Molecular Pathways: Targeting the TGF-β Pathway for Cancer Therapy

Anna L. Smith1, Tyler P. Robin1,2, and Heide L. Ford3,4

Abstract

TGF-β is a ubiquitous cytokine that plays an active role in many cellular processes. Nearly every cell type has the ability to secrete TGF-β, as well as the ability to respond to TGF-β via the presence of TGF-β receptors on the cell surface. Consequently, gain or loss of function of the TGF-β pathway and its components are known to lead to a variety of diseases, including cancer. In epithelial cells, TGF-β functions as a tumor suppressor, where it inhibits proliferation, induces apoptosis, and mediates differentiation. Conversely, in other contexts, TGF-β promotes tumor progression through increasing tumor cell invasion and metastasis. Thus, TGF-β can have opposing roles, likely dependent, in part, on whether the cancer is early or late stage. The effects of TGF-β on tumor suppression and promotion are not limited to the tumor cell itself; rather, these effects can also be mediated through the stroma and the immune system. The dichotomous role of TGF-β in cancer highlights our need to understand the contextual effects of this cytokine to better guide patient selection for the use of anti-TGF-β therapies currently in clinical trials. Clin Cancer Res; 18(17); 4514–21. ©2012 AACR.

Background

TGF-β signaling

TGF-β is part of a large family of structurally related cytokines that include bone morphogenetic proteins, growth and differentiation factors, activins, and inhibins. There are 3 isoforms of TGF-β ligand (TGF-β 1–3), and as ubiquitous cytokines, they play an important role in numerous cellular processes, including proliferation, adhesion, motility, apoptosis, differentiation, and immune regulation (1).

The TGF-β-signaling cascade is initiated when active TGF-β binds to a family of transmembrane serine–threonine kinases known as the Type I and Type II TGF-β receptors (TβRI and TβRII, respectively). The TGF-β ligand first binds to TβRII, which then recruits TβRI to form a complex. This ligand-bound receptor complex allows TβRII to cross-phosphorylate TβRI, resulting in its activation (2). Canonical TGF-β signaling continues with the recruitment of receptor-activated Smad proteins (R-Smads: Smad2 and Smad3) to the active TβRI. The R-Smads bind to active TβRI and are subsequently directly phosphorylated by the receptor complexes (3), after which they associate with the co-Smad, Smad4. This heteromeric Smad2/3/4 complex then translocates to the nucleus where, together with cofactors, it binds DNA and alters the expression of many genes (ref. 2; Fig. 1).

In addition to stimulation of the canonical signaling pathway, ligand-activated TGF-β receptors can also activate additional intracellular pathways, including the mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K)/AKT, and Rho-like GTPase signaling pathways. Furthermore, R-Smad proteins have recently been implicated in miRNA processing (4), adding to the complexity of noncanonical outcomes for TGF-β activation. It is now clear that a combination of canonical Smad-mediated and non-Smad-mediated functions will determine the final outcome of the TGF-β cellular response (5).

TGF-β as a tumor suppressor

TGF-β is an important cytostatic regulator in epithelial cells due to its ability to activate the transcription of cell-cycle inhibitors and/or apoptotic regulators. Inhibition of the cell cycle occurs via TGF-β/Smad-mediated upregulation of cyclin-dependent kinases, p15ink4b, p21cip1, and p57kip2, and downregulation of proliferative genes such as c-Myc and the ID family of proteins. The ability of TGF-β to control apoptosis includes both Smad-dependent and Smad-independent mechanisms in a context-dependent manner. For example, TGF-β induces changes in expression of Bcl2 family members through Smad-mediated transcription of the proapoptotic factor Bim (6). In addition, non-Smad-mediated activation of the p38 MAPK pathway by TGF-β can induce caspase-8 and subsequently activate Bid.
to induce apoptosis (7). Importantly, the proapoptotic response of TGF-β includes activation of both the intrinsic and extrinsic apoptotic programs (8). Because of the cytostatic/apoptotic functions of TGF-β, it is not surprising that mutations in the core components of this pathway are found in numerous human cancers. For example, mutations or inactivation of TβRII are commonly found in colon, pancreatic, lung, and brain cancers (9), whereas mutations...
in TBRI are less prevalent, but can be found in prostate, biliary, endometrial, ovarian, pancreatic, and gastric tumors (9, 10). Although the presence of Smad2 or Smad3 mutations in cancer is rare, Smad4 inactivation in cancer is commonly found. Smad4 is mutated in half of all pancreatic cancers (11) and can also be found in colon, non–small cell lung cancers (NSCLC), and esophageal cancers (12).

In addition to the cell-autonomous role of TGF-β in growth inhibition, this cytokine also uses paracrine signaling in the stromal compartment to control growth of nearby cells. A stromal tumor–suppressive role for TGF-β was elegantly shown by Bhowmick and colleagues, who conditionally ablated TBRII from fibroblasts resulting in the induction of prostate intraepithelial neoplasia and squamous cell carcinoma in the forestomach (13). Tumor-suppressive roles for TGF-β signaling have also been observed in stromal compartments such as T cells, as selective loss of Smad4 in mice leads to spontaneous gastrointestinal tumors (14).

**Tumor-promotional effects of TGF-β: The "TGF-β paradox"**

The "TGF-β paradox" has been coined to describe the observation that TGF-β switches from tumor suppressive in early-stage tumors to tumor promotional in later-stage tumors (15). As cancer progresses, tumor cells often lose the ability to respond to TGF-β–mediated growth inhibition and instead use TGF-β signaling to increase epithelial-to-mesenchymal transition (EMT), invasion, and metastasis. Although many cancers obliterate the growth-suppressive function of TGF-β through mutation of pathway components, certain cancer types, such as breast and prostate cancers, as well as gliomas, often retain functional TGF-β signaling and instead selectively inhibit the tumor-suppressive arm of the pathway. Thus, induction and/or repression of genes required for TGF-β–mediated growth suppression is disabled in these tumors (16). One example of such a mechanism occurs in gastric cancer, in which upregulation of a cluster of microRNAs (miRNA), the miR-106b-25 cluster, leads to inhibition of p21 as well as the prosapoptotic factor, Bim, effectively impairing the growth-suppressive arm of TGF-β (17). Recently, our laboratory has shown that the homeoprotein and prometastatic regulator Six1 is capable of switching TGF-β from tumor suppressive to promotional in breast cancer cells (18) through a mechanism that likely involves Six1-mediated upregulation of the miR-106b-25 cluster (19). Interestingly, we found that these miRNAs are not only involved in the impairment of TGF-β growth suppression but are also capable of activating this pathway through repression of the inhibitory Smad7 protein (19), suggesting that one cluster of miRNAs may be sufficient to both inhibit TGF-β growth suppression and simultaneously activate the tumor-promotional arm of TGF-β signaling. For a complete review of mechanisms by which TGF-β switches from tumor suppressive to tumor promotional, see Inman (20).

Tumor cells that are able to bypass the cytostatic program of TGF-β are free to take advantage of the tumor-promotional functions of TGF-β. Indeed, TGF-β is a potent inducer of EMT, a process by which cells lose their epithelial characteristics and gain mesenchymal characteristics, resulting in enhanced migratory and invasive capabilities. The TGF-β–induced EMT is characterized by decreased expression of epithelial genes such as E-cadherin, ZO-1, and desmoplakin and by upregulation of the mesenchymal protein Vimentin (21). Smad-dependent mechanisms are important for TGF-β–induced EMT, as genetic ablation of Smads 2, 3, or 4 inhibits EMT induction in response to TGF-β treatment (22, 23). Furthermore, Smad-dependent transcription is associated with the induction of several other transcription factors central to the oncogenic EMT process, such as Snail and Twist (24). TGF-β also has been associated with the ZEB family of E-cadherin repressors and induces the expression of ZEB proteins during EMT (25). The ZEB1 protein then binds other corepressors, including Smad3, to transcriptionally repress epithelial marker genes such as E-cadherin (26). Finally, TGF-β signaling is itself activated by EMT-inducing transcription factors such as Six1 and is required for the ability of Six1 to mediate an EMT (27). Thus, TGF-β signaling is clearly central to the EMT process.

Importantly, TGF-β can induce EMT via both canonical and noncanonical pathways. Pathways downstream of TGF-β such as Ras/MAPK, PI3K/Akt, and RhO/ROCK signaling are critical effectors of the TGF-β–induced EMT in certain contexts (26). Because independent inhibition of both Smad proteins and alternative pathways results in failure of TGF-β–induced EMT, it is likely that TGF-β–mediated EMT occurs through a combination of Smad-dependent and Smad-independent signals.

