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UAB to lead pioneering cancer trial

Ovarian cancer patients in the study to be treated with tumor-killing virus

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After five years of work and \$2.5 million in funding, UAB researchers are about to inject critically ill ovarian cancer patients with a barrier-breaking experimental treatment, a replicating virus designed to seek and destroy tumor cells.

It will be the first human therapy using a virus intentionally made more infectious so it can penetrate cancer's stubborn defenses, said Dr. David T. Curiel, director of the Division of Human Gene Therapy at the University of Alabama at Birmingham.

"That's taking a big biological leap," Curiel said.

The Food and Drug Administration, National Institutes of Health and UAB's Institutional Review Board have all signed off on the first human trial, which is expected to start in May, Curiel said.

The trial will be led by Dr. Ronald D. Alvarez, director of the UAB Division of Gynecologic Oncology, and will involve seven groups of as many as six women who have recurrent ovarian cancer and are not responding well to usual treatments. The treatment will be injected into the women's abdomens, starting with a small amount, and the dose will be increased as each group is observed for side effects.

If all goes well, Alvarez estimated, a treatment based on the virus could be widely available in as few as five years. "There's still lots of work to be done, but this would be a giant step in the right direction," Alvarez said.

The Phase 1 trial will focus on ensuring that the virus - an adenovirus known as Delta-24-RGD - is safe for patients. Normally, Phase 1 safety trials don't cause much excitement, but Curiel said this one is important for a number of reasons:

It will break a scