Endothelin B Receptor, a New Target in Cancer Immune Therapy

Lana E. Kandalaft, Andrea Facciabene, Ron J. Buckanovich, and George Coukos

Abstract

The endotelin system comprises four endothelin (ET) peptide ligands, ET-1, 2, 3 (1), and the recently discovered ET-4 (2); their two G protein-coupled receptors (GPCR), ETAR (3) and ETBR (4); and the endotelin-converting enzymes (ECEs), which catalyze the generation of the biologically active ETs. ETs derive from precursor proteins after cleavage by membrane-bound metalloproteinase ECEs (5) and are well known for their overall vasoconstricting activity. Among them, ET-1 is the most potent ligand and the most widely expressed in endothelial cells (6). The endotelin peptides exert their function through binding to their cognate receptors A and B, whereby they trigger divergent intracellular effects by activating numerous downstream signaling pathways. Members of the endotelin system have been identified in neuronal, renal, and vascular tissues, and their involvement has been well documented in an array of physiological processes such as embryonic development, reproduction, angiogenesis, and cardiovascular homeostasis (4, 7–9).

Role of the endotelin system in disease

The role of the endotelin system has been well characterized in cardiovascular and renal disorders (10–13). ET-1 is produced by endothelial cells and exerts autocrine-paracrine functions by binding to ETAR and ETBR on vascular endothelial cells and pericytes. Balanced activation of the two receptors maintains vascular tone and regulates endothelial cell proliferation (14, 15), whereas imbalance in this system contributes to the onset of hemodynamic disorders. The same applies to the renal vasculature, in which endotelin play a major role in maintaining normal vascular tone through both the A (13, 16) and B receptor (17). Endotelin and their receptors have also been implicated in pulmonary hypertension (18), asthma (19), and pulmonary fibrosis. ET-1 immunostaining was detected in normal lung epithelium and vasculature (20). ETAR is found on vascular and airway smooth muscle, whereas ETBR is mostly often found on the endothelium and smooth muscle cells. Activation of both A and B receptors on lung smooth muscle cells results in vasoconstriction, whereas ETAR activation alone leads to bronchoconstriction (21).

ETAR and ETBR are also involved in inflammatory processes. Both ETAR and ETBR expression in bronchial smooth muscle cells is increased upon experimentally induced airway inflammation (22). ETAR activation is also required for endotoxin-induced inflammation (23) or T-cell homing to the lungs after allergic or inflammatory stimuli, whereas experimental airway inflammation is abrogated by ETAR inhibition (24, 25). The role of the endotelin axis in inflammation extends beyond the respiratory tract. ETAR activation mediates renal inflammation and transforming growth factor-β (TGF-β) production in diabetes (26). Owing to its proinflammatory properties (27, 28), ET-1 contributes to the progression of various diseases such as glomerulosclerosis and atherosclerosis and the pathogenesis of autoimmune diseases such as scleroderma and lupus erythematosus (29, 30). Importantly, ET-1 is synthesized by lymphocytes and other leukocytes, and has been shown to activate the proinflammatory transcriptional factor nuclear factor-κB (NF-κB) in human monocytes via ETAR and to stimulate the production of inflammatory interleukins and tumor necrosis factor-α (TNF-α) (ref. 31). ET-1 is also a chemoattractant for monocytes in vitro, via stimulation of IL-8/CXCL8 and monocyte chemoattractant protein-1 (MCP-1)/CCL2 (32, 33).
Role of the endothelin system in cancer

**Endothelin 1.** The role of the endothelin system in cancer has been reviewed extensively by Bagnato and colleagues (34) and others in the field. Kusuhara and colleagues were among the first to report ET-1 overexpression by breast, colon, stomach, prostate, and glioblastoma cell lines (35, 36). Ovarian, neuroblastoma, and human papilloma virus (HPV)-positive human cervical carcinoma cell lines also overexpress ET-1 (37, 38), whereas increased immunopositivity for ET-1 was detected in vivo in human colorectal cancer (39). Compiling clinical evidence shows elevated plasma ET-1 levels in patients diagnosed with various solid tumors, including hepatocellular, gastric, and prostate cancer (40–42). Interestingly, condensed breath of patients with non small cell lung carcinoma (NSCLC) showed increased ET-1 levels (43), proposing ET-1 as an early detection marker (44). Finally, in ovarian carcinoma, high ET-1 levels were detected in ascites (45). In summary, the endothelin 1 ligand is overexpressed by many tumors.

