Targeting prostate cancer with radiolabelled bombesins

Theodosia Maina*, Berthold Nock* and Stephen Mather†

*Institute of Radioisotopes – Radiodiagnostic Products, NCSR ‘Demokritos’, Athens, Greece; †Centre for Cancer Imaging, Barts and the London Queen Mary School of Medicine and Dentistry, London, UK

Corresponding address: Prof Stephen J Mather, Department of Nuclear Medicine, St Bartholomew’s Hospital, London EC1A 7BE, UK. E-mail: Stephen.Mather@cancer.org.uk

Date accepted for publication 30 August 2006

Abstract

The fact that a number of common human tumours, including those of breast and prostate, express increased levels of the gastrin-releasing peptide receptor (GRP-R) means that this receptor is a potential target for peptide receptor mediated scintigraphy and targeted radionuclide therapy. Although clinical application is yet in its infancy, there is a considerable literature on preclinical studies aimed at developing suitable radioligands for potential clinical application. This brief review provides an overview of this research and also describes some of the limited clinical studies that have been published.

Keywords: Bombesin; gastrin-releasing peptide; imaging; prostate; cancer.

Introduction

Bombesin (BB) is a linear tetradecapeptide with the sequence Glu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH₂ first isolated from the skin of the European frog Bombina bombina[1]. Bombesin and the corresponding mammalian peptides gastrin-releasing peptide (GRP) and neuromedin B (NMB) exert a variety of physiological actions in the nervous system and the gut. These actions are elicited after binding to G-protein coupled receptors which are situated at the outer membrane of target cells and comprise three members in mammals, the GRP-receptor (GRP-R) with high affinity for the GRP, the NMB-receptor (NMB-R) with high affinity for NMB and the orphan BB₃-receptor (BB₃-R), for which an endogenous ligand has not yet been identified. Amphibian bombesin displays a high affinity for all the above receptor subtypes[2,3]. The role of bombesin-like peptides, and especially of GRP and its interaction with the GRP-R, in promoting tumour growth in human cancer cells both in culture and in nude mice xenografts has been established by numerous studies[4–6]. Most interestingly, the expression of GRP-Rs has been documented in several frequently occurring human cancers, such as in prostate and breast carcinomas[7–11].

As a result, bombesin antagonists and anti-GRP/GRP-R antibodies have been used for treatment of GRP-R-expressing malignancies[12,13]. In an alternative strategy, bombesin-like peptides have been employed as molecular carriers of cytotoxic drugs or diagnostic/therapeutic radionuclides to GRP-R-expressing tumours for diagnosis and therapy[14–17]. For this purpose, agonists are usually preferred, due to their tendency to rapidly internalise after binding to their receptor resulting in increased target accumulation[17–20]. A brief discussion will follow on the attempts so far undertaken to obtain clinically useful GRP-R-targeting radiopeptides, comprising radiohalogenated, technetium, bi- and trivalent radiometal carrying groups of compounds.

Development and preclinical studies on radiolabelled bombesins

The prime aim of any radiopharmaceutical development programme is to produce a metabolically robust radiotracer having a well-defined structure that shows...
the maximal uptake in target tissues (i.e. tumour in this instance) and minimal uptake in normal, non-target tissues including those involved in metabolism and excretion of the tracer. In addition to selection of a receptor binding sequence and a suitable radionuclide, a labelling strategy must be developed which results in a hydrophilic conjugate that is excreted through the renal system and not the hepatobiliary/gastrointestinal tract. First attempts to radioiodinate bombesin for clinical oncology SPECT (single photon emission computed tomography) imaging applications were reported more than a decade ago[21,22]. The first in vivo study in an ovarian carcinoma nude mouse model emphasised the need for using prosthetic groups for obtaining in vivo stable radioiodinated bombesins[23]. For PET (positron emission tomography) studies, [18F with its half-life of 109.7 min and low ß+ energy (0.64 MeV) represents the ideal radionuclide[24]. The first 18F-bombesins were recently evaluated in mice bearing human GRP-R-expressing xenografts[25]. In view of the expanding use of PET cameras in combination with new elegant radiofluorination techniques, it is to be expected that new, improved [18F-based bombesins for oncological PET applications will soon appear. In view of the availability of iodinated analogues, it may also be feasible to use I-124 for PET imaging.

