATATE treatments, OR was achieved in 29% of patients and minor response in 16%, stable disease was present in 35%, and progressive disease was present in 20%.[13,25] It also is important that quality of life improves significantly after treatment with ^{177}Lu-DOTATATE.[26]

The median duration of the therapy response for ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE is 30 and 40 months, respectively. Side effects of PRRT are few and mostly mild, certainly when using renal protective agents. Serious, delayed side effects, such as myelodysplastic syndrome or renal failure, are rare.

These data about PRRT compare favorably to the limited number of alternative treatment approaches, such as chemotherapy. Therefore, PRRT might become the therapy of first choice in patients with metastasized or inoperable GEP tumors.

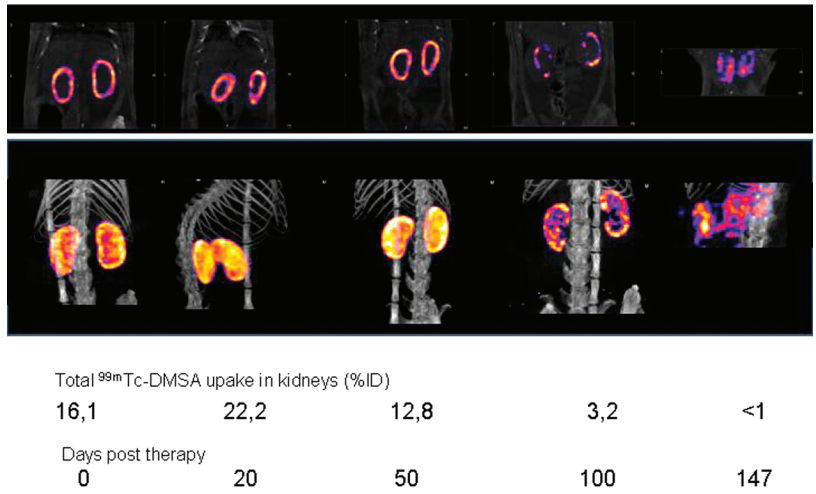

FIGURE 4. Kidney uptake of ^{99m}Tc-DMSA, a marker of renal tubular function. Kidney uptake of ^{99m}Tc-DMSA *in vivo* in a rat was visualized over time by SPECT/CT after treatment with a very high dose of ^{177}Lu-DOTA,Tyr^3-octreotate, leading to renal toxicity. Note the decreasing ^{99m}Tc-DMSA uptake as a result of the developing renal toxicity.[21] (Upper row) Longitudinal views. (Lower row) Maximum intensity projections.

Also, the role in somatostatin receptor-expressing non-GEP tumors, such as metastasized paraganglioma/pheochromocytoma and nonradioiodine-avid differentiated thyroid carcinoma, might become more important.

3.4. Optimization Strategies. Although many advantages have already been associated with the use of radiopeptides as targeting molecules, strategies to improve receptor targeting using optimized analogues are of interest. Improvement of receptor affinity and stabilization of the analogues have been applied to optimize the biodistribution profile of new radiopeptides[27−30] to obtain better tumor/background ratios for diagnosis and therapeutic applications.

Apart from somatostatin analogues, different radiolabeled peptide analogues of other peptide families, such as CCK, gastrin, bombesin, substance P, RGD, and NP-Y analogues, have been introduced and evaluated for tumor imaging and therapy as well.[27,28,30−37] Discussion of these analogues is beyond the scope of this Account.

3.4.1. Multireceptor Targeting. Many tumors simultaneously overexpress receptors for different peptides,[38−40] leading to a number of possible advantages when using simultaneously multiple radiolabeled ligands for PRI or PRRT: (1) *in vivo* application of multireceptor targeting selectively increases the radioactivity accumulation in tumors; (2) some of the receptors are not homogeneously expressed, and from multireceptor targeting, it might be possible to achieve a higher uptake; and (3) because of tumor dedifferentiation and the subsequent loss of certain peptide receptors during therapy, PRRT may fail. Using multireceptor targeting, this risk is reduced.