Strong evidence suggests a role for members of the endothelin system in the growth and progression of multiple tumors. Exogenous addition of ET-1 to a range of cell lines promotes various aspects of tumorigenesis. In prostate cancer cell lines, ET-1 increased survival and proliferation (42, 46). Exposure of breast cancer cells to ET-1 led to invasive phenotype, which involved matrix metalloproteinase (MMP) activity (47). The same mechanism occurred in osteosarcoma, in which ET-1 was shown to promote MMP-2 and MMP-9 induction (48). Lastly, in colon cancer ET-1 overexpression was shown to rescue cancer cells from apoptosis and growth arrest by promoting the onco gene β-catenin (49).

**ETAR.** The effects of ET-1 on cancer cells are mostly mediated by ETAR. Importantly, ETAR was shown to be overexpressed in renal and cervical cancer cell lines (50, 51) as well as several cancer types in vivo including colorectal, bladder, prostate, and nasopharyngeal carcinomas (46, 52–55). ETAR is also overexpressed in approximately 85% of primary and metastatic ovarian carcinomas. In this study, all ovarian carcinoma-derived cell lines were positive for both ET-1 and ETAR mRNA (56). Concomitant up-regulation of ET-1 and ETAR on tumor cells contributes to cell autonomy and malignant progression and triggers complex pathways driving tumorigenesis, including cell proliferation, inhibition of apoptosis, matrix remodeling, invasion, and metastatic dissemination (57). ET-1/ETAR also increases invasion and migration of tumor cells through downstream effects on MMPs, cadherins, connexins, and integrins. Increased cell proliferation is mediated by increased Ca^{2+} uptake and activation of the PKC, PLC, MAPK, and AKT pathways. ET-1/ETAR interaction can also activate the AKT and the NF-κB pathways to promote tumor cell survival (34).

The mitogenic activity of ET-1 can also be augmented by growth factors (57). One example is the cross-signaling between ETAR and the epidermal growth factor receptor (EGFR) (ref. 34). EGFR has been identified as a downstream mediator of ETAR receptor activation by ET-1 in ovarian cancer (58). The mechanism is triggered by ET-1, which causes EGFR transactivation. This event leads to activation of the RAS/MAPK pathway and AKT activation through the formation of Shc/Grb-2 complexes (45, 58), subsequently contributing to the mitogenic signaling induced by ET-1. This cross-signaling between the EGFR and ETAR pathways provides the rationale for combining EGFR inhibitors with ETAR antagonists to treat ovarian carcinoma. It has been shown that ZD4054, a specific ETAR antagonist, reduces ET-1-induced EGFR transactivation, whereas the EGFR inhibitor gefitinib significantly inhibited EGF and ET-1 induced EGFR phosphorylation (59). This drug combination simultaneously disables multiple signaling pathways, offering improvements in ovarian carcinoma treatment (59).

ET-1 increases the expression of cyclooxygenase (COX)-1 and COX-2, prostaglandin (PG)E2, and VEGF production by ovarian cancer cells via ETAR activation (60). The effect of ET-1 on VEGF expression is mediated through HIF-1α (61). Elevated expression of ET-1 has been associated with increased VEGF expression, lymphatic vessel invasion, and unfavorable outcome in invasive ductal breast carcinoma (62). A correlation between ET-1 expression and VEGF expression has also been shown in lung cancer (63). Additionally, inhibition of human ovarian tumor growth in nude mice after treatment with the potent ETAR-selective antagonist ABT-627 was associated with reduced COX-2 and VEGF expression by the tumor (60). Thus, overexpression of the ligand ET-1 and its receptor, ETAR, account for autocrine-paracrine activation of the endothelin axis in many solid tumors, which plays important and multifaceted roles in tumor cell progression. The ETAR is therefore a very attractive target for cancer therapy.