A special category of bombesin-based radiopeptides are those labelled with 99mTc due to the preeminence of 99mTc in diagnostic nuclear medicine[18–20,26]. Recent advances in SPECT technology, such as dynamic SPECT and/or fused SPECT/CT imaging, are expected to rapidly boost the evolution of 99mTc-based bombesin radiotracers toward clinically useful compounds. By attaching the strong N2S2 (DADT) 99mTc-binding centre to [Lys3]BB a 99mTcO4−-chelated analogue was obtained but this showed high radioactivity accumulation in the abdomen[27]. By coupling DADT to [DTPA1-Lys3,Tyr4]BB a much more hydrophilic radiotracer was obtained due to the presence of four pendant DTPA1-carboxylate groups. This analogue showed good GRP-R-targeting in mice and excretion via the renal pathway[28,29]. Neutral 99mTcO3+-complexes are also obtained by coupling tripeptide N3S-donors to BB or BB(7-14), either directly or via a spacer[30–34]. For example, 99mTc-RP527, a BB(7-14) analogue linked at the N-terminus via a glycine-5-aminoovaleric acid spacer to the tri-peptide chelator, dimethylglycyl-L-ser-L-cys, reached a 2%ID/g at 1 h pi in PC-3 xenografts in SCID (severe combined immunodeficiency) mice[30,31].

Bombesins incorporating hydrophilic [trans-99mTcO2]+-cores have also been investigated. Thus, coupling of air-stable hydrophilic phosphine containing P2S2-chelators to BB(7-14) yielded radiotracers of high receptor affinity and good GRP-R-targeting in mice[35,36]. Alternatively, acyclic tetraamines have been coupled to both BB and BB(7-14) to afford high specific activity radiotracers which localised in high percentage in human PC-3 xenografts in nude mice (up to 11%ID/g at 1 h pi)[37]. In view of the toxicity risks inherent in the intravenous injection of pharmacologically active peptides in humans, an acyclic tetraamine was also coupled to the potent antagonist [D(Phe6-Leu-NHEt13,des-Met14)]BB(6-14). The resulting radiopptide exhibited impressively high uptake in PC-3 xenografts (16%ID/g at 1 h pi) in nude mice[38,39].

A versatile route for labelling bombesin via the {[99mTc]fucc-(CO)3(H2O)2}+−-synthon[40] involved coupling of N3-histidinyl-acetic or 2-picolylamine-N,N-diaceatic acid to BB(7-14)[41,42]. But the resulting radiopptides failed to accumulate effectively in PC-3 xenografts in nude mice (<0.6%ID/g at 1.5 h pi). However, convincingly high uptake in PC-3 xenografts (up to 3.7%ID/g at 1 h pi) was exhibited by {[99mTc]fucc-(CO)3(X)-Dpr-(Ser)3][BB(7-14)] analogues (X = H2O or P(CH2OH3)[1,43,44].

These studies have resulted in the availability of clinically useful 99mTc-labelled GRP-R-specific radiotracers as described below. Furthermore, owing to the similarities of technetium and rhenium chemistry these studies also assist the development of matched-pair 186Re/188Re-bombesin radiotherapeutic agents[45].

Another often used diagnostic radionuclide is the cyclotron produced 111In. In targeted radionuclide therapy, peptide analogues labelled with 111In are often used as surrogates to determine the biodistribution and dosimetry of therapeutic radiopharmaceuticals radiolabelled with bi- and trivalent metals[46,47]. For this purpose, DTPA (DTPA = diethylenetriaminepentaacetic acid) or macroyclic derivatives like the universal chelator DOTA (DOTA = ethylenediamine-N,N,N′,N′′-tetraacetic acid) or [43,44].

Clinical studies with radiolabelled bombesin analogues

Detailed published accounts of clinical imaging studies of labelled GRP analogues describe the use of two such tracers. The first of these was 99mTc-RP527, developed by the Canadian Biotech company Resolution Pharmaceuticals Inc. Two papers by Van de Wiele have been published describing small-scale studies with this agent[63,64]. A study in six normal volunteers[63] reported
Pharmacokinetics and biodistribution studies of a Tc-labelled bombesin analogue, RP527

