Trojan horse

EGEN's polymer delivery system sneaks past defenses to wallop cancer

By Diana LaChance

Huntsville's EGEN Inc. has developed a polymer-based protein delivery system that could revive the promise of Interleukin-12 (IL-12) in cancer treatment. IL-12, a group of proteins that the body produces naturally in response to antigenic stimulation, was found in the 1980s to destroy cancer cells without harming cells that were not cancerous. Scientists then theorized that if doctors could introduce more cancer-fighting IL-12 to end-stage patients in whom IL-12 was very low, the cancer would be destroyed and the patient returned to health.

Unfortunately, says Dr. Khursheed Anwer, president and chief scientific officer of EGEN Inc., based at the HudsonAlpha Institute for Biotechnology, it didn't quite work out that way. "Any time you introduce a gene to a human, it's considered foreign. The body gets suspicious that it's a virus or bacteria and destroys it," he says. That's what happened when IL-12 was introduced to patients. To compensate, doctors tried introducing more IL-12, but with even more disastrous results. "It turned out to cause liver and blood toxicity, and so people shied away," says Anwer. What had looked like an ideal solution was then abandoned until, Anwer says, "we decided to take another look in 2003."

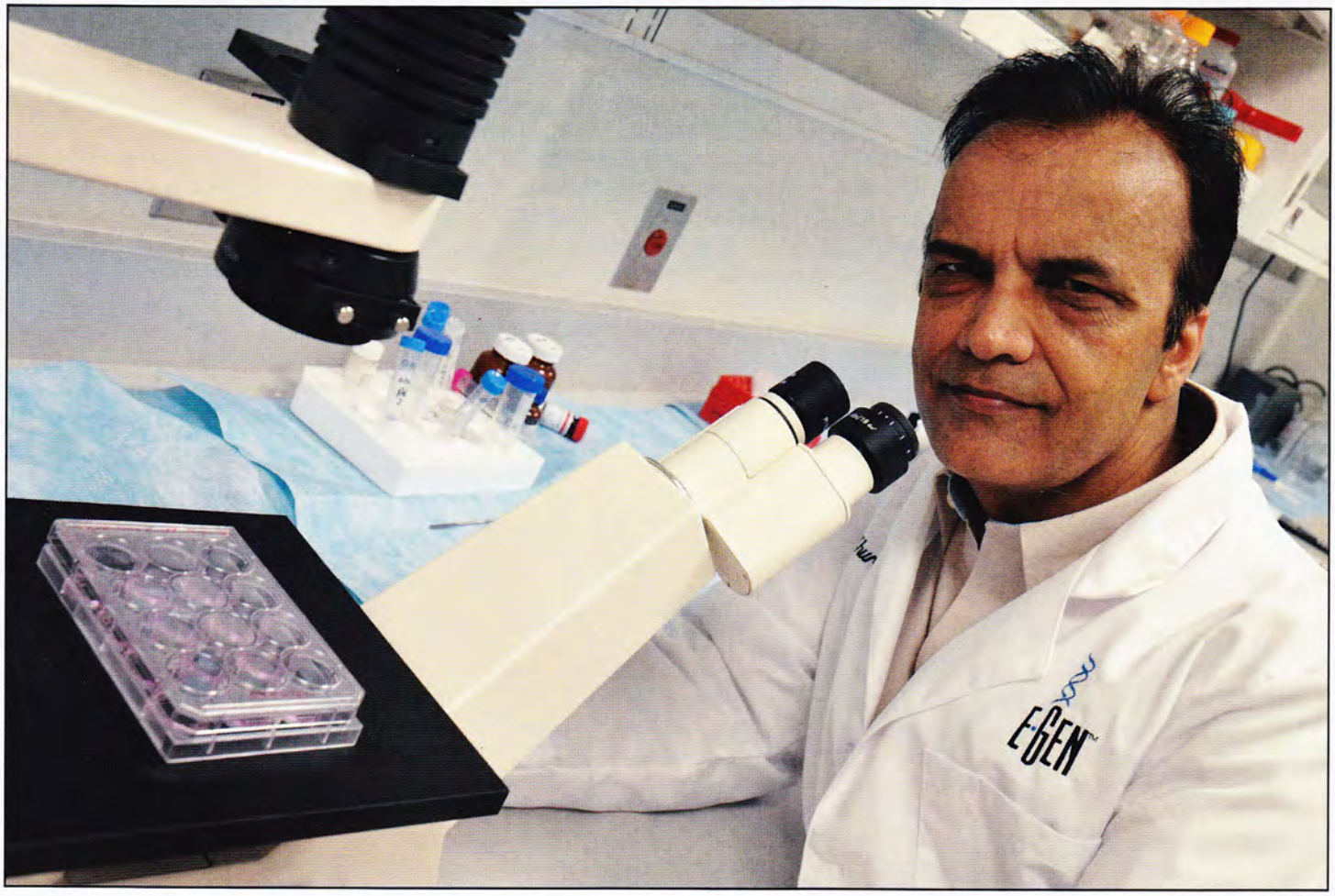
Because of past efforts, Anwer knew that delivering IL-12 directly wouldn't work. "If you take a growing tumor and throw IL-12 at it, the IL-12 is going to affect both the tumor and the healthy cells," he says. "But what if you delivered the IL-12 gene instead of the protein? Then it can be introduced to the nucleus of the cancer cell, where the protein the gene makes can target the tumor and not affect the healthy cells as much." The issue isn't whether or not IL-12 is effective at fighting cancer. It's known to boost the patient's immune system and act as a chemo-attractant, increasing the signal to fight the tumor and calling immune cells to the tumor site. The issue is how to deliver the IL-12 effectively. Enter TheraPlas, EGEN's proprietary gene delivery system designed to treat ovarian cancer.

