Integrins as Target: First Phase III Trial Launches, but Questions Remain

By Andrea Carter

Cellular glue, signaling molecule, cancer accessory—scientists have described various functions for the integrin cellular receptors since the 1970s. And now they may be adding another role to the list: For the first time, an integrin as a target for cancer therapy has made it to a phase III clinical trial.

Merck KGaA, based in Germany, is sponsoring the trial to test cilengitide, an RGD (arginine–glycine–aspartic acid) peptide targeting an integrin involved in angiogenesis, for the brain cancer glioblastoma. The study, led by Roger Stupp, M.D., at the University of Lausanne Hospital in Lausanne, Switzerland, is currently recruiting more than 500 patients from Asia, Europe, and North America.

“Cilengitide is up front, and if it continues to look good, it will be the first drug of this kind to be approved,” said David Cheresh, Ph.D., at the University of California at San Diego in La Jolla, who worked on the early preclinical studies with the drug.

But whether more integrin-targeted drugs will appear remains uncertain. One unanswered question about anti-integrin drugs in general concerns their effects on normal cells. What makes integrins a potentially effective cancer therapy target, their key role in cell survival, also makes them a tricky mark because many of the receptors are active in both normal and cancer cells. Also, some preclinical studies suggest that anti-integrin compounds can promote cancerous activity.

“The limitation of these drugs could be toxicity,” said Filippo Giancotti, M.D., Ph.D., at the Sloan–Kettering Institute in New York, who studies integrins in normal development and cancer.

Molecular Glue

Integrin’s name reflects its function. Scientists saw these receptors, first described as the molecular glue that holds cells onto the extracellular matrix (ECM), as integrating the inside of the cell to the outside environment. Each integrin has an α and a β transmembrane subunit. These subunits combine in different ways to form 24 different integrins in the body. The receptors link the cell’s cytoskeleton to the ECM by binding to their ligands, such as vitronectin, laminin, fibronectin, and collagen, creating a molecular scaffold that gives tissues their structure. This connection is also necessary for cells’ health. Normal cells that detach from the ECM can undergo apoptosis.

Then in the 1980s scientists found that integrins not only had a mechanical function but also were true signaling molecules. Each cell type expresses its own repertoire of integrins that act as cell sensors, interpreting cues from the microenvironment and telling the cell how to behave.

“The integrin senses, interprets, and distributes information in a functional way, so cells can respond to their microenvironment,” said Peter Brooks, Ph.D., at the Center for Molecular Medicine at the Maine Medical Center Research Institute in Scarborough, who worked on preclinical studies with cilengitide.

This sensory role can go awry in cancer. Cells that turn cancerous can change the types of integrins they express to suit...
their needs. Scientists have implicated integrins in cell proliferation, invasion, metastasis, and angiogenesis. Integrins team up with tyrosine kinase receptors in cancer cells to trigger cascades that lead to tumorigenesis.

“In cancer” instead of sensing their environment, the cells become rogue and start invading,” said Scott Kuwada, M.D., at the University of Hawaii, who studies β1 integrins in the gut lining.

The biology—how the drug’s integrin target, αβ, is expressed in cancer—was highlighted in a 1994 Science paper in which Cheresh and Brooks reported that the αβ, integrin played a key role in angiogenesis. Integrins offer a docking site for endothelial cells, endothelial stem cells, inflammatory cells, and others to bind to the site of angiogenesis. They also activate signals for cell migration and survival to form the vessel structures. The scientists induced angiogenesis on the chick chorioallantoic membrane assay, where an early chick embryo forms blood vessels to gather nutrients from the yolk, and found that αβ, expression increased fourfold. They also showed that a monoclonal antibody to the integrin blocked blood vessel growth.

Around that time Merck KGaA was interested in developing anti-integrin targets. They teamed up with Cheresh, supplying his lab with peptides to test. In the mid-1990s the company developed cilengitide, an antagonist to both αβ, and αβ, also expressed in angiogenesis. Cheresh and others realized that the peptide could be useful in treating brain tumors when they discovered that the tumor cells also expressed αβ,.

In the January 2001 issue of Neurosurgery, Cheresh and Walter Laug, M.D., reported that cilengitide did indeed have an effect. They injected human brain cancer cells in the forebrain of mice and treated them with the peptide. Treated mice lived about 16 weeks, compared with 4 – 6 weeks for untreated control mice. And the tumors either disappeared or were microscopic compared with those of the untreated mice, whose tumor sizes were 3 – 5 mm.

“The therapy hit two birds with one stone: newly formed blood vessels and the tumor cells themselves,” said Brunhilde Felding-Habermann, Ph.D., who was a Merck-funded postdoctoral fellow in Cheresh’s lab at the time and is now at the Scripps Research Institute in La Jolla, Calif.