The tracer showed rapid blood clearance and a mixed route of hepatobiliary and renal excretion with diffuse uptake and retention only in the normal breast in women and the testes in man. No side effects were observed and a low effective radiation dose of 0.01 mSv/MBq was calculated. A second study was performed in 10 patients, four with prostate cancer and six with breast cancer. Planar and SPECT images were acquired one and 5–6 h pi of 555 MBq of HPLC purified material. 99mTc-RP527 showed selective uptake in one of the four prostate cancer patients all of which had androgen-resistant disease with bone metastases. In this patient about half of the bone lesions were imaged. Four of the six patients with breast cancer showed tumour uptake all involving lymph nodes and bone metastases. Tumour identification was clearer on the later images due to a decrease in background activity over this time. Normal uptake was seen in the organs of hepatobiliary and renal excretion as well as in the pancreas and normal breast tissue in some subjects. The conclusions drawn from these studies were that the agent was safe for administration and showed promise for imaging of GRP-expressing tumours but that a more extensive study was required to assess the clinical potential of the tracer and to correlate the in vivo uptake of the tracer with the presence of the receptor as measured on resected tissue samples after imaging. Shortly after these studies were completed, Resolution Pharmaceuticals and the rights to RP527 were acquired by Bracco Diagnostics Inc. Bracco has recently begun a phase I study of an Lu-177 labelled bombesin analogue based on RP527 (54) (177Lu-DOTA-[4-aminobenzoyl]–BB(6-14)) (K. Linder pers. comm.).

The second analogue to be studied in some detail was developed as a result of an academic collaboration between NCSR ‘Demokritos’ in Athens and Universita La Sapienza in Rome. The peptide which has the sequence cysteine-(6-amino-n-hexanoic acid)–BB(2-14) can function as autocrine growth factors in human small-cell lung cancer and can function as a hormone in amphibians. [Tc-99m] and [111In]Ga-DOTA bombesin analogues have also been performed using [68Ga-DOTA] bombesin analogues. For example Maecke et al. studied 11 patients with prostate cancer (58) and imaged the primary tumour in all patients within 30 min of injection. In three lymph node metastases were also found. Clearance of the tracer was entirely via the kidneys. In some patients a mild reversible systolic blood pressure reduction was observed in the first 2 min after administration and, in some, a significant uptake in the pancreas. Pancreatic uptake was also observed by Fröberg et al. after injection of 111In or 99mTc labelled bombesin analogues (70). Brief reports of imaging with 68Ga-DOTA bombesin analogues have also appeared in abstract form (71,72).

References

[1] Anastasi A, Erspamer V, Bucci M. Isolation and structure of bombesin and alytensin, two analogous active peptides from the skin of the European amphibians Bombina and Alytes. Experientia 1971; 34: 5–30.
[2] Erspamer V. Discovery, isolation, and characterization of bombesin-like peptides. Ann NY Acad Sci 1988; 547: 3–9.
[3] Kooij GS, Jensen RT, Battey JF. Mammalian bombesin receptors. Med Res Rev 1995; 15: 389–417.
[4] Rozengurt E. Bombesin stimulation of mitogenesis. Specific receptors, signal transduction and early events. Am Rev Respir Dis 1990; 142: S11–S15.
[5] Sunday ME, Kaplan LM, Motoyama E, Chin WW, Spindel ER. Biology of disease. Gastrin releasing peptide (mammalian peptide) gene expression in health and disease. Lab Invest 1988; 59: 5–24.
[6] Cutitta F, Carney DN, Mulshine J et al. Bombesin-like peptides can function as autocrine growth factors in human small-cell lung cancer.

[7] the biodistribution by planar gamma camera imaging up to 48 h pi of 555 MBq of HPLC purified material. The tracer showed rapid blood clearance and a mixed route of hepatobiliary and renal excretion with diffuse uptake and retention only in the normal breast in women and the testes in man. No side effects were observed and a low effective radiation dose of 0.01 mSv/MBq was calculated. A second study was performed in 10 patients, four with prostate cancer and six with breast cancer. Planar and SPECT images were acquired one and 5–6 h pi of 555 MBq of HPLC purified material.

[8] 99mTc-RP527 showed selective uptake in one of the four prostate cancer patients all of which had androgen-resistant disease with bone metastases. In this patient about half of the bone lesions were imaged. Four of the six patients with breast cancer showed tumour uptake all involving lymph nodes and bone metastases. Tumour identification was clearer on the later images due to a decrease in background activity over this time. Normal uptake was seen in the organs of hepatobiliary and renal excretion as well as in the pancreas and normal breast tissue in some subjects. The conclusions drawn from these studies were that the agent was safe for administration and showed promise for imaging of GRP-expressing tumours but that a more extensive study was required to assess the clinical potential of the tracer and to correlate the in vivo uptake of the tracer with the presence of the receptor as measured on resected tissue samples after imaging. Shortly after these studies were completed, Resolution Pharmaceuticals and the rights to RP527 were acquired by Bracco Diagnostics Inc. Bracco has recently begun a phase I study of an Lu-177 labelled bombesin analogue based on RP527 (54) (177Lu-DOTA-[4-aminobenzoyl]–BB(6-14)) (K. Linder pers. comm.).