**ETBR.** Investigation of the role of ET-1/ETBR in tumor cell biology has been more limited. In normal cells, ETBR counter-regulates ET-1/ETAR activity through multiple mechanisms including increasing production of nitric oxide, promoting ET-1 clearance, triggering apoptotic pathways, and blocking cell growth; but it is unclear whether such antagonism also operates in tumor cells (64). Interestingly, ETBR is overexpressed and correlates with melanoma development and progression. Expression profiling of human melanoma biopsies indicated ETBR overexpression to be associated with aggressive tumor phenotype (65), and ETBR was proposed as a tumor progression marker (66). Underscoring the role of ETBR in melanoma growth, the specific antagonist BQ-788 was found to inhibit the growth of human melanoma cell lines and to reduce human melanoma tumor growth in a nude mouse model (67, 68). The B receptor is also expressed in Kaposi’s sarcoma and glioblastoma (69–71). The role of ETBR in cancer angiogenesis has been thoroughly investigated and reviewed by Bagnato and colleagues (34). ET-1 has been shown to directly promote tumor angiogenesis by inducing endothelial cell survival, proliferation, and invasion through ETBR (61). ET-1 promotes angiogenesis also indirectly, by upregulating VEGF production in the vasculature, also through ETBR activation (72), and increases vascular permeability through VEGF in response to tissue hypoxia (73). Furthermore, ET-1 upregulates expression of the extra domain-B containing fibronectin (EDB+ FN) in human vascular endothelial cells (74, 75). EDB+ FN is a recently proposed marker of angiogenesis expressed in human cancers and in ocular neovascularization in patients with proliferative diabetic retinopathy. There is a strong correlation between ETBr and VEGF expression in a number of different tumor specimens (76).

**Clinical-Translational Advances**

**ETAR and ETBR antagonists in cancer therapy.** ETAR and ETBR represent interesting targets for cancer chemoprevention and therapy. Many receptor antagonists have been developed...
and undergone preclinical and clinical testing. Some compounds have preferential A or B receptor inhibitory activity, whereas others exhibit mixed A and B antagonism. Given the prominent role of ET\(_A\)R in tumor cell biology, ET\(_A\)R-selective antagonists have been developed more extensively than ET\(_B\)R antagonists to treat malignancy (see Table 1). The first ET\(_A\)R-selective peptide antagonist, BQ-123 (77), was shown to inhibit cervical cancer growth in preclinical models (78). Furthermore, nonpeptide ET\(_A\)R antagonists such as Atrasentan, ZD4054, and YM598 have been shown to have a static effect on ovarian tumor growth in xenograft models (79); to delay progression of prostate cancer (80, 81); and to attenuate growth and metastasis of human gastric carcinoma (82). ET\(_A\)R inhibitors are currently undergoing clinical testing for various cancer indications. A list of endothelin antagonists under preclinical or clinical development for cancer and various other indications is provided in Table 1. Notably, phase II results with Atrasentan in hormone refractory prostate cancer (HRPC) were encouraging (83). However, subsequent phase III trials in metastatic and nonmetastatic HRPC showed no significant therapeutic effects despite evidence of biologic effects on serum markers of disease burden (84, 85). Large geographic differences in the median time to progression were also noted: U.S. patients showed less gain in time to progression relative to non-U.S. patients (85). Given the role of ET\(_A\)R in melanoma cells, ET\(_B\)R antagonists have been tested in

