Companies Waver in Efforts To Target Transforming Growth Factor $\beta$ in Cancer

By Ken Garber

More than 30 years after its discovery, transforming growth factor $\beta$ (TGF-$\beta$) engages developmental biologists, immunologists, cell biologists, and cancer researchers. New findings are reported weekly for this multifunctional cytokine family. In cancer, researchers continue to deconstruct TGF-$\beta$’s dual role as a tumor suppressor and promoter. Interest in its biology is greater than ever.

Unfortunately, the same can’t be said about therapies targeting TGF-$\beta$ in cancer. Earlier this decade, spurred by reports that TGF-$\beta$ inhibition was safe and effective in animal models, many drug and biotech companies launched programs to develop TGF-$\beta$ inhibitors. But several of these programs have recently been abandoned, and most companies that remain in the race are proceeding slowly and cautiously (see sidebar). The future of TGF-$\beta$ therapy, once so bright, is now in doubt.

From the Start

TGF-$\beta$ and cancer were linked from the start. In 1978, Joe De LaRco, Ph.D., and George Todaro, M.D., at the National Cancer Institute partially purified a substance that allowed normal cells to form colonies in soft agar unsupported by any solid structure—a defining trait of cancer cells. They called the mysterious substance sarcoma growth factor. One fraction of sarcoma growth factor proved responsible for this anchorage-independent growth. Called TGF-$\beta$, it was purified in 1981 by Anita Roberts, Ph.D., in the NCI lab of Mike Sporn, M.D., and by Harold Moses, M.D., then at the Mayo Clinic in Rochester, Minn. In 1980 Todaro and Sporn speculated that tumor cells manufacture their own proteins such as TGF-$\beta$ in order to grow—the autocrine secretion hypothesis—and that specific inhibitors might control such cancer cells.

Their prediction proved prescient, but it was only part of the story; TGF-$\beta$ turned out to be much more complicated. In 1984, Moses’ group reported that TGF-$\beta$ was a growth inhibitor in certain cell types. The following year, Roberts showed that TGF-$\beta$ could promote or inhibit growth in the very same cells, depending on conditions. This was clearly a new and fiendishly complex kind of growth factor.

The mechanics of TGF-$\beta$ signaling, in contrast, proved relatively straightforward. TGF-$\beta$ binds to a receptor complex on the cell’s surface. The receptor then phosphorylates (donates a phosphate group to) transcription factors called Smads, which form a complex with the protein called Smad4. The complex then moves into the nucleus and triggers target gene transcription. The versatility of TGF-$\beta$ stems from the fact that the Smads need coactivators to work, and the cell shuffles a vast variety of cofactors depending on conditions. “All of TGF-$\beta$ signaling, I think, is context dependent.”

On the other side, tumor cells manufacture their own proteins, including TGF-$\beta$, and in some cases, more than the normal cell. “It’s like taking the emergency brake off and now the cells are in uncontrolled growth,” said Steve Albelda, M.D., a cancer researcher at the University of Pennsylvania in Philadelphia. TGF-$\beta$ signaling then favors tumor growth and spread. “It’s like taking the emergency brake off and now the cells are in uncontrolled growth,” McPherson said. “Those cells start to produce large amounts of TGF-$\beta$ in what appears to be a desperate attempt to control proliferation.” This process results in immune suppression, promotion of metastasis, and direct growth stimulation through effects on the tumor microenvironment. “The most invasive and the most metastatic cancers produce large amounts of TGF-$\beta$,” said Akhurst. “It’s like a vicious circle.”
By the early 1990s, TGF-β’s protumor effects made it an obvious drug target. But drug companies ignored it. Fear of side effects was the main reason, said McPherson. For example, TGF-β-knockout mice self-destruct from massive inflammation. “Everyone was terrified of the prospect of neutralizing TGF-β,” he said.

Then, in 2002, groups led by Lalage Wakefield, Ph.D., of the NCI and Carlos Arteaga, M.D., at Vanderbilt showed that inhibiting TGF-β in transgenic mice with cancer dramatically reduced metastases with no major side effects, even after lifetime exposure to the TGF-β inhibitors.

This surprising result changed the whole climate. “Suddenly all the companies started jumping on top of TGF-β,” Akhurst said. Other encouraging reports began to appear, and the race was on. One 2006 review listed eight companies developing 16 different TGF-β inhibitors, three of them in the clinic. So much activity testified to the potential payoff, despite the risk. “TGF-β antagonists . . . could prove as useful clinically as Herceptin (trastuzumab),” wrote Akhurst in 2002. “They would also be expected to have a wider range of applications.”

