# Theranostic Prospects of Gastrin-Releasing Peptide Receptor–Radioantagonists in Oncology

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**KEYWORDS**

• Gastrin-releasing peptide receptor targeting • Theranostics • Receptor antagonist • $^{68}$Ga-radiotracer • Prostate cancer • Breast cancer

**KEY POINTS**

- The overexpression of gastrin-releasing peptide receptors (GRPRs) in prostate and breast cancer provides opportunities for diagnosis and therapy with GRPR-directed radiopeptides.
- Radiolabeled analogues of amphibian bombesin have been developed for GRPR-targeted tumor diagnosis and therapy.
- GRPR-radioantagonists, although unable to internalize in cancer cells, show considerable advantages for tumor targeting in human over their agonist counterparts, such as higher biosafety and superior pharmacokinetics.
- Translational studies have highlighted the excellent tolerability and the high diagnostic value of GRPR-radioantagonists in patients with prostate and breast cancer.

## INTRODUCTION

The advent of radiolabeled somatostatin analogues in the diagnosis and therapy for neuroendocrine tumors (NETs) has paved new avenues for a theranostic patient-tailored management of cancer.[1,2] The successful application of somatostatin analogues in the clinic has relied on the high-density expression of somatostatin subtype 2 receptors ($sst_2$) in NETs compared with healthy background tissues.[3,4] Likewise, other peptide receptors and receptor subtypes are overexpressed in other types of human tumors providing the molecular basis for diagnostic imaging and radionuclide therapies with radiolabeled peptide analogues.[5,6] Research in this area offers excellent opportunities to expand the clinical indications of theranostic radiopeptides beyond the boundaries of $sst_2$-positive NETs and to upgrade the current armory of clinical oncology with a wider range of new effective molecular tools.

Much attention has been directed to gastrin-releasing peptide receptors (GRPRs) because of their expression in high numbers in major human cancers, such as in prostate and breast cancer.[7–10] Specifically, high-density expression of GRPR has been shown in primary prostate cancer in contrast not only to surrounding healthy tissue but also to

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the hyperplastic prostate that remains devoid of GRPR expression.[11] Hence, early neoplastic events in the prostate can be detected after administration of GRPR-directed peptide radiotracers with high specificity. In most cases, disease infiltrated to adjacent lymph nodes still retains a high GRPR-expression level, allowing for follow-up of metastatic spread. Yet, GRPR-expression seems to decline in advanced states of androgen-independent prostate cancer, especially when metastases involve the bone.[12–14] Likewise, in 60% to 75% cases of primary breast cancer, the GRPR is expressed at high densities with the expression levels fully retained in all lymph-node metastases originating from GRPR-positive primaries, allowing for follow-up of disease spread.[10,15,16] Other GRPR-positive cancers include lung cancer,[17–21] gastrinomas,[22] gastrointestinal stromal tumors,[23] as well as ovarian cancer whereby GRPR-expression is associated to tumor vasculature.[24,25]

In view of the above, much effort has been directed to the development of GRPR-seeking peptide radioligands.[26–28] Most of these analogues have been based on the amphibian tetradecapeptide bombesin (BBN, Pyr-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-$NH_2$) and its C-terminal fragments still retaining the ability to recognize and interact with the GRPR. Alternatively, C-terminal fragments of the 27mer gastrin-releasing peptide (GRP) (Val-Pro-Leu-Pro-Ala-Gly-Gly-Gly-Thr-Val-Leu-Thr-Lys-Met-Tyr-Pro-Arg-Gly-Asn-His-Trp-Ala-Val-Gly-His-Leu-Met-$NH_2$) native in mammals, for example, GRP(18–27) or neuromedin C, have likewise served as motifs for the development of GRPR-specific peptide radioligands.[29–31] Frog BBN binds both the GRPR and the neuromedin B receptor with equal affinity, whereas the human sequences are GRPR preferring.[7] Usually, peptide analogues of the aforementioned motifs have been further modified by covalent coupling of a bifunctional chelating agent (BFCA) at the N-terminus, either directly or via a spacer, to allow for stable binding of clinically relevant radiometals. This approach has provided a plethora of GRPR-seeking radiopeptides proposed for diagnostic imaging with single-photon emission computed tomography (SPECT) ($^{99m}$Tc, $^{111}$In)[14,32–34] or PET ($^{68}$Ga, $^{64}$Cu)[35–38] and for radionuclide therapy with the use of beta ($^{90}$Y, $^{177}$Lu)[39–41] or alpha emitters ($^{213}$Bi).[42]

It should be noted that native BBN- and GRP-based peptides will bind and activate the GRPR after injection in the living organism. Thus, by acting as receptor agonists they induce potent adverse effects, especially in the gastrointestinal system, which restrict their clinical applicability.[43–47] The severity of such effects would depend on several factors, including receptor binding affinity and potency of each analogue, dose and route of administration, as well as metabolic stability and bioavailability. The recent advent of GRPR-directed radiopeptides with antagonistic profile at the GRPR has offered an elegant way to circumvent the major biosafety concerns raised by the application of GRPR-activating radioligands.[48] In the present brief review the authors discuss significant breakthroughs in the development of GRPR antagonists and their radiolabeled analogues. Furthermore, the authors present promising new data in favor of the clinical application of GRPR radioantagonists in nuclear oncology.

## TOWARD GASTRIN-RELEASING PEPTIDE RECEPTOR ANTAGONISTS AND THEIR RADIOLABELED ANALOGUES FOR USE IN GASTRIN-RELEASING PEPTIDE RECEPTOR–EXPRESSING TUMOR IMAGING AND THERAPY

The BBN-like peptide agonists after systemic administration exert a wide spectrum of biological actions on binding and activation of the GRPR, such as the release of gastrointestinal peptide hormones, the stimulation of exocrine gland secretion, and the contraction of smooth musculature, all synergistically translating into potent adverse reactions in the gastrointestinal system.[43,45–47,49,50] Furthermore, they have been implicated in the pathogenesis of human cancers via autocrine routes on GRPR-positive tumor cells, such as small cell lung carcinomas, prostate, or breast cancer.[17,19,51–54] Based on these facts, the use of BBN-like peptide agonist motifs for the development of GRPR-directed radioligands for diagnosis and therapy in clinical oncology seems to be entangled with biosafety risks. In the case of radionuclide therapy, whereby higher amounts of peptide analogues are typically administered, these risks become considerable. Biosafety issues became clearly evident during the clinical validation of $^{177}$Lu-AMBA ($^{177}$Lu-DOTA-Gly-4-aminobenzoyl-Gln-Trp-Ala-Val-Gly-His-Leu-Met-$NH_2$) as a candidate radiopharmaceutical in the GRPR-targeted treatment of human prostate cancer.[41,42,44] In view of the aforementioned information, research efforts have recently switched from the development of radiolabeled BBN-/GRP-based agonists to GRPR-radioantagonists.[48]

Further positive support in the pursuit of this new research direction has been offered by a parallel shift of paradigm in the field of somatostatin. Accumulating evidence has shown that radiolabeled somatostatin analogues with an antagonistic profile at the $sst_2$ outperform their agonist-based counterparts in animal models and most importantly also