Then, in early clinical trials with glioblastoma, an aggressive brain cancer that is difficult to treat, the drug showed some promise. The National Cancer Institute’s Cancer Therapy Evaluation Program started the phase I clinical trial, and researchers have conducted two phase II trials for newly diagnosed glioblastoma patients who took cilengitide along with standard treatment. The first was in Europe, sponsored by Merck KGaA. The second was in the U.S., sponsored by the Cancer Therapy Evaluation Program, for which a written report is pending. Merck KGaA also sponsored a phase II trial for patients with recurrent glioblastoma who took cilengitide along with standard treatment. The first was in Europe, sponsored by Merck KGaA. The second was in the U.S., sponsored by the Cancer Therapy Evaluation Program, for which a written report is pending. Merck KGaA also sponsored a phase II trial for patients with recurrent glioblastoma who took only cilengitide and for whom other treatment had failed. “I wouldn’t say the results are dramatic, but they are encouraging,” said David Reardon, M.D., at Duke University, who led the phase II trial for recurrent glioblastoma.

The median historical survival rate for glioblastoma is 15 months, according to Burt Nabors, M.D., of the department of neurology at the University of Alabama, who was involved in phase I and phase II trials. “Our patients are living 20 months,” he said.

Cilengitide may also be effective in other cancers. Scientists have found αβ, expression on melanoma, breast, prostate, cervical, and pancreatic carcinoma cells. Merck is testing cilengitide in lung and prostate cancer. Other potential targets are in the pipeline. Volociximab, an antibody that targets the αβ, integrin, also involved in angiogenesis, is in various phase I clinical trials sponsored by Biogen IDEC, PDL Biopharma, and Facet Biotech. And ATN-161, a peptide that also targets αβ, completed an NCI-sponsored phase I clinical trial.

**Tumor Promoter?**

However, some scientists are skeptical about the potential of anti-integrin drugs. In a 2009 Nature Medicine article, Andrew Reynolds, Ph.D., and Kairbaan Hodivala-Dilke, Ph.D., reported that cilengitide and another similar peptide promoted angiogenesis and tumor growth in mouse models at nanomolar levels. The researchers, from the Institute of Cancer Research, and the Barts and London School of Medicine and Dentistry, both in London, injected mice subcutaneously with melanoma and lung carcinoma cells. Mice treated with the therapies at low doses had a 30%–60% increase in blood vessel proliferation compared with untreated mice. However, they did see inhibition of blood vessel formation at higher doses. These results follow soon after other preclinical studies suggesting that anti-integrin and other antiangiogenic compounds can stimulate cancerous cell activity.

“The take-home message is that the drugs currently available to target integrins could be inhibiting or promoting angiogenesis, depending on the dose and the tumor type,” said Reynolds.

But Cheresh said that it is not clear that these preclinical results are relevant to cilengitide in the clinic. “The preclinical studies are not entirely designed in a physiological manner to replicate what has taken place in the clinic,” he wrote in an email. “This has to do with the dose and the manner the drug was delivered.”

Specificity is another challenge to developing therapies against integrins. Drugs need to distinguish between integrins expressed in healthy and cancerous tissue. Also, many integrins have multiple ligands. Which one they bind to determines how they direct cell activity.
“We have to be cautious with which integrins we target,” said Brooks. “A lot of β1 integrins are expressed in normal cells, while α,β, level of expression in normal tissue is much lower.”

Some scientists believe that targeting ligands with which the integrin interacts to promote tumorigenesis may be a way around this obstacle. For example, in tumor growth collagen often degrades or denatures. The integrin recognizes this decrepit collagen and binds to it, causing a tumorigenic response, such as cell proliferation, resistance to chemotherapy, and invasion. Brooks’ lab is looking for antibodies to target these cancerous ligands.

Other scientists are interested in targeting the integrins’ interaction with other receptors. For example, the α,β, integrins can team up with the vascular endothelial growth factor receptor to activate angiogenesis. “In developing drugs you don’t want to just target the integrin,” said Tatiana Byzova, Ph.D., at the Lerner Research Institute at the Cleveland Clinic in Ohio. “You want to block the integrin and [vascular endothelial growth factor] receptor complex. That’s the direction we are going.”

Despite the controversies and ambiguities, many scientists feel that therapies against integrins have a future in some form, either alone or with other drugs. “Integrins have been the domain of basic science,” said Kuwada. “The field [of clinical application] is in its infancy. We will see more and more therapies against integrins because they are important for cell function and cancer.”

Others caution that there is a long way to go. “When these drugs are approved for treatment in patients, then we can say that they are successful; until then, we can’t say if they are a great drug or not,” Reynolds said.

Dr. Byzova has a patent pending on inhibitors of angiogenesis based on a crosstalk between α,β, and VEGFR2 (an approach still in development). Dr. Brooks is co-inventor on a patent covering integrin-related technology.

© Oxford University Press 2010. DOI: 10.1093/jnci/djq186