Table 1. Endothelin targeting agents and their indications

<table>
<thead>
<tr>
<th>Compound</th>
<th>Target</th>
<th>Dosing</th>
<th>Clinical testing-indication</th>
<th>Phase</th>
<th>Cancer preclinical testing</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrasentan</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>Prostate cancer, Renal carcinoma, Ovarian cancer, FT cancer, Brain tumors, NSCLC, Malignant glioma, ED, HT, CVD, PAH</td>
<td>II-III</td>
<td>51, 79, 80</td>
<td>Abbott</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>PP, USS, CVD, DN, PAH, HT</td>
<td>II</td>
<td>Approved</td>
<td>—</td>
</tr>
<tr>
<td>Avosentan</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>HI, PAH, MI, CKD, HT</td>
<td>I-II</td>
<td>Approved</td>
<td>—</td>
</tr>
<tr>
<td>BQ123</td>
<td>ET(_A)R</td>
<td>IV</td>
<td>HI, PAH, MI, CKD, HT</td>
<td>I</td>
<td>36, 108, 109</td>
<td>Merck Biosciences</td>
</tr>
<tr>
<td>Clazosentan</td>
<td>ET(_A)R</td>
<td>IV</td>
<td>SAH, HT, CAD, ED, CHF, END, PAH</td>
<td>Approved</td>
<td>—</td>
<td>Actelion</td>
</tr>
<tr>
<td>Darusentan</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>HT, CAD, ED, CHF, END, PAH</td>
<td>III</td>
<td>—</td>
<td>Gilead Sciences</td>
</tr>
<tr>
<td>Edonentan</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>CHF</td>
<td>II</td>
<td>—</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Sitaxsentan</td>
<td>ET(_A)R</td>
<td>IV-Oral</td>
<td>PAH, CHF</td>
<td>III</td>
<td>—</td>
<td>Encysive Pharmaceuticals/ICOS Texas Biotech</td>
</tr>
<tr>
<td>S-0139</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>CHF</td>
<td>II</td>
<td>—</td>
<td>Shionogi-GSK</td>
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<tr>
<td>TBC-3711</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>HT</td>
<td>II</td>
<td>—</td>
<td>Encysive Pharmaceuticals</td>
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<tr>
<td>YM598</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>Prostate cancer, Bone metastasis, NSCLC, CVD</td>
<td>II</td>
<td>67, 69, 113, 114</td>
<td>AstraZeneca</td>
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<tr>
<td>ZD4054</td>
<td>ET(_A)R</td>
<td>Oral</td>
<td>Prostate cancer</td>
<td>II</td>
<td>82, 110</td>
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<tr>
<td>BQ788</td>
<td>ET(_A)R</td>
<td>IV</td>
<td>CVD</td>
<td>I</td>
<td>67, 69, 113, 114</td>
<td>Merck Biosciences</td>
</tr>
<tr>
<td>IRL-1620</td>
<td>ET(_A)R agonist</td>
<td>IV</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Sigma</td>
</tr>
<tr>
<td>SPI-1620</td>
<td>ET(_A)R agonist</td>
<td>IV</td>
<td>Carcinoma, Short cervix, AHF, HT</td>
<td>III</td>
<td>—</td>
<td>Spectrum Pharmaceuticals</td>
</tr>
<tr>
<td>Enrasentan</td>
<td>ET(_A)R/ET(_B)R</td>
<td>Oral</td>
<td>Metastatic melanoma, HT, PAH, CHF-HT</td>
<td>II</td>
<td>115, 116</td>
<td>Actelion</td>
</tr>
<tr>
<td>Bosentan</td>
<td>ET(_A)R/ET(_B)R</td>
<td>Oral</td>
<td>Metastatic melanoma, HT, PAH, CHF-HT</td>
<td>Approved</td>
<td>—</td>
<td>Banyu/Merck</td>
</tr>
</tbody>
</table>

Abbreviations: AHF, acute heart failure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cardiovascular diseases; DN, diabetic nephropathy; ED, erectile dysfunction; END, endothelial dysfunction; FT, fallopian tube; HD, heart disease; HI, hyperinsulinemia; HT, hypertension; IPF, idiopathic pulmonary fibrosis; MD, microvascular dysfunction; MI, myocardial infarction; PAH, pulmonary arterial hypertension; PC, prostate cancer; PH, pulmonary hypertension; SAH, subarachnoid hemorrhage; USS, ulcer scleroderma, systemic.
melanoma, in which they proved efficacious (67, 68). Interestingly, IRL1620, an ET BR agonist, was shown to improve both delivery and therapeutic efficacy of paclitaxel in breast tumor-bearing mice (86).

**ETBR and the tumor endothelial barrier to T-cell homing.** The focus of cancer therapy targeting ET-1 to date has been to antagonize the autocrine-paracrine effects of ET-1 on tumor cells, mediated mainly by ETAR. Our laboratory recently showed a novel application of ETBR blockade in tumor therapy. Specifically, ETBR blockade at the tumor endothelium proved to be therapeutically efficient for tumor immune therapy (Fig. 1) (ref. 87). The success of immune therapy depends on the ability of effector T cells to infiltrate tumors. Although current tumor vaccines have proven effective in producing an antitumor immune response as measured by blood assays, they have fallen short of clinical expectations. Endothelium is a crucial controller of T-cell trafficking in homeostasis, autoimmunity, and transplantation in humans. We showed that the endothelial barrier also exists in tumors and is partly mediated by ETBR.