3.4.2. Agonists versus Antagonists. Studies in patients have thus far been performed with somatostatin receptor agonists, because such agonists are internalized in the (tumor) cells and radioactivity is retained in the cell. Somatostatin receptor antagonists are not internalized and, therefore, thought to be inappropriate for imaging and therapy. In a preclinical study, Ginj et al.[41] recently demonstrated almost twice as high tumor retention of a radiolabeled sst_2 antagonist compared to an agonist, despite a lower receptor affinity of the antagonist for the sst_2. This was thought to be caused by binding of the antagonist to a larger variety of receptor conformations. If these findings can be translated to the patient situation, antagonists can be applied to increase tumor radioactivity retention during PRI and PRRT.

3.4.3. Reduction of Uptake in Kidneys and Bone Marrow. Most peptide analogues are rapidly cleared from the body via the kidneys but partly re-absorbed in the tubuli of these organs (Figure 4), leading to a high absorbed radiation dose. A possibility to improve the results of the treatment with ^{177}Lu-DOTATATE or other radiolabeled somatostatin analogues is to reduce the amount of radiation to critical normal tissues, such as kidneys and bone marrow. In clinical practice, PRRT with radiolabeled somatostatin analogues should always be administered with renal protective agents, e.g., lysine and arginine or a commercially available mixture of amino acids. These amino acids cause a reduced renal uptake of radioactivity in the proximal tubuli.[42,43] Recently, it was found that the plasma expander Gelofusin can be used for this purpose as well.[44,45] Animal studies indicated that the addition of Gelofusin to lysine and arginine can further decrease

the renal uptake.[46] Another possible way to reduce the toxic effects of radiation on both kidneys and bone marrow could be to administer Amifostine. Amifostine is being used in patients treated with external beam radiation therapy and reduces side effects without affecting therapeutic antitumor effects. In animal studies using high activity of ^{177}Lu-DOTATATE, co-administration of Amifostine clearly reduced renal damage.[47]

These strategies protecting normal organs allow for an increase of the cumulative administered activity and the tumor radiation dose during PRRT.

3.4.4. Combination Therapy. The use of different radiolabeled somatostatin analogues in the same patient can be considered interesting because of the different physical properties of, e.g., ^{90}Y and ^{177}Lu. It became clear that ^{90}Y-labeled somatostatin analogues may be more effective for larger tumors, ^{177}Lu-labeled somatostatin analogues may be more effective for smaller tumors, and their combination may be the most effective. In a study in rats with various tumor sizes, therapy with a mixture of ^{90}Y- and ^{177}Lu-labeled DOTATATE had better remission rates than either ^{90}Y- or ^{177}Lu-labeled DOTATATE alone.[48]

Therefore, in future PRRT studies, not only should different radiolabeled peptide analogues and different radionuclides be evaluated but also PRRT with several combinations, preferably in a randomized clinical trial.

Another future direction to improve PRRT effects may be the use of radiosensitizing chemotherapeutical agents [e.g., 5-fluorouracil (5-FU) or capecitabine] in combination with radiopeptides. We recently finished a pilot trial using capecitabine and ^{177}Lu-DOTATATE and found that this new combination is safe and feasible.[49] With this knowledge, we recently started a randomized, clinical, multicenter trial comparing treatment to ^{177}Lu-DOTATATE with and without capecitabine in patients with GEP tumors.

4. Future Outlook

Our aim is to optimize PRI and PRRT by the following: (1) Developing new peptide analogues with increased receptor binding affinity and improved stability might lead to higher accumulation of radioactivity inside tumor cells. Many new analogues of somatostatin have been developed and widely studied; much profit can also be gained by improving peptide analogues targeting other tumor-related receptors. (2) Increasing the number of receptors on tumor cells by, e.g., gene therapy, will result in a higher contrast during PRI and a higher tumor radiation dose during PRRT. Also, upregulation of the somatostatin receptor has been reported after low-dose preincubation with radiolabeled somatostatin analogues.[50] (3) We will use combinations of labeled peptides for PRI. For PRRT, we will apply radiopeptides in combination with other treatment modalities, such as chemotherapy or radiosensitizer pretreatment. Also, administration of higher radioactivity doses enabled by combinations of PRRT with strategies reducing the radiation dose to normal organs will improve the outcome of tumor treatment.

