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Review

# Progesterone receptor targeting with radiolabelled steroids: An approach in predicting breast cancer response to therapy

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ABSTRACT

Steroid receptors have demonstrated to be potentially useful biological targets for the diagnosis and therapy follow-up of hormonally responsive cancers. The over-expression of these proteins in human cancer cells as well as their binding characteristics provides a favourable mechanism for the localization of malignant tumours. The need for newer and more selective probes to non-invasively assess steroid receptor expression in hormone-responsive tumours has encouraged the synthesis and the biological evaluation of several steroidal derivatives labelled with positron and gamma emitters. The physiological effects of the steroid hormone progesterone are mediated by the progesterone receptor (PR). Since PR expression is stimulated by the oestrogen receptor (ER), PR status has been considered as a biomarker of ER activity and its value for predicting and monitoring therapeutic efficacy of hormonal therapy has been studied. Imaging of PR-expressing breast cancer patients under hormonal therapy may be advantageous, since the response to therapy can be more accurately predicted after quantification of both ER and PR status. Thus, ligands for PR targeting, although much less explored than ER ligands, have gained some importance lately as potential PET and SPECT tumour imaging agents. In this review, we present a brief survey of explored approaches for progesterone targeting using radiolabelled progestins as potential clinical probes to predict responsiveness to breast cancer therapy.

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**Contents**



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## 1. Introduction

Breast cancer is the most commonly diagnosed form of cancer and one of the major causes of death among women [1–3]. Currently, the mortality rates have decreased in many industrialized societies, probably due to more effective early detection efforts and advances in adjuvant systemic therapy. As a result, breast cancer ranks as the fifth cause of death from cancer overall, but it is still one of the leading causes of mortality in women in both developing and developed countries, where the estimated deaths are almost equal to the estimated number of deaths from lung cancer. Fortunately, cure rates ranging up to 70% seem possible in early-stages of the disease. However, even with the recent advances in systemic therapy, recurrent or metastatic breast cancer still is considered untreatable [4–6].

The effective management of breast cancer requires its early detection and accurate staging to improve the probability of survival. Mammography is still the diagnostic method most often used, allowing to identify the cancer before the appearance of physical symptoms. This technique uses X-rays to visualize an abnormal anatomical structure within the breast. Other imaging modalities include ultrasonography and magnetic resonance imaging (MRI). Ultrasonography allows discriminating between fluid-filled and solid tissue structures and is generally used to evaluate a limited region of the breast. MRI uses a magnetic field to create a detailed anatomic image but is not as reliable as mammography for certain breast conditions, such as ductal carcinoma *in situ*. All these diagnostic methods are non-invasive and, together with self-breast and clinical exams represent, the basis for breast cancer detection. However, these imaging modalities only provide information on tissue abnormalities, which may or may not be malignant, and a biopsy is always necessary to confirm if the abnormal tissue is a carcinoma. Therefore, alternative molecular imaging modalities such as nuclear imaging techniques that give not only anatomic but also functional information of the lesions are required to detect breast cancer non-invasively.

Distinct features of breast cancer can be used to establish prognosis and also to predict the responsiveness to specific therapies. Together with the standard clinical prognostic factors well-known molecular biomarkers of breast cancer, such as oestrogen receptor (ER) and progesterone receptor (PR), play important roles in determining the tumour response to endocrine therapies and in the development of resistance to these treatments [7]. The hormone responsive tumours, which constitute one of the major forms of cancer among women in the age group 26–55 years, are characterized by their growth and spread in the presence of estradiol and progesterone [8–11]. The overexpression of ER and PR in human tumour cells as well as their binding characteristics, which involve a prolonged retention of the hormone as compared to non-hormone compounds, provide a favourable mechanism for the localization of tumours [12,13].

The design of molecular probes for tumour receptor targeting as well as the imaging strategies for early detection still remain a challenging issue, owing to the receptors' unique features. Most of these receptors display high binding affinities for their cognate ligands and are usually effective even at ligands concentrations as low as in the nano-molar range. Consequently, when dealing with radiodiagnostic agents for breast cancer patients, radioligands with high specific activity are needed, since even small molar quantities of an imaging agent may saturate the receptor and limit the ability to visualize receptor expression [13,14].

Both ER and PR status are good predictors of tumour responsiveness to therapy. The ER subtype α (ERα) is expressed in nearly 70% of breast cancers and is a relevant predictive factor for targeted therapy [15–19]. Patients with ERα-positive (ERα+) tumours usually have longer overall survival than patients with ERα-negative (ERα−) tumours and are more likely to respond to hormone-based therapies. About one-half of ERα+ tumours are also described to be PR-positive (PR+), and nearly 75% of these (ERα+/PR+) tumours respond positively to endocrine therapy [20]. Hence, knowledge of ERα and PR expression can help to identify the patients that may benefit from this therapy. Response rates in advanced disease average 33% in tumours positive for one receptor and 50–70% in tumours positive for both ER and PR [19,21,22]. ERα and PR are quantified in newly diagnosed breast cancer, as a matter of clinical routine, most commonly by immunohistochemistry (IHC), the current standard diagnostic technique for the detection of steroid hormones [23]. However, IHC receptor assays present some shortcomings. Most notably, they provide only limited information about the functional status of receptors. Moreover, one cannot presume that recurrent or metastatic lesions retain the same steroid hormone profile as the primary tumour. In fact, the receptor status of recurrent or metastatic disease may be even a better predictor of response to therapy. However, metastatic lesions are technically difficult to biopsy and because the biopsy of multiple lesions is not viable, the receptor content cannot be assessed easily in malignant tissues. Thus, a non-invasive imaging method that can quantify reliably the receptors and determine their functional status in individual lesions is of utmost importance in identifying patients likely to benefit from hormone therapy.

In general, the available molecular imaging modalities include MRI, optical imaging, using fluorescence or bioluminescence, targeted ultrasound, or radionuclide-based imaging modalities such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) [24–27]. However, in the case of tumour receptors imaging, PET and SPECT appear to be the only feasible approach, since the limited capacity of the receptor binding system demands a tracer with high specific activity. PET and SPECT are the most sensitive molecular imaging techniques as they are able to determine picomolar concentrations of specific biomolecules. The development of a receptor-based breast cancer imaging methodology requires a receptor ligand, labelled with an appropriate radionuclide for SPECT (*e.g.* $^{123}$I) or PET (*e.g.* $^{18}$F). These imaging agents, provided that they have high binding affinity towards the receptor and low non-specific binding affinity as well as a suitable chemical and metabolic stability, can afford a non-invasive method to localize primary and metastatic tumours that will help in predicting the chances of the patient's survival as well as their response to various therapies [25].

Several classes of ER and PR targeting compounds have been designed and evaluated over the years as potentially useful chemotherapeutic/chemopreventive agents and as radioimaging agents. Non-invasive imaging of breast tumours based on their hormonal receptor's status can be used for therapy follow-up by SPECT or PET. The need for newer and better selective probes to non-invasively assess steroid receptor expression in tumours has encouraged the synthesis and biological evaluation of several steroid derivatives labelled with positron and gamma emitters [28–34]. While many reviews have been written regarding the radiosynthesis and clinical application of various PET and SPECT radiotracers [35–38], few of these agents have actually reached the clinical stage [39–42]. Several synthetic progestins, although not so intensively studied as ER ligands nor for such a long time, have exhibited high affinity for the PR and have shown promising results in animal models. Some radioiodinated and radiofluorinated progestins have been reported as potential probes for PR imaging [43–46]. A few $^{99m}$Tc-labelled progestins have also been described, but most of them have shown low uptake in the target tissue *versus* a relatively high accumulation of radioactivity in non-target organs and will not be considered in the scope of this review [47,48]. Carbon-11, although particularly suited for labelling endogenous substances has not been explored for labelling progestins. To the