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Clinical Cancer Research

Molecular Pathways: Blockade of the PRLR Signaling Pathway as a Novel Antihormonal Approach for the Treatment of Breast and Prostate Cancer

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Abstract

The prolactin (PRL)–prolactin receptor (PRLR) signaling complex has been implicated in the pathology of breast and prostate carcinoma. A multitude of pro-oncogenic intracellular signaling pathways are activated by PRL in breast and prostate epithelial cells, leading to enhanced cellular proliferation, survival, and tumorigenesis in numerous model systems. Emerging evidence suggests that targeting the PRL–PRLR axis in human cancer may represent an unexploited avenue for therapeutic intervention and, given the extensive cross-talk between PRLR and other signal transduction pathways, a potential means through which other anticancer agents could be rendered more efficacious in the clinic. LFA102 is a potent anti-PRLR neutralizing antibody that efficiently abrogates the function of this receptor *in vivo*, mediating significant antitumor effects in preclinical models. The clean safety profile of this antibody in animals and in the clinical experiences to date suggests that blocking the PRLR signaling pathway in human tumors may have few significant toxicologic consequences and may be a promising approach to treating cancer. A phase I trial in patients with breast and prostate cancer is underway to better understand the clinical utility of LFA102 and the contribution of PRL to the maintenance and progression of human cancer. *Clin Cancer Res; 19(7); 1644–50. ©2013 AACR.*

Background

The polypeptide hormone prolactin (PRL) mediates its physiologic functions through the engagement of prolactin receptor (PRLR), a type I cytokine receptor expressed on the surface of numerous cell types, including breast and prostate epithelial cells. Through genetic knockout studies in rodents, PRL has been shown to play a critical role in reproductive biology by mediating mammary gland development, lactation, maintenance of the corpus luteum, and other functions (1, 2). Outside of a clear role in lactation, the role of PRL in human reproduction is less definitive (1). In the context of oncology, mounting evidence suggests that this hormone may also contribute to the initiation or progression of breast and prostate cancer. PRLR lacks intrinsic kinase activity, but when dimerized and associated with a single molecule of PRL in a ternary complex, the receptor undergoes a conformational change and elicits a multitude of downstream intracellular signaling events. Figure 1 highlights many of the signaling pathways triggered by the activation of PRLR in breast or prostate cancer cells. Upon engagement of its extracellular ligand–binding domain by PRL, growth hormone (GH), or placental lactogen (PL), PRLR may activate the Jak2/Stat5 and Jak1/Stat3 (3, 4) pathways. Depending on the cellular context, Jak2/Stat5-independent PRLR signaling can also occur through the activation of Src family kinases and focal adhesion kinase (FAK), contributing to the induction of phosphoinositide 3-kinase (PI3K)/Akt and Raf/Mek/Erk in cancer cell lines (5, 6). For example, all of these signaling pathways have been shown to be activated in parallel in T47D cells following PRL exposure (5), whereas in HCC1500 cells, PRL activates Stat5 but not Erk1/2 (7). By triggering these intracellular signaling cascades, PRLR mediates progrowth, prosurvival, and prometastatic phenotypes in human cancer cells (5, 8–10) and thus represents an attractive target for new antineoplastic agents.

Role of PRL in breast and prostate cancer

With more than 40,000 deaths per year in the United States in 2011 alone (11), breast cancer remains a disease of high unmet medical need. The evidence supporting a role for PRL–PRLR signaling in breast cancer is multifold. Directed expression of PRL in the mammary gland in mice induces a high frequency of mammary tumor development (12), whereas genetic knockout of the PRLR loci inhibits the growth of mammary tumors (13). In humans, PRLR protein and/or mRNA have been detected in the majority of breast tumors examined (7) and is overexpressed in malignant epithelium when compared with matched normal breast epithelium (14). In addition, high-serum PRL levels confer

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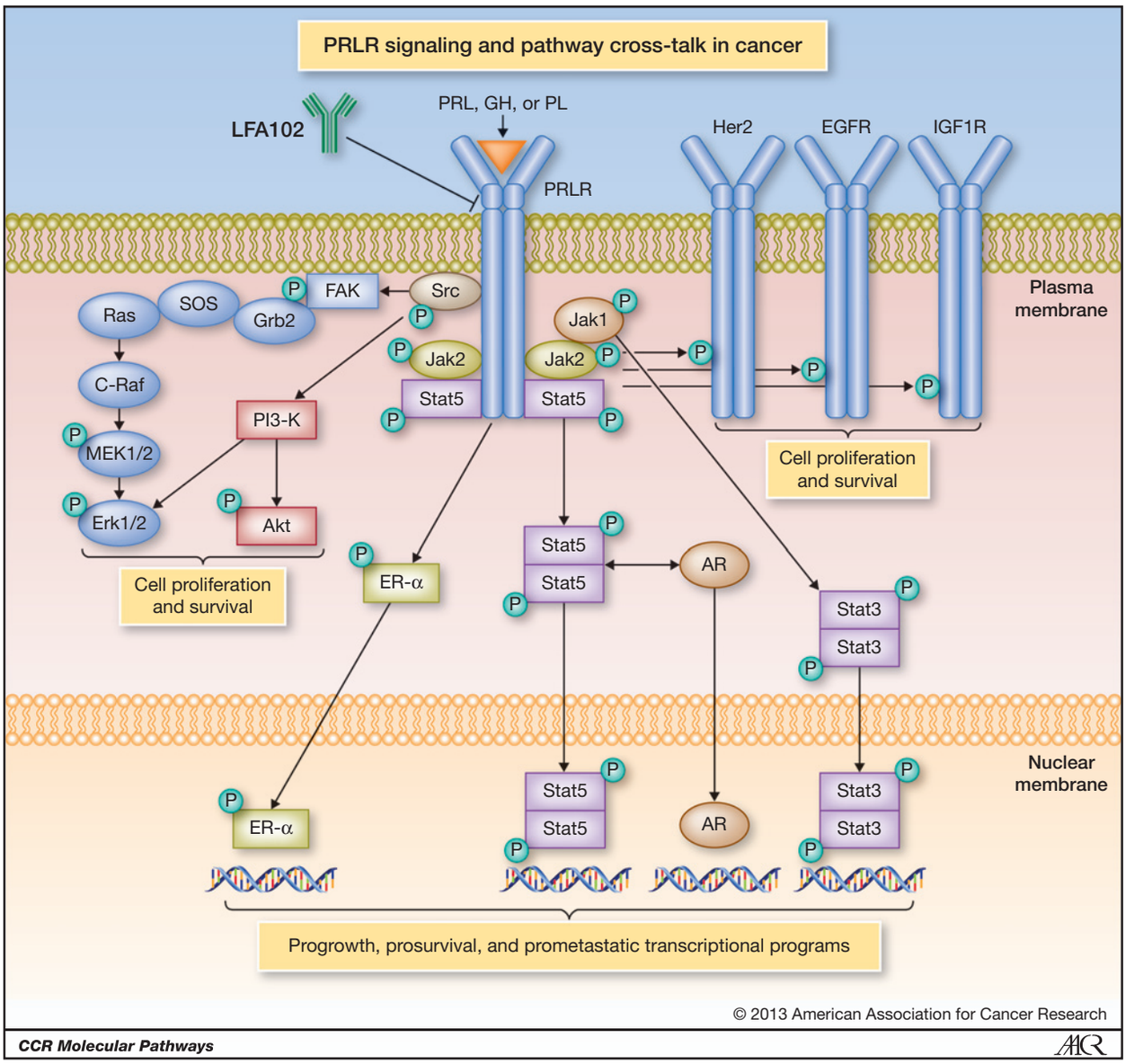

Figure 1. PRLR signaling and pathway cross-talk in cancer. Signaling partners activated by PRLR after binding of PRL, growth hormone (GH), or placental lactogen (PL) are shown. All signaling pathways represented in this diagram have been found to be operative in the breast cancer cell context, whereas evidence to date supports a predominant role of Jak2/Stat5 in PRLR signaling and PRLR–AR cross-talk in prostate cancer cells.

a significantly increased risk for developing breast cancer in women (15), and high systemic or tumor autocrine PRL in breast cancer has been correlated with incidence of metastasis, disease progression, lower responses to tamoxifen, and a worse clinical prognosis (16–18). Taken together, these observations suggest that PRLR signaling may be a key growth and survival pathway used by breast tumors.

Despite initial responses to androgen ablation therapies, the vast majority of patients with prostate cancer will relapse and develop an aggressive and ultimately fatal form of the disease known as castration-resistant prostate cancer (CRPC; ref. 19). Recent evidence has illuminated a potentially important role for the PRLR/Stat5 signaling axis in the pathogenesis of this disease (20–22). Prostate-directed expression of PRL in mice led to the activation of Stat5 in prostate tissue, as well as hyperplasia, high-grade prostatic intraepithelial neoplasms (PIN), and eventually prostate adenocarcinoma (23), mimicking the course of disease in human prostate cancer. These pathologies were diminished by coexpression of the PRL peptide antagonist Δ1-9-G129R, which contains PRLR-binding elements from wild-type PRL, but does not activate the receptor (a ligand-competitive antagonist). These studies showed

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a therapeutic proof of concept for a PRLR antagonist in this disease model. Mice with prostate-specific PRL expression also exhibit an expansion of the luminal and p63/Sca-1–positive basal cells, the latter cell population being recently hypothesized to contain the tumor-initiating cells in humans (24). Epidemiologically, the presence of PRL and p-Stat5 in human prostate tumors has been correlated with high tumor grade and a more aggressive course of disease (25). The fact that p-Stat5 is detected in 95% of recurrent hormone therapy–refractory prostate tumors (25), along with other biologic and epidemiologic evidence (26–29), suggests that activated PRLR/Stat5 may contribute to the emergence of castration-resistant disease. Given the observation that the majority of primary human prostate tumors express PRLR (7), these lines of evidence indicate that autocrine/paracrine PRL-mediated activation of Stat5 could be an attractive new pathway to be neutralized in the treatment of prostate cancer.

Targeting the PRLR signaling pathway in the clinic

Decades ago, several attempts were made to change the course of breast cancer progression using antiprolactinemic agents acting on the pituitary gland (D2 dopamine receptor agonists). Despite these drugs showing some indications of activity, the results were largely variable and unimpressive (30–32). On the basis of the knowledge that these types of agents do not affect growth hormone levels (which can also bind and activate PRLR) or extra-pituitary sources of PRL (33), peptide-based PRL antagonists were explored to directly antagonize PRLR function in a manner analogous to the growth hormone peptide antagonists developed previously (34). Although these PRL antagonists have proven to be useful research tools to understand PRLR biology, most lack key properties (e.g., potency, systemic half-life, lack of agonism) that would enable their development as viable therapeutics in humans, especially as chronically administered drugs (34, 35). Over the years, efforts have focused on rectifying these liabilities, but, to date, no human trials using PRL peptide antagonists have been reported. As an alternative approach, the anti-PRLR antibody LFA102 was developed as a pure PRLR antagonist with high potency and a long systemic half-life. This antibody has the ability to potently abrogate all arms of PRLR signaling examined *in vitro* and to mediate sustained functional inhibition of the receptor in PRL-sensitive tumor models *in vivo* (36). LFA102 binds to the membrane-proximal D2 domain of PRLR, which is believed to contain the dimerization interface of the receptor and not the main part of the ligand-binding pocket, which is found in the D1 domain. Thus, this antagonist associates with PRLR without competing with PRL. Given the location of the binding site, the antibody may function by interfering with receptor dimerization or activation by direct or allosteric mechanisms in the "stem" of PRLR, which contains both the putative dimerization interface and an activation "switch" for PRLR (37, 38). By avoiding direct competition with PRLR ligands for binding to the receptor, this mechanism of antagonization may endow LFA102 with the ability to efficiently neutralize even high concentrations of autocrine/paracrine/endocrine PRL, making it ideally suited to maximally inhibit this signaling pathway in patients with cancer. In concordance with observations from PRLR knockout mice (2), this therapeutic was very well tolerated in preclinical safety studies, suggesting that targeting the PRL–PRLR pathway in human tumors with PRLR antagonists could result in few (if any) significant toxic side effects.