In addition to inducing EMT, TGF-β also enhances tumor vascularization, as it directly induces the expression of key angiogenic factors including VEGF (28) and connective tissue growth factor (29). This TGF-β–induced increase in vascularization may allow for larger tumor growth and for tumor cells to escape the primary site and metastasize. However, TGF-β further stimulates tumor progression via a potent immunosuppressive role, as the cytokine has been shown to inhibit the proliferation and cytolytic activities of CD8+ T-lymphocytes (CTL). CTLs play important roles in tumor cell clearance, and accordingly, systemic attenuation of TGF-β in vivo increases immune-mediated recognition and clearance of tumor cells (30). Furthermore, TGF-β produced by cancer cells works as a chemoattractant for infiltrating monocytes and macrophages into the tumor microenvironment (31). The increase of monocytes and macrophages in the tumor stroma is known to increase tumor invasion and metastasis through facilitating angiogenesis and extracellular matrix breakdown, as well as reinforcing the immunosuppressive environment through further release of TGF-β (32). In addition, immature Gr-1+CD11b+ myeloid cells, also called myeloid-derived suppressor cells (mDSC), are commonly found in the tumor microenvironment and produce high levels of TGF-β and matrix metalloproteinases, leading to increased tumor invasion and metastasis (33). Interestingly, genetic deletion of TBRII in mammary...
carcinoma cells leads to the recruitment of MDSCs, thus enhancing the protumorigenic effect of TGF-β signaling in the microenvironment (34). Therefore, the "switch" in TGF-β signaling from suppressive to promotional encompasses both cell-autonomous and nonautonomous alterations.

The functions of TGF-β in EMT, immune suppression, and myeloid cell recruitment all support the eventual metastatic spread of cancer cells. Indeed, the role of TGF-β in metastasis was first realized when increased levels of TGF-β were observed in metastatic breast tumors versus primary tumors (35). It was then found that in breast cancers, TGF-β promotes bone metastasis through Smad-dependent induction of pro-osteolytic factors, such as parathyroid hormone–related protein (PTHrP). The increased levels of PTHrP subsequently stimulate production of RANK ligand (RANKL) in osteoblasts, which in turn promote the differentiation of osteoclast precursors and bone resorption, leading to increased bone colonization by metastatic cancer cells (36). Additional functions for canonical TGF-β signaling in breast cancer include induction of angiopoietin-like 4 (Angptl4) in tumor cells, leading to enhanced lung metastasis through an increase in their transendothelial passage (37).

Although a strong body of evidence supports a role for TGF-β in metastasis, conflicting studies exist. For example, whereas expression of constitutively active TGF-β1 or TβRI in the mammary gland of transgenic mice increases lung metastasis in neu-induced mammary tumors (38), targeted deletion of TβRII in mammary epithelial cells of PyVmtT transgenic mice also increases metastasis (39). Thus, the context, including the tumor-initiating mutation, the choice of TGF-β manipulation, and the timing of the TGF-β signal, seems to dictate whether TGF-β is tumor promotional or tumor suppressive (40).

Clinical–Translational Advances

The presence of elevated levels of TGF-β in tumor cells and the tumor microenvironment, as well as the overwhelming evidence for the prometastatic role of TGF-β, has made this cytokine an attractive target for therapeutic intervention. Preclinical studies have supported the use of anti–TGF-β therapies, and many of these strategies are currently in clinical trials. The 3 main approaches to inhibiting TGF-β or its pathway components include (i) antisense oligonucleotides (ASO) delivered directly into the tumor or engineered into immune cells; (ii) TGF-β–neutralizing antibodies which block access of TGF-β ligand to its receptor; and (iii) TGF-β receptor kinase inhibitors (Fig. 1). The greatest challenge for successful use of anti–TGF-β therapies lies in the dual nature of this pathway. Can we target only the tumor-promoting arm of TGF-β, while maintaining the tumor-suppressive arm? Moreover, can we select patient populations who will respond to these therapies and eliminate those that may be harmed by such treatments? These questions remain as we move forward with anti–TGF-β therapies; however, results from ongoing clinical trials continue to show promise for targeting this pathway in cancer.

Antisense TGF-β oligonucleotides

Antisense oligonucleotides are single-stranded polynucleotide molecules that are designed to hybridize to complementary RNA sequences and inhibit translation of these molecules. Several challenges exist in the development of ASOs as therapeutic targets, including off-target effects, delivery to target tissue, and RNA-binding affinity. However, recent advances in technology of these molecules have allowed several ASOs to enter clinical trials.

Antisense Pharma developed AP 12009, a phosphorothioate oligodeoxynucleotide designed to be complimentary to TGF-β2 ligand mRNA, resulting in inhibition of the pathway. AP 12009 was specifically designed for clinical use in highly aggressive TGF-β2–overexpressing tumors, such as malignant melanoma and high-grade gliomas. Three independent phase I/II clinical trials for AP 12009 using convection-enhanced delivery in patients with recurrent high-grade glioma have shown that the drug is well tolerated with no severe side effects (41). Survival benefits of AP 12009 were also shown at this stage with 7 of 24 patients showing stable disease and 2 patients exhibiting complete tumor remission (41). An additional phase III trial with AP 12009 in glioma patients showed a higher median survival in all treatment arms of the drug versus chemotherapy. Currently, a large phase III trial for AP 12009 in high-grade gliomas has been initiated, and more phase I trials for this drug have been initiated in melanoma, pancreatic, and colorectal carcinomas (Table 1). In addition, an ASO against TGF-β1 ligand has been developed by Antisense Pharma, AP 11014, for the treatment of NSCLC, prostate, and colorectal cancers. This drug remains in an advanced stage of preclinical development (42).

The ASO technology is also currently being used in anticancer vaccines. NovaRx Corp has developed a nonviral gene-based tumor cell vaccine, belagenpumatucel-L (Lucanix), which is a mixture of 4 allogeneic human NSCLC cell lines modified to express an ASO targeting TGF-β2. The rationale for this approach is that inhibition of TGF-β2 will result in increased immunogenicity of the gene-modified cancer cells. The local immune response directed toward the injected allogeneic vaccine cells is suspected to enhance an overall immune response against shared tumor antigens between the tumor vaccine cell and the patient's lung cancer. An initial phase II trial of Lucanix showed that this drug is safe and well tolerated (43). A dose-related survival advantage was shown in patients who received 2.5 × 10^7 cells/injection or more. In addition, increased cytokine production [IFN-γ, interleukin (IL)-6, and IL-4] was observed in responders (43). On the basis of these results, a randomized phase III trial in patients with advanced-stage NSCLC has been initiated (Table 1).

Anti–TGF-β antibodies

Monoclonal antibodies (mAb) targeting the TGF-β pathway have been successfully developed for many cancers

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TGF-β–neutralizing antibodies directed against TGF-β ligands are the preferred method of inhibiting TGF-β signaling because they directly bind to the ligand and prevent access to its receptor. Two pan-TGF-β mAbs, IDII (Genzyme) and 2G7 (Genetech), have been thoroughly tested and described in preclinical models. Both of these murine antibodies are panneutralizing for all 3 active TGF-β isoforms and exhibit antitumor and antimetastatic properties in vivo (45). IDII treatment in a 4T1 breast cancer model reveals that efficacy of the drug relies on a cooperation of TGF-β inhibition in many cellular compartments, including both the tumor parenchyma and microenvironment (46). These data support the idea that both cell-autonomous and cell-nonautonomous functions of TGF-β should be targeted. On the basis of strong preclinical data, Genzyme developed a human pan–TGF-β–neutralizing mAb, GC1008, for which clinical trials were initiated for the treatment of many cancers. Safety and efficacy of the drug has passed phase I trials for malignant melanoma, advanced renal cell carcinoma, and mesothelioma, and additional trials were initiated with recruitment to a safety and imaging clinical trial in gliomas, as well as to a combined radiotherapy and GC1008 trial in metastatic breast cancers (Table 1). Unfortunately, clinical development of GC1008 for oncology trials has been suspended by Sanofi Aventis, who recently acquired Genzyme Corp.; however, clinical development of the antibody for fibrotic disease is continuing (John McPherson; personal communication).

Similar to neutralizing antibodies, soluble TBRII and TBRIII ligand traps have been developed. These molecules express the extracellular domain of the receptor and prevent ligand access to the TGF-β receptors. Preclinical studies have used soluble TβRII fused to the Fc domain of murine IgG1. This strategy generates a highly stable TGF-β antagonist that has shown antitumor efficacy in mesothelioma, liver, and pancreatic models (47).

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<td>AP12009 Antisense Pharma</td>
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<td>Renal cell carcinoma, malignant melanoma, mesothelioma</td>
<td>Human pan–TGF-β monoclonal neutralizing antibody</td>
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<td>Belagenpumatucel-L (Lucanix) NovaRx Corp</td>
<td>NCT00431561 (phase III)</td>
<td>Advanced-stage NSCLC</td>
<td>Mixture of 4 allogenic NSCLC cell lines engineered to express ASO to TGF-β2 mRNA</td>
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<td>Anti–TGF-β antibodies and ligand traps</td>
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<td>GC1008* Genzyme</td>
<td>NCT01472731 (phase I)</td>
<td>Malignant glioma</td>
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<td>*Oncology trials recently suspended</td>
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<tr>
<td>Fc:TβRII</td>
<td>Preclinical (47–49)</td>
<td>Mesothelioma, liver, breast, and pancreatic cancers</td>
<td>Soluble TβRII fused to Fc domain of murine IgG1</td>
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<td>TGF-β receptor kinase inhibitors</td>
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<td>Targets the ATP-binding site of TβRII kinase</td>
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<td>Colon, pancreatic, and breast cancer</td>
<td>Dual TβRII/TβRII kinase inhibitor</td>
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Table 1. Oncology clinical trials with compounds targeting the TGF-β pathway

(44) TGF-β–neutralizing antibodies directed against TGF-β ligands are the preferred method of inhibiting TGF-β signaling because they directly bind to the ligand and prevent access to its receptor. Two pan-TGF-β mAbs, IDII (Genzyme) and 2G7 (Genetech), have been thoroughly tested and described in preclinical models. Both of these murine antibodies are panneutralizing for all 3 active TGF-β isoforms and exhibit antitumor and antimetastatic properties in vivo (45). IDII treatment in a 4T1 breast cancer model reveals that efficacy of the drug relies on a cooperation of TGF-β inhibition in many cellular compartments, including both the tumor parenchyma and microenvironment (46). These data support the idea that both cell-autonomous and cell-nonautonomous functions of TGF-β should be targeted. On the basis of strong preclinical data, Genzyme developed a human pan–TGF-β–neutralizing mAb, GC1008, for which clinical trials were initiated for the treatment of many cancers. Safety and efficacy of the drug has passed phase I trials for malignant melanoma, advanced renal cell carcinoma, and mesothelioma, and additional trials were initiated with recruitment to a safety and imaging clinical trial in gliomas, as well as to a combined radiotherapy and GC1008 trial in metastatic breast cancers (Table 1). Unfortunately, clinical development of GC1008 for oncology trials has been suspended by Sanofi Aventis, who recently acquired Genzyme Corp.; however, clinical development of the antibody for fibrotic disease is continuing (John McPherson; personal communication).

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Additional studies in breast cancer models showed that systemic administration of Fc:TβRII reduces tumor cell motility, invasion, and lung metastases (48). Yang and colleagues further showed that transgenic mice expressing Fc:TβRII are not only resistant to developing metastasis but also show no adverse side effects to lifetime exposure of the drug (49). At this point, no clinical trials using soluble TGF-β receptors have been reported.

**TGF-β receptor kinase inhibitors**

Another therapeutic approach entails inhibiting the kinase activity of the TGF-β receptors, thereby arresting downstream canonical and noncanonical signaling. Initial attempts to target the kinase activity of the receptors focused on the type I receptor. Kinase inhibitors targeting the ATP-binding site of the TβRI kinase include small molecules such as SD-208 (Scios), SB431542 or SB505124 (GlaxoSmithKline), and LY-2157299 (Lilly Research Laboratories). Early successes in preclinical models include those with SD-208, in which treatment leads to decreased tumor growth and invasiveness of mouse and human glioma cells, as well as increased immunogenicity of mouse gliomas when the agent is delivered systemically (50). In addition, treatment of human malignant glioma cell lines with SB-431542 leads to a reduction of cell proliferation and motility, as well as in the expression of angiogenic factors (51). The LY2157299 compound has proved effective as an orally administered drug in a NSCLC and breast cancer preclinical mouse model (52). Preclinical models and phase 1 safety and pharmacokinetics studies have pushed this compound into further clinical trials; patients are currently being recruited for the treatment of hepatocellular carcinoma (Table 1). Through a compound library search, Eli Lilly and Company has also discovered a TβRI and TβRII dual inhibitor, LY2109761, which inhibits metastasis in colon and pancreatic cancer models (53, 54), and has recently shown efficacy against glioma-initiating cells in patient-derived primary cultures of tumor cells (55). A study of breast cancer bone metastasis in a xenograft mouse model, however, shows that the ability of LY2109761 to reduce metastasis is more effective early in metastasis and curative treatment of well-established bone metastasis is less effective (56).

Finally, combined therapy approaches using chemotherapeutic agents and TGF-β kinase inhibitors show significant promise in preclinical models and are being moved into clinical trials. Chemotherapy can activate TGF-β signaling and can, in fact, increase metastasis of MDA-MB-231 cells in an orthotopic breast cancer model. In this model, metastasis can be significantly blocked with combined treatment of doxorubicin and a TβRI kinase inhibitor (57). Furthermore, treatment of gemcitabine-resistant pancreatic cancer cells with SB525334 sensitizes these cells to drug treatment (58). The promise for such combined therapy has led to the initiation of clinical trials, including 2 trials using LY2157299: a phase I/II trial with combined radiochemotherapy for malignant glioma (Table 1) and a phase I/II trial for combined use with gemcitabine in metastatic pancreatic cancers (Table 1).

**Limitations of anti–TGF-β therapy**

The preclinical and clinical data for anti–TGF-β therapy show promise for targeting this pathway as an anticancer therapeutic. However, as described above, TGF-β has a complex and dichotomous role in cancer. For this reason, the importance of patient selection will be critical in moving forward with anti–TGF-β treatments.

Clinical trials carried out to date using anti–TGF-β therapies have mostly reported positive results for safety and efficacy. However, a few reports have noted adverse effects in certain patients. For example, the phase I/II trials of AP 12009 reported 2 cases of adverse events that were classified as grade 3, including 1 case of intracranial edema that was associated with treatment of AP 12009 (59). In addition, the phase I study of the panneutralizing anti–TGF-β antibody, GC1008, reported 1 serious event possibly related to treatment, in which a patient with a previous history of skin cancer developed a well-differentiated squamous cell skin carcinoma (47).

Because high circulating or tissue TGF-β levels are correlated with worse prognosis in many cancers, it is proposed that TGF-β levels could stratify patients into treatment populations. This approach, however, does not account for patients whose tumors may actually be responding to TGF-β as a tumor suppressor. To this end, it would be beneficial to identify molecular biomarkers that may identify tumors that have lost TGF-β-mediated growth inhibition. Many possible biomarkers have been proposed, including genetic and epigenetic changes such as p53 mutation, hypomethylation of platelet-derived growth factor β, overexpression of Six1, or loss of Smad4 (20). Additional studies, however, are needed to verify the prognostic value of these targets for response to TGF-β–targeted therapies.

The advancement of bioinformatic tools in the clinic may also help to facilitate better analysis of patients who would benefit from TGF-β therapy. Traditionally, molecular biomarkers are identified by immunohistochemical staining in the clinical setting. However, gene expression analysis may more accurately assess the TGF-β response in tumors. To this end, Padua and colleagues established a TGF-β response signature that can be applied to identify tumors with active TGF-β signaling (37). This strategy, however, might be even more powerful if one could differentiate between the tumor-promotional and tumor-suppressive TGF-β signature to identify tumors in which the TGF-β tumor-suppressive signature has been lost.

In addition to the multifunctional role of TGF-β, it is also important to remember the ubiquitous nature of this cytokine. Because TGF-β is involved in many normal physiologic processes, systemic inhibition of TGF-β may have deleterious side effects. In clinical trials of the allogenic tumor vaccine Lucanix, adverse events were only reported...
in 10% of patients but included pain, fatigue, nausea, headaches, cough, and weakness (43). In trials mentioned above with CC1008, adverse events included fatigue, headache, gingival bleeding, and gastrointestinal symptoms, although all adverse events were classified as grade 2 or less (47). On the basis of these data, it is likely that the potential benefit of these treatments will outweigh the possible complications.

Overall, the complexity of TGF-β highlights the need for an improved understanding of the biologic and pathologic mechanisms that control response to TGF-β signaling. The clinical studies under way have already shown TGF-β as a promising target for cancer therapy. Improving patient selection criteria will thus likely be a powerful means to enhance the outcomes of these therapies.

Disclosure of Potential Conflict of Interest
H. Ford and A. Smith own a patent on mRIs for which they receive no compensation. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions
Conception and design: A.L. Smith
Development of methodology: A.L. Smith
Writing, review, and/or revision of the manuscript: A.L. Smith, T.P. Robin, H.L. Ford

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References
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