5. Conclusion

Imaging and targeted radionuclide therapy using radiolabeled peptides, currently especially somatostatin analogues, play an important role in molecular imaging and management of certain tumors. The challenge of balancing benefits (clinical response to radionuclide therapy) and risks (normal organ radiotoxicity) is a significant one; careful assessment of biodistribution, dosimetry, and toxicity is essential, preferably on an individualized basis. Improvements in the field can be expected from new compounds with higher or broader receptor affinity, induction of increased receptor expresion on tumor cells, and the use of combination therapy, espcially combinations of different radiolabeled peptides and combinations of radiolabeled peptides plus chemotherapy or radiosensitizer pretreatment.

BIOGRAPHICAL INFORMATION

Marion de Jong received her M.Sc. degree in biology and biochemistry from the Agricultural University in Wageningen, The Netherlands. She obtained her Ph.D. degree from Erasmus University in Rotterdam in 1993. Her thesis dealt with the significance of thyroid hormone transport systems (Department of Internal Medicine). She joined the research group of Prof. Eric Krenning at the department of Nuclear Medicine of Erasmus MC in 1994. Her research mainly focuses on the use of radiolabeled peptides and other radiopharmaceuticals for multimodal molecular imaging and radionuclide therapy. In 2006, she was appointed Professor of Nuclear Biology. Marion is a member of the Molecular Imaging Committee of the EANM, and she serves as a member of the editorial board and as a reviewer for several international journals in the field of nuclear medicine and molecular imaging. She is the (co-)author of >200 articles and chapters in peer-reviewed international journals and books.

Wouter A. P. Breeman received his B.Sc. degree in chemical engineering and biochemistry in The Netherlands. He obtained his Ph.D. degree (on receptor scintigraphy) from Erasmus University in Rotterdam in 1995, at the Department of Nuclear Medicine. Wouter has been at the Department of Nuclear Medicine of Erasmus MC since 1985 and participated from the very start of the research on radiolabeled peptides in 1986. He is the (co-)au-

thor of approximately 100 articles and chapters in peer-reviewed international journals and books.

Dik J. Kwekkeboom performed his thesis on pituitary adenomas in 1989 and, from 1990 to 1994, worked as a research associate at the Department of Nuclear Medicine in Rotterdam, investigating the value of somatostatin receptor imaging in patients with neuroendocrine and other receptor-expressing tumors. He registered as a nuclear medicine physician in 1998 and, from then on, worked as a staff member at the Department of Nuclear Medicine at the University Hospital Rotterdam. His major research topic is peptide receptor imaging, and he coordinates the studies on therapy with the radiolabeled somatin analogue ^{177}Lu-octreotate in patients with neuroendocrine tumors. He has numerous publications in international journals and textbooks, mainly in the field of endocrinology and peptide receptor scintigraphy and therapy.

Roelf Valkema received his degree in medicine in 1983 from the State University in Leiden, The Netherlands. He obtained his Ph.D. degree from the State University in Leiden in 1992. His thesis dealt with bone densitometry and the use of bisphosphonates in osteoporosis. He joined the group of Prof. Eric Krenning at the Department of Nuclear Medicine of Erasmus MC in 1995. His main research interests are imaging, dosimetry, and therapy using radiolabeled peptides. He is the (co-)author of over 100 articles and chapters in peer-reviewed international journals and books.

Eric P. Krenning completed his M.D. degree in 1972 and achieved a Ph.D. degree by thesis at the University of Rotterdam in 1983. He has, at present, positions as Head of the Department of Nuclear Medicine at Erasmus MC, Rotterdam (since 1985) and Professor of Nuclear Medicine (since 1990) and was made a Fellow of the Royal College of Physicians, London, U.K., in 1999. Dr. Krenning has participated in the educational responsibilities at Erasmus MC, lecturing in internal medicine, nuclear medicine, and endocrinology throughout his career. Dr. Krenning has been involved in research since 1975. His main interests include thyroidology and molecular medicine with radioactive-labeled peptides for imaging and therapy. Dr. Krenning has been the (co-)author of more than 350 peer-reviewed articles since 1975. In these fields, he also received awards and invitations to give honorable lectures.

FOOTNOTES

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