"The delivery system has to be something the body can recognize as friendly and non-threating," says Anwer. "And it also has to know how to overcome all the barriers." He describes it as "a marriage between biology and chemistry – the biologist understands the body and the chemist understands the delivery system." EGEN's patented system relies on a polymer that has been functionalized by attaching certain specialized elements to it. "Some elements are membrane-permeating agents, which facilitate delivery through the cell membrane," says Anwer. "And some are stabilizing agents, which protect the gene against degradation." When combined with a gene vector, the result is a nanopharmaceutical agent known as EGEN-001. EGEN-001 delivers the IL-12 gene to the site of action in the cancer cell's nucleus, where it initiates the production of the needed IL-12 protein.

COMPETITION AND TESTING

Anwer and his team are not the only ones working on this approach. "There are several companies that specialize in delivery systems," he says. The difference is that EGEN-001 uses polymers, which Anwer says are safer compared to the viruses and lipids used as membrane-permeating agents in competing delivery systems. "EGEN-001 is also more efficient," he adds, "because it has both stabilizing and membrane-permeating agents." As a result of this increased efficiency, the drug is now slowly working its way through the phases of FDA approval.

"The first phase, which began at the end of 2005, was to demonstrate that the drug was safe," says Anwer. By that time, he already knew from experiments conducted on animals that the drug did in fact kill tumors. The concern, however, was whether or not it was safe for humans, and if so, in what dosage. "Based on those animal experiments, we took the toxic dose and divided it by five to 10," he says, which is standard in such studies. "That gave us the starting dose for humans." Their patients for Phase I consisted solely of end-stage ovarian cancer patients with six to eight months to live. "When we gave our drugs in various doses to those patients," Anwer says, "many lived for two to three years." Moreover, he adds, "we found the higher dosage was more effective, so we escalated the doses in Phase I to see the toxicity." The result? "There were no toxic effects." The IL-12 protein was staying in the cancer site and fighting the tumor



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Dr. Anwer with a phase contrast microscope looking at the effect of Egen's cancer drug on the growth of cancer cells.

as intended, with only mild, short-term side effects.

The next step was to make sure that the drug didn't interact when given in conjunction with traditional chemotherapy drugs. "Normally one drug isn't enough to treat cancer, so they're often combined," says Anwer. "So after looking at the drug by itself, we then tested it in combination with chemotherapy." Again, he says, that study showed it didn't add to the adverse effects of chemotherapy. By this time, Anwer's success had attracted the attention of the National Cancer Institute, which is now governing the study, and the Cancer Treatment Centers of America (CTCA), which was interested in expanding the approach to treat colon, pancreatic and liver cancers. As a result, the CTCA agreed to provide additional end-stage patients as Anwer and his team moved into Phase II.

"We've been in Phase II for about a year now," says Anwer. "We identified the highest dose in Phase I and now we're looking into a larger number of patients." Currently they have 17, but they are hoping to enroll 60. As for those 17, Anwer says that although it's too early to say anything about the drug's long-term success, some have lived longer than expected. That bodes well for the drug moving to a Phase III study. But while Anwer and his team have facilities in-house to do in vitro and in vivo testing, the company won't be able to do the Phase III studies itself because that will be a multinational endeavor involving thousands of patients.

What he is hoping instead is to gain the interest of a big pharmaceutical company. "They can either purchase the whole drug up front or they can make milestone payments as the drug moves along," says Anwer. "And if it gets into the market, we can then receive royalties." Not just any big pharmaceutical company will do, however. "It has to be the right match, and they have to have an interest in ovarian cancer, or otherwise they might undervalue the drug." The goal is to find a partner by the end of 2013, by which time Anwer says EGEN intends to have the Phase II studies close to completion.

As EGEN looks for a partner, Anwer and his team are continuing to work in the field of cancer treatments, but this time on a very different type of therapy. Whereas TheraPlas is designed to deliver IL-12 genes to a cancer site to produce IL-12 protein, another product called TheraSilence works by inhibiting or destroying a gene's ability to make proteins. "Basically we want to deliver a decoy that can shut down, or silence, a particular gene," says Anwer, "and that has huge applications not only with regard to cancer, but also to cardiovascular disease." ■