**Rationalizing Treatment**

Since 2002, Wakefield’s group, which receives part of its funding from Genzyme through an NCI Cooperative Research and Development Agreement, has been studying how TGF-β inhibitors blunt metastasis without affecting the protein’s crucial functions in normal cells. Using an anti-TGF-β antibody in a mouse model of breast cancer, they found a constellation of different antitumor effects working cooperatively on the tumor microenvironment, on the immune response, and on the tumor itself to cause “a death by a thousand cuts,” Wakefield said. “All the molecular effects were small, and as far as we could tell most of them were occurring quite locally at the tumor microenvironment. I think [that] was one of the factors that contributed to the relative lack of toxicity.”

There are other possible explanations. Anti-TGF-β antibodies may not reach TGF-β that’s activated locally on or within normal cells, but they do reduce the large quantities in and around tumors. Also, the antibodies do not eliminate TGF-β but may only bring down levels enough to inhibit tumors without affecting normal biology. “We are trying to turn down TGF-β; we are not trying to turn it off,” McPherson said. “That’s a big difference.”

Genzyme’s GC1008, a human anti-TGF-β antibody, was well tolerated in about 180 primates, with no observed induction of autoimmune diseases, cancer, cardiovascular abnormalities, or adverse effects on bone remodeling. But cancer remains a worry. TGF-β is a powerful tumor suppressor, and blocking it could convert premalignant lesions to new cancers. “That’s not an issue to be dismissed—we’re all concerned about that possibility,” McPherson said. But in the antibody’s phase I safety trial, the resulting side effects were transient and reversible. Two of 21 melanoma patients developed nonmalignant lesions called keratoacanthomas that disappeared when treatment was suspended. A third patient developed an apparent squamous cell carcinoma that was removed surgically. “We don’t know whether it would have resolved or not,” said McPherson. TGF-β may have triggered growth of these lesions in the skin at sites of previous damage, but the keratoacanthomas, at least, were not cancer. Five patients achieved stable disease and there was one partial response.

**Industry Backs Off**

GC1008 is not on the fast track for cancer. The company has put plans for a phase II trial in metastatic melanoma on hold. There are no immediate plans for company-sponsored trials of GC1008 in cancer. Instead, Genzyme plans to support selected small-scale cancer trials by independent investigators. On the basis of the results, these may lead to larger trials later.

For example, Albelda hopes to try GC1008 supplied by Genzyme in malignant mesothelioma, a virulent cancer caused by asbestos exposure. Mesothelioma is one of a few cancers—glioblastoma is another—in which TGF-β plays a tumor-promoting role throughout the life cycle of the tumor, so it’s an obvious cancer to target. Progression-free survival for these patients on chemotherapy is a scant 3 months. But other companies are dropping out. GlaxoSmithKline, Scios, and Biogen Idec all suspended their small-molecule TGF-β inhibitor programs in the last few years. Even Eli Lilly’s highly regarded program may be at risk. According to Lilly, its small-molecule drug “continues in active phase I development.” But it has been in phase I since at least 2006. “Companies are moving forward very carefully, fully aware of how difficult a problem this is,” said Wakefield. “There are plenty of easier, superficially easier, targets out there.” Caution is warranted, the experts say, but there’s a danger that more companies will drop out. “Let’s hope they don’t, because I think there certainly could be some very nice applications in the long run,” said Akhurst, who has received past research support from Eli Lilly.

Only one company, Antisense Pharma in Germany, is proceeding decisively in the clinic. In April it launched a multinational randomized, controlled phase III trial of...
trabedersen, its anti–TGF-β2 antisense oligonucleotide, in anaplastic astrocytoma. A phase I/II trial in pancreatic and colorectal cancers and melanoma is also ongoing.

Phase IIIb results suggested superiority for trabedersen in anaplastic astrocytoma compared with standard chemotherapy, in terms of response rate and in median overall survival (39 months compared with 22 months, at one dose level). But the patient numbers in this subgroup were too small for the survival difference to be interpretable, hence the phase III trial, enrolling a planned 132 patients. The European Medicines Agency and the U.S. Food and Drug Administration are looking at different approval endpoints, but success on either continent would validate TGF-β as a viable target in cancer and revitalize the field.

But, unlike monoclonal antibodies and kinase inhibitors, no successful track record exists for antisense drugs in cancer or any other major disease. Success depends on the right target and is a question of time, said Hubert Heinrichs, M.D., Antisense Pharma’s chief medical officer. TGF-β2’s immunosuppressive, proliferative, angiogenic, and prometastatic effects, in his view, make it a “pivotal molecule” in cancer and an excellent target.

### Combining With Immunotherapy

But as primarily antimetastasis agents, TGF-β inhibitors alone aren’t likely to eradicate tumors. “I don’t think it’s going to be a magic bullet,” said Akhurst. “But certainly in combination with other therapies it could be.” Combining anti–TGF-β drugs with chemotherapy makes sense, because TGF-β in tumors impairs drug delivery by building a web of fibrous connective tissue and blood vessels around the tumor. This process creates internal pressure that keeps drugs out. Blocking TGF-β could reverse the effect.

An obvious approach is combining TGF-β inhibitors with immunotherapy. Cancer immunotherapy, overall, has met with very limited success, largely because tumors downregulate the immune response. TGF-β plays a big part in this. It suppresses cytotoxic T cells and natural killer cells and recruits macrophages that produce immunosuppressive cytokines. It also works directly on cancer cells to downregulate surface molecules important for immune system recognition and activity. Combining TGF-β inhibitors with immunotherapy should, in theory, enhance the overall antitumor effect. Some researchers have had promising results with such combinations in animal models. “Using it to augment immunotherapy is a great application,” Akhurst said, “because you don’t need to have long-term treatment.”

But there are practical obstacles. Few if any immunotherapies are proven successes, so drug companies are loath to try them in combination with an experimental drug, because there is no clear path to FDA approval for such combinations. “Try to get the FDA to buy into a phase II trial or something like that then you have attenuation or loss of TGF-β signaling,” Akhurst said, “because you don’t need to have long-term treatment.”

### Shrinking List

Companies are proceeding cautiously in their development of TGF-β inhibitors, and some have dropped out of the race in recent years.

<table>
<thead>
<tr>
<th>Company</th>
<th>Agent</th>
<th>Indications</th>
<th>Stage</th>
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<tbody>
<tr>
<td>Antisense Pharma GmbH</td>
<td>AP12009 (trabedersen), antisense oligonucleotide against TGF-β2</td>
<td>Anaplastic astrocytoma</td>
<td>Phase III</td>
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<tr>
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<td>Pancreatic, metastatic melanoma, colorectal</td>
<td>Phase I/II</td>
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<td>GC1008 anti–TGF-β monoclonal antibody</td>
<td>Metastatic melanoma; other indications pending</td>
<td>Phase I complete; investigator-sponsored trials pending</td>
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<tr>
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<td>LY2157299, small molecule vs. TGF-β receptor 1 (kinase domain)</td>
<td>Various</td>
<td>Phase I</td>
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<td>GlaxoSmithKline</td>
<td>TGF-β type 1 receptor kinase inhibitor</td>
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inhibiting TGF-β. The explanation may be that those models don’t completely knock out TGF-β, whereas Moses’ models do. “When you’re treating with a drug, you’re only downregulating,” said Akhurst. “You’ve still got some residual signaling.” That residual TGF-β signaling may be enough to check cell proliferation, while the overall loss of TGF-β works against the tumor.

But Moses believes that it’s not TGF-β signaling that drives most tumor invasion and metastasis but rather loss of TGF-β signaling. “In later stages of tumor progression, then you have attenuation or loss of TGF-β signaling in carcinoma cells,” he said. “This results in the loss of growth-inhibitory effect.” Others disagree, pointing out that Smad2 is phosphorylated in most tumors, indicating an active pathway. “Virtually everything that TGF-β does late in tumorigenesis is protumorigenic,” said Akhurst.

The controversy matters, because if Moses is right and TGF-β signaling is lost in most advanced tumors, TGF-β inhibitors are less likely to be effective. Although he’s generally pessimistic about anti–TGF-β therapy in cancer, “there are contexts where it could be beneficial,” said Moses, “perhaps in subsets of...”
human breast cancer.” Combining with immunotherapy, he said, might also work.

The excitement and optimism of 2002–2006 have not entirely faded. For example, Wakefield, Akhurst, and Albelda all agree that targeting TGF-β together with immunotherapy holds great promise. And because the opportunities still seem so great, they don’t want to see drug companies exit the field.

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