The second analogue to be studied in some detail was developed as a result of an academic collaboration between NCSR ‘Demokritos’ in Athens and Universita La Sapienza in Rome. The peptide which has the sequence cysteine-(6-amino-n-hexanoic acid)–BB(2-14) can function as autocrine growth factors in human small-cell lung cancer and can function as a hormone in amphibians. [Tc-99m] and [111In]Ga-DOTA bombesin analogues have also been performed using [68Ga-DOTA] bombesin analogues. For example Maecke et al. studied 11 patients with prostate cancer (58) and imaged the primary tumour in all patients within 30 min of injection. In three lymph node metastases were also found. Clearance of the tracer was entirely via the kidneys. In some patients a mild reversible systolic blood pressure reduction was observed in the first 2 min after administration and, in some, a significant uptake in the pancreas. Pancreatic uptake was also observed by Fröberg et al. after injection of 111In or 99mTc labelled bombesin analogues (70). Brief reports of imaging with [68Ga-DOTA] bombesin analogues have also appeared in abstract form (71,72).
cancer. Nature 1985; 316: 823–6.

[7] Reubi JC, Wenger S, Schmuckli-Maurer J, Schaer JC, Gugger M. Bombesin receptor subtypes in human cancers: detection with the universal radioligand (125)I-[D-Tyr(6),beta-Ala(11),Phe(13),Nle(14)]bombesin-(6-14). Clin Cancer Res 2002; 8: 1139–46.

[8] Markwalder R, Reubi JC. Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. Cancer Res 1999; 59: 1192–9.

[9] Halmos G, Wittliff JL, Schally AV. Characterization of bombesin/gastrin-releasing peptide receptors in human breast cancer and their relationship to steroid receptor expression. Cancer Res 1995; 55: 280–7.

[10] Gugger M, Reubi JC. Gastrin releasing peptide receptors in non-neoplastic and neoplastic human breast, Ann J Pathol 1999; 155: 2067–76.

[11] Reubi C, Gugger M, Wasser B. Coexpressed peptide receptors in breast cancers as molecular basis for in vivo multireceptor tumor targeting. Eur J Nucl Med Mol Imaging 2002; 29: 855–62.

[12] de Castiglione R, Gozzini L. Bombesin receptor antagonists. Crit Rev Oncol Hematol 1996; 24: 117–51.

[13] Zhou J, Chen J, Mokotoff M, Nagy A. Cancer chemotherapy based on targeting of gastrin-releasing peptide receptor-positive tumors. Nucl Med Biol 2005; 32: 733–40.

[14] Schally AV, Nagy A, Connors GM, et al. Bombesin/gastrin releasing peptide receptor targeted radiopharmaceuticals: a concise update. Nucl Med Biol 2003; 30: 861–8.

[15] Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocrinol Rev 2003; 24: 389–427.

[16] Van den Bossche B, Van de Wiele C. Receptor imaging in oncology by means of nuclear medicine: current status. J Clin Oncol 2004; 22: 3593–607.

[17] Van de Wiele C, Dumont F, Van Belle S, Slegers G, Peers SH, Dierckx RA. Is there a role for agonist gastrin-releasing peptide radioligands in tumour imaging? Nucl Med Commun 2001; 22: 5–15.

[18] Smith CJ, Volkert WA, Hoffman TJ. Gastrin releasing peptide (GRP) receptor targeted radiotherapeutics: a concise update. Nucl Med Biol 2003; 30: 861–8.

[19] Varvarigou A, Bouziotis P, Zikos C, Scopinaro F, De Vincenzi G. Gastrin-releasing peptide (GRP) analogues for cancer imaging. Cancer Biother Radiopharm 2004; 19: 219–29.

[20] Smith CJ, Volkert WA, Hoffman TJ. Radiolabeled peptide conjugates for targeting of the bombesin receptor superfamily subtypes. Nucl Med Biol 2005; 32: 733–40.

[21] Hoffmann TI, Sieckman GL, Volkert WA. Targeting small cell lung cancer using iodinated peptide analogs. J Label Comp Radiopharm 1995; 1: 37: 321–3.

[22] Hoffmann TI, Sieckman GL, Volkert WA. Iodinated bombesin analogs: effect of N-terminal versus side chain iodine attachment on BBN/GRP receptor binding. J Nucl Med 1999; 37: 185P.

[23] Smith CJ, Volkert WA, Hoffman TJ. Gastrin releasing peptide (GRP) receptor targeted radiotherapeutics: a concise update. Nucl Med Biol 2003; 30: 861–8.

[24] Varvarigou A, Bouziotis P, Zikos C, Scopinaro F, De Vincenzi G. Gastrin-releasing peptide (GRP) analogues for cancer imaging. Cancer Biother Radiopharm 2004; 19: 219–29.

[25] Smith CJ, Volkert WA, Hoffman TJ. Radiolabeled peptide conjugates for targeting of the bombesin receptor superfamily subtypes. Nucl Med Biol 2005; 32: 733–40.

[26] Hoffmann TI, Sieckman GL, Volkert WA. Targeting small cell lung cancer using iodinated peptide analogs. J Label Comp Radiopharm 1995; 1: 37: 321–3.

[27] Hoffmann TI, Sieckman GL, Volkert WA. Iodinated bombesin analogs: effect of N-terminal versus side chain iodine attachment on BBN/GRP receptor binding. J Nucl Med 1999; 37: 185P.

[28] Rogers BE, Rosenfeld ME, Khazaeli MB et al. Localization of iodine-125-mip-Des-Met1-14-bombesin(7-13)NH2 in ovarian carcinoma induced to express the gastrin releasing peptide receptor by adenosinergic vector-mediated gene transfer. J Nucl Med 1997; 38: 1221–9.

[29] Lang L, Eckelmann WC. One-step synthesis of 18F-labeled [18F]N-succinimidy 4-(fluoromethyl)benzoate for protein labeling. Appl Radiat Isot 1994; 45: 1155–63.

[30] Zang X, Cai W, Cao F et al. 18F-Labeled bombesin analogs for targeting GRP receptor-expressing prostate cancer. J Nucl Med 2006; 47: 492–501.

[31] Liu S, Edwards DS. 99mTc-labeled small peptides as diagnostic radiotherapeutics. Chem Rev 1999; 99: 2235–68.

[32] Baidoo KE, Lin KS, Zhan Y, Finley P, Scheffel U, Wagner Jr. Design, synthesis and initial evaluation of high-affinity technetium bombesin bombesin analogues. Bioconjugate Chem 1998; 9: 218–25.

[33] Lin KS, Lau A, Baidoo KE et al. A new high affinity technetium-99m-bombesin analogue of bombesin containing DTPA as a pharmacokinetic modifier. Bioconjugate Chem 2004; 15: 1416–23.
Targeting prostate cancer with radiolabelled bombesins

[47] Liu S. The role of coordination chemistry in the development of target-specific radiopharmaceuticals. Chem Soc Rev 2004; 33: 445–61.

[48] Breeman WA, Hofland LJ, de Jong M et al. Evaluation of radiolabelled bombesin analogues for receptor-targeted scintigraphy and radiotherapy. Int J Cancer 1999; 81: 658–65.

[49] Breeman WA, De Jong M, Bernard BF et al. Pre-clinical evaluation of [111In-DTPA-Pro1, Tyle4]bombesin, a new radioligand for bombesin-receptor scintigraphy. Int J Cancer 1999; 83: 657–63.

[50] Breeman WA, De Jong M, Erion JL et al. Preclinical comparison of [111In]labeled DTPA- or DOTA-bombesin analogs for receptor-targeted scintigraphy and radionuclide therapy. J Nucl Med 2002; 43: 1650–6.

[51] Hoffman TJ, Gali H, Smith CI et al. Novel series of [111In]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: 823–31.

[52] Zhang H, Chen J, Waldhaefer C et al. Synthesis and evaluation of bombesin derivatives on the basis of pan-bombesin peptides labeled with indium-111, lutetium-177, and yttrium-90 for targeting bombesin receptor-expressing tumors. Cancer Res 2004; 64: 6707–15.

[53] Smith CI, Gali H, Sieckman GL et al. Radiochemical investigations of [177Lu-DOTA-8-Aox-BBN(7-14)NH2]: an in vitro/vivo assessment of the targeting ability of this new radiopharmaceutical for PC-3 human prostate cancer cells. Nucl Med Biol 2003; 30: 101–9.

[54] Lantry LE, Cappelletti E, Maddalena ME et al. [177Lu-AMB-A]-synthesis and characterization of a selective [177Lu]-labeled GRP-R agonist for systemic radiotherapy of prostate cancer. J Nucl Med 2006; 47: 1144–52.

[55] Hu F, Cutler CS, Hoffman T, Sieckman G, Volkert WA, Jurisson SS. Pm-149 DOTA bombesin analogs for potential radiotherapy. In vivo comparison with Sm-153 and Lu-177 labeled DO3A-amide-βAla-BBN(7-14)NH2. Nucl Med Biol 2002; 29: 423–30.

[56] Scheffel U, Pomper MG. PET imaging of GRP receptor expression in prostate cancer. J Nucl Med 2004; 45: 1277–8.

[57] Meyer GJ, Macke H, Schuhmacher J, Knapp WH, Hofmann M. 68Ga-labeled DOTA-derivatised peptide ligands. Eur J Nucl Med Mol Imaging 2004; 31: 1097–104.

[58] Moecke HR, Hofmann M, Haberkorn U. 68Ga-labeled peptides in tumor imaging. J Nucl Med 2005; 46: 172S–85.

[59] Rogers BE, Bigott HM, McCarthy DW et al. MicroPET imaging of a gastrin-releasing peptide receptor-positive tumor in a mouse model of human prostate cancer using a 68Ga-labeled bombesin analogue. Bioconjugate Chem 2003; 14: 756–63.

[60] Chen X, Park R, Hou Y et al. MicroPET and autoradiographic imaging of GRP receptor expression with 64Cu-DOTA-[Lys6]bombesin in human prostate adenocarcinoma xenografts. J Nucl Med 2004; 45: 1390–7.

[61] Yang YS, Zhang X, Xiong Z, Chen X. Comparative in vitro and in vivo evaluation of two 64Cu-labeled bombesin analogs in a mouse model of human prostate adenocarcinoma. Nucl Med Biol 2006; 33: 371–80.

[62] Schuhmacher J, Zhang H, Doll J et al. GRP receptor-targeted PET of a rat pancreas carcinoma xenograft in nude mice with a 68Ga-labeled bombesin(6-14) analog. J Nucl Med 2005; 46: 691–9.

[63] Van de Wiele C, Dumont F, Vanden Broecke R et al. Technetium-99m RP527, a GRP analogue for visualization of GRP receptor-expressing malignancies: a feasibility study. Eur J Nucl Med 2000; 27: 1694–9.

[64] Van de Wiele C, Dumont F, Dierckx RA et al. Biodistribution and dosimetry of 99mTc-RP527, a gastrin-releasing peptide (GRP) agonist for the visualization of GRP receptor-expressing malignancies. J Nucl Med 2001; 42: 1722–7.

[65] Varvarigou AD, Scopinaro F, Leondiadi L et al. Synthesis, chemical, radiochemical and radiobiological evaluation of a new 99mTc-labelled bombesin-like peptide. Cancer Biother Radiopharm 2002; 17: 317–26.

[66] Solari A, Scopinaro F, De Vincentis G et al. 99mTc[13]LEU bombesin and a new gamma camera, the imaging probe, are able to guide mammamate breast biopsy. Anticancer Res 2003; 23: 2139–42.

[67] Scopinaro F, De Vincentis G, Varvarigou AD et al. 99mTc-bombesin detects prostate cancer and invasion of pelvic lymph nodes. Eur J Nucl Med Mol Imaging 2003; 30: 1378–82.

[68] Scopinaro F, De Vincentis G, Corazziari E et al. Detection of colon cancer with 99mTc-labelled bombesin derivative (99mTc-leu13-BN1). Cancer Biother Radiopharm 2004; 19: 245–52.

[69] Scopinaro F, Di Santo GP, Tofani A et al. Fast cancer uptake of 99mTc-labelled bombesin (99mTc-BN1). In Vivo 2005; 19: 1071–6.

[70] Fröberg A, Visser M, Maina T et al. Are GRP-receptors present in the human pancreas? J Nucl Med 2006; 47: 429P.

[71] Dimitrakopoulou-Strauss A, Hohenberger P, Schuhmacher J, Haberkorn U, Strauss LG. Noninvasive measurements of bombesin receptor expression in tumors using a Ga-68-labeled bombesin analogue. Eur J Nucl Med Mol Imaging 2005; 32: 281.

[72] Dimitrakopoulou-Strauss A, Hohenberger P, Eisenhut M, Moecke H, Haberkorn U, Strauss L. Receptor expression in patients with gastrointestinal stromal tumors (GIST) using a Ga-68-labeled bombesin analogue. J Nucl Med 2006; 47: 102P, 290.