This mechanism was uncovered in human ovarian cancer, in which endothelial cells were microdissected from tumors with brisk tumor-infiltrating lymphocytes (TILs) and tumors lacking TILs, to examine differences in their molecular profile. ETBr mRNA or protein overexpression was associated with absence or paucity of TILs, especially of intraepithelial (also called intratumoral) T cells (87). These are T cells infiltrating the epithelial component of the tumor (tumor islets), which predict longer survival in ovarian cancer (88). ET-1 is
overexpressed in ovarian cancer cells (34), and it was found that ET-1 mRNA was significantly higher in microdissected (cytokeratin-positive) tumor cells from tumors lacking TILs relative to tumors with brisk TILs. Thus, the entire ET-1/ETαR (tumor-endothelial) paracrine axis seems upregulated in ovarian cancers lacking TILs. Importantly, we showed that recombinant human ET-1 blocks adhesion of activated T cells to human umbilical vein endothelial cells in vitro. These results establish a vascular mechanism of tumor immune evasion mediated by the endothelin system (87).

TNF-α is a major inflammatory cytokine implicated in carcinogenesis, tumor angiogenesis, and progression, and it is upregulated in ovarian cancer (89). It has been previously reported that the overall TNF-α mRNA levels are similar in ovarian tumors with or without intraepithelial T cells (88). This was counterintuitive, as TNF-α is a major factor activating endothelium and promoting adhesion of T cells. It has been now found that ET-1 efficiently blocks adhesion of T cells to endothelial cells even when endothelial cells are activated with TNF-α (87). This observation explains the paradox of how tumors may exhibit inflammation yet be prohibitive to T-cell infiltration, thus establishing immune privilege even in the face of inflammation.

ET-1 was found to abrogate T-cell adhesion to endothelium via ETαR and through suppression of endothelial intercellular adhesion molecule-1 (ICAM-1) expression at base line as well as following endothelial activation with TNF-α. Furthermore, it was found that ETαR-induced suppression of ICAM-1 expression and surface clustering was mediated by nitric oxide (NO). ETαR blockade with the selective antagonist BQ-788 upregulated endothelial ICAM-1 expression, promoted ICAM-1 clustering at the cell surface, and restored adhesion of T cells to ET-1-treated endothelial cells. ICAM-1 neutralizing antibody abrogated the effect of ETαR blockade to promote T-cell adhesion to endothelium in vitro (87). These observations indicate that the endothelin system is crucial for controlling lymphocyte homing in tumors and that endothelial ETαR overexpression, which can sway the vascular ETαR/ETβR balance toward ETβR hyperactivity, results in suppression of T-cell homing. This evidence is substantiated by complementary data in lung inflammation: ETβR activation is required for endotoxin-induced inflammation (23), whereas T-cell homing to lungs in response to an inflammatory stimulus is abrogated by ETαR blockade (24, 25). Thus, vascular ETβR activation results in increased T-cell homing, whereas increased ETαR signaling facilitates immune privileged status.

**ETβR blockade in cancer immune therapy.** To test the activity of ETβR in controlling T-cell homing to tumors and the effects of its blockade in vivo in the context of immunotherapy, vaccine approaches that have no efficacy in delaying tumor growth were used. It was found that vaccine failure was associated with poor accumulation of T cells at the tumor site, in spite of detectable systemic antitumor immune response. ETαR blockade with specific antagonist BQ-788 greatly enhanced the efficacy of prevention and therapeutic vaccines. BQ-788 did not increase systemic immune response to the vaccine in vivo, but rather greatly enhanced T-cell infiltration in tumors following vaccine (87). This was attenuated by ICAM-1 neutralizing antibody, confirming the requirement for adhesive interactions mediated by ICAM-1 following ETαR blockade in vivo. Furthermore, BQ-788 markedly increased homing of T cells to tumors after adoptive transfer in mice. Thus, in many tumors there is hyperactivation of a paracrine ET-1/ETαR axis established between tumor cells and endothelium, whereby tumor cells overexpress and release ET-1 whereas the tumor endothelium overexpresses ETβR. This axis tonically suppresses T-cell homing (even in the presence of tumor inflammation), and can be disrupted by ETβR blockade, which in vivo markedly enhances tumor immune therapy (87). This mechanism may not be unique to ovarian cancer. For example, ETβR is also overexpressed in breast cancer vasculature (86). Interestingly, ETβR upregulation predicts poor outcome both in breast and ovarian cancer (47, 90). The mechanisms underlying ETβR overexpression in tumor endothelium are not fully understood, but VEGF may be implicated (91, 92).

Our results argue that ETβR antagonists warrant testing in combination with passive or adoptive immunotherapy. There are unique features that render ETβR blockade an attractive strategy in cancer immunotherapy. First, as outlined above, the axis ET-1/ETβR seems to be selectively upregulated in the tumor compartment but not in normal tissues. Indeed, in mouse experiments, ETβR blockade by BQ-788 did not result in systemic inflammation or illness, and frequency of CD45^+ lymphocytes or CD3^+ T cells in liver, spleen, lungs, or kidneys after vaccine or adoptive T-cell transfer was not affected by BQ-788 (87). This is in contrast to current immunomodulatory approaches, which achieve systemic activation of effector cells by attenuating peripheral tolerance or other homeostatic checkpoint mechanisms and can result in significant autoimmune toxicity (93). Second, ETβR-selective antagonists, including BQ-788, have been tested in humans and are well tolerated even in patients with cardiovascular disease (94–96). Thus, ETβR can be pharmacologically perturbed with existing drugs to enhance the efficacy of immune therapy. Third, ETβR blockade is likely to have also direct antiangiogenic effects through suppression of endothelial nitric oxide. Unlike in patients with sepsis (97), NO inhibition is safe and has been well tolerated in cancer patients (98). Although the anticanic effect of ETβR (or NO) blockade as monotherapy may be modest, the concomitant administration of immunotherapy may act synergistically against angiogenesis (86, 99).

**Implications for pure ETβR antagonists.** Currently, on the basis of results obtained mostly with xenograft tumor models in immunodeficient mice, cancer therapy targeting ET is focused on ETαR blockade. However, previous evidence shows that ETαR signaling is required for T-cell homing (24, 25), whereas our work indicates that increased ETαR activity in tumor endothelium results in reduced T-cell homing and ETαR blockade is required to improve T-cell homing to tumors. Because of the tonic antagonism between ETαR and ETβR signaling in the vasculature, pharmacologic ETαR blockade could tilt the balance toward increased ETαR signaling in the tumor vasculature. This could possibly result in increased angiogenesis and, on the basis of our work, could suppress T-cell homing to tumors. It has been previously shown that patients with ovarian cancer whose tumors are infiltrated by intraepithelial T cells survive longer (88), a concept validated by several groups (100–103). Similar observations were made in other solid tumors. In colon cancer, tumor-infiltrating T cells predict survival better than conventional anatomical staging (104), whereas in prostate cancer TIL represent a strong independent prognosticator of longer survival (105). Although the function of tumor-infiltrating T cells is not fully understood, it is possible that they contribute to controlling tumor growth during or after conventional cancer therapy. For example, the
long-term therapeutic effects of VEGF receptor 2 blockade, a major antiangiogenic pharmacologic intervention, were fully dependent on CD8+ T cell infiltration in tumors (106). Furthermore, conventional chemotherapy agents have immunomodulatory effects and their long-term efficacy may depend in part on immune effector mechanisms (107). If this were the case, ET$_{A}$R blockade alone might increase ET$_{A}$R signaling and reduce T-cell infiltration in tumors. This could negate some of the potential efficacy of cancer therapies and explain in part the failure of pure ET$_{A}$R antagonists to produce significant clinical results in tumors in which TIL may affect survival. Our results argue that ET$_{A}$R/ET$_{B}$R mixed antagonists might offer the advantage of simultaneously targeting the tumor cell (through ET$_{B}$R) and enhancing antitumor immune mechanisms (through vascular ET$_{B}$R) and should be the focus of future therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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ETBR and Cancer ImmuneTherapy


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