Clinical–Translational Advances

PRLR pathway cross-talk and synergistic therapeutic opportunities

PRLR and estrogen receptor. Multiple studies have shown that the PRLR and estrogen receptor-α (ERα) signaling pathways interact in the context of breast cancer (39–42). Most human breast tumors coexpress both of these hormone receptors (14), and high circulating PRL levels are known to confer a significantly increased risk for ER-positive (ER+), but not ER-negative (ER−), breast cancer in humans (15). Pathway cross-talk is also supported by biologic evidence *in vitro*, as PRL and estradiol can synergize to induce the transcription of estrogen target genes and to greatly enhance proliferation in breast cancer cells (40). PRL may also induce the phosphorylation (activation) of ERα in the absence of estradiol (41, 42), suggesting that even in cases in which estradiol levels may be well suppressed by aromatase inhibitors, PRLR could function as a surrogate activator of ER function or sensitize breast cancer cells to low levels of residual estradiol. The observation that ER+ mammary tumors induced by PRL overexpression in mice are estrogen insensitive and resistant to estrogen deprivation is also suggestive that PRL could play a role in the development of endocrine therapy–resistant disease in certain settings (12, 39). To investigate the impact of simultaneously inhibiting both PRLR and ER in breast tumors, we used a transplantable carcinogen-induced rat mammary cancer model that expresses both hormone receptors (36). Rats with established tumors were treated with LFA102, resulting in significant tumor growth inhibition (with 20% of tumors regressing), whereas a suboptimal dose of the aromatase inhibitor letrozole had little impact on tumor growth and induced no tumor regressions. When these 2 agents were administered in combination, a profound impact on tumor growth was observed, with 47% of tumors undergoing complete regression. These results highlight the clinical potential of simultaneously abrogating the signaling of PRLR and ER with targeted therapeutics.

PRLR and androgen receptor. Similar to the cross-talk observed between PRLR and ER, other investigations have found that PRLR-Stat5 signaling may also impact androgen receptor (AR) function (27, 43). PRLR and AR can synergize to induce gene transcription and cell survival in prostate cancer cells (27, 43), whereas activated Stat5 and liganded AR have been shown to directly associate and enhance the nuclear localization of one another (27). This evidence suggests that PRLR may lower the cellular threshold for androgen-dependent physiologic responses. Given the hypersensitivity of CRPC cells to androgens (44), restricting

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PRLR-Stat5 influence on AR signaling may be an innovative approach to increase the activity of the new classes of antiandrogen therapeutics showing promise in CRPC or to help inhibit the progression of early-stage disease to CRPC.

PRLR and growth factor receptors. PRLR is also known to directly or indirectly influence the function of a number of other growth factor receptors, including Her2, EGF receptor (EGFR), and insulin-like growth factor-1 receptor (IGF-1R), which have well-established oncogenic functions and clinical relevance in breast cancer (refs. 45–47; see Fig. 1). PRL derived from tumor cells or from stromal cells has been shown to induce the phosphorylation of Her2 in breast cancer cells (48–50), whereas PRL and EGF may also synergize to potentiate EGFR function (51), indicating cross-talk can occur between PRLR and Erbb family members. In addition, PRL has been found to enhance IGF-1R phosphorylation and to synergize with IGF-1 to induce phosphorylation of Akt and Erk1/2 in breast cancer cells (52). Thus, the function of many receptor tyrosine kinases expressed in human breast tumors may be augmented by PRLR activation and therefore represent potential points of synergy between LFA102 and other targeted therapeutics such as trastuzumab or cetuximab.

PRL-induced chemoresistance. In addition to being a mitogen, PRL also has the capacity to inhibit cell death induced by cisplatin, doxorubicin, taxol, and other agents in cancer cells (53, 54). Mechanistically, in breast cancer cells, this can occur through drug detoxification arising from PRL-induced activation of glutathione *S*-transferase (54) or potentially via PRL-mediated upregulation of antiapoptotic proteins such as Bcl-2 (55). In humans, several small clinical studies have shown that patients treated with antiprolactinemic agents in combination with docetaxel had better responses than those treated with docetaxel alone (56, 57). Therefore, LFA102 also has the potential to be used as a chemosensitizing agent with low toxicity in humans.

Applicability of LFA102 treatment in breast and prostate cancer

Endocrine therapy plays a central role in the treatment of ER+ metastatic breast cancer. Despite the availability of initially effective hormone therapies, resistance develops in almost all tumors in the advanced setting. Endocrine resistance has been linked to cross-talk between signal transduction pathways, particularly with ER signaling and PI3K/AKT/mTOR. Dysregulation of any of these signaling constituents can contribute to reactivation of the growth and survival pathways used by hormone receptors. The use of selective inhibitors of these alternate signaling pathways, in association with antihormonal agents, offers a therapeutic opportunity to restore endocrine sensitivity and improve clinical outcomes. For example, combinations of endocrine therapies with EGFR inhibitors and HER-2 inhibitors were shown to lead to longer progression-free survival (58, 59). The most compelling evidence in favor of this strategy was provided by the use of the mTOR inhibitor everolimus in combination with examestane (an aromatase inhibitor) in ER+ metastatic breast cancer. This combination led to significantly longer progression-free survival and overall response, which supported the registration of everolimus in this setting (60). On the basis of the interactions observed between the PRL–PRLR axis and different signaling pathways activated in endocrine-resistant conditions, the use of LFA102 could add a new therapeutic option for patients with this disease (see Fig. 2).

Androgen deprivation therapy with medical or surgical castration represents the standard treatment for patients with advanced metastatic prostate cancer; however, nearly all patients will progress to CRPC. Currently, the chemotherapeutics docetaxel and cabizataxel exist as first- and second-line options for patients with this disease, providing improvement of survival of 2.5 to 3.0 months at the cost of significant morbidity caused by severe drug-related toxicities. New well-tolerated targeted agents are thus needed to better manage this disease and provide improved clinical outcomes. Two new antihormonal agents targeting the AR axis, abiraterone (an inhibitor of androgen biosynthesis) and enzalutamide (an AR antagonist), have recently been approved for the treatment of CRPC after docetaxel failure and are expected to become significant parts of the CRPC treatment landscape in the coming years (19, 61, 62). Multiple clinical variables (performance status, tumor burden, symptoms, pace of disease, visceral vs. limited bone disease) and drug tolerability ultimately will determine the choice between the many therapeutic options available (see Fig. 2). Within this context, the PRLR-Stat5 pathway stands out as a novel nonandrogenic signaling pathway that holds promise for the treatment of patients who are either resistant to these new compounds or who cannot tolerate their side effects and are in need of alternative therapeutic approaches.

Conclusions

As high unmet medical need continues to plague the fields of metastatic breast cancer and advanced prostate cancer, new targeted therapeutic approaches are urgently needed to stem the progression and mortality of these diseases. Recent evidence suggests that the PRL–PRLR signaling axis may influence a number of oncogenic processes in breast and prostate cancer and therefore may be an unexploited therapeutic avenue for enhancing clinical outcomes. The anti-PRLR antibody LFA102 has been found to be a highly effective antagonist of PRLR signaling and function in numerous preclinical models, carrying no overt toxicologic consequences of note. As opposed to the alternative route of inhibiting downstream signaling mediators such as Jak2 or Stat5 directly with low molecular weight (chemical) inhibitors, the selectivity of a monoclonal antibody approach to targeting the PRLR pathway (LFA102) may result in fewer dose-limiting toxicities in patients while maximally inhibiting receptor signaling, including that mediated through Jak2/Stat5-independent mechanisms. The extensive cross-talk between PRLR and the other signaling networks highlighted here also suggests that ample opportunities exist for synergistic combination approaches composed of LFA102 and various standards of care.

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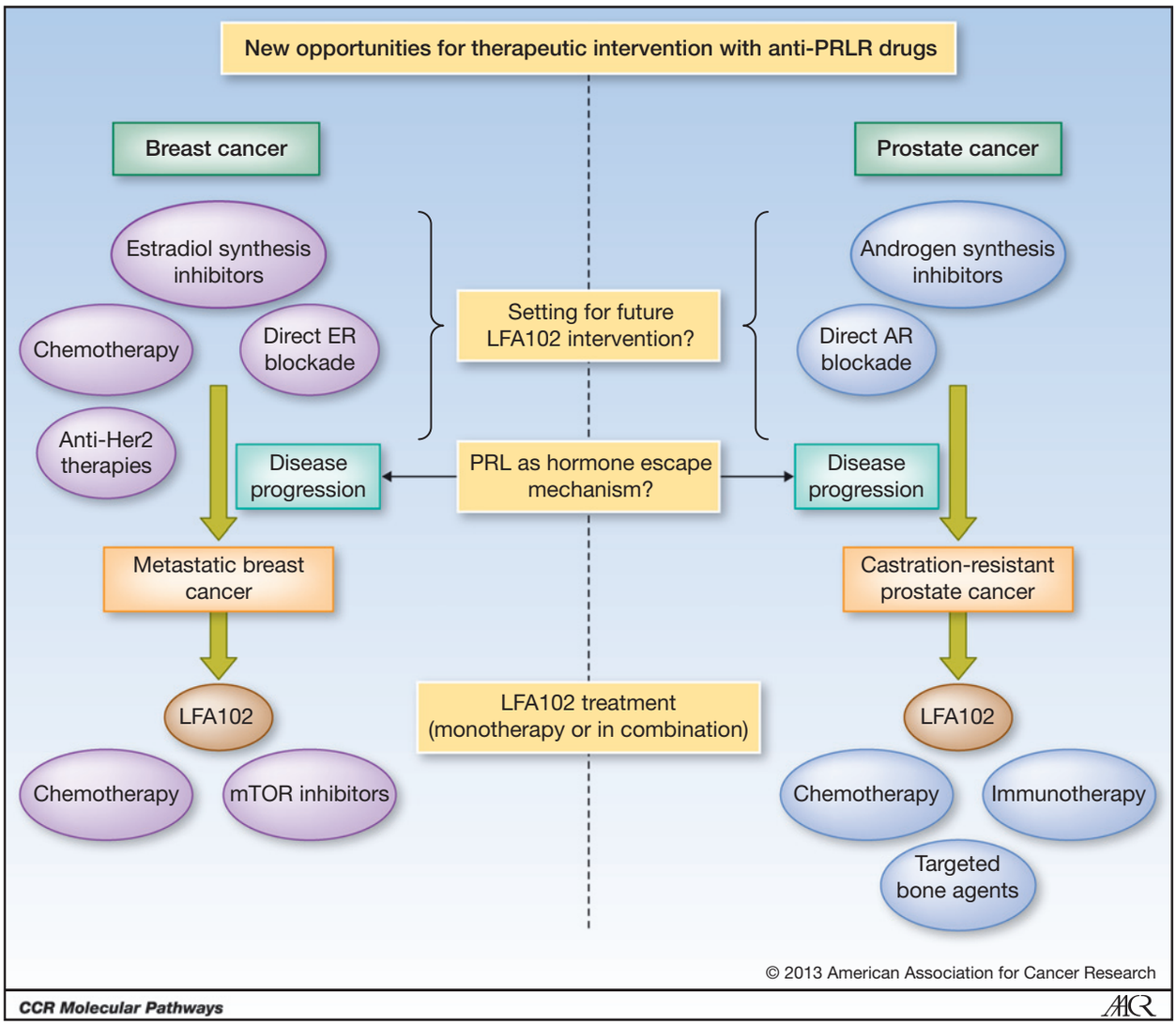

Figure 2. New opportunities for clinical intervention with anti-PRLR therapeutics.

Ongoing and future clinical trials with this agent will indicate whether LFA102 therapy can impact the course of advanced cancer, block the emergence of endocrine- or drug-resistant disease, and help elucidate the true role of PRL biology in human cancer.

Disclosure of Potential Conflicts of Interest

J.S. Damiano and E. Wasserman own stock in Novartis.

Authors' Contributions

Conception and design: J.S. Damiano
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.S. Damiano
Writing, review, and/or revision of the manuscript: J.S. Damiano, E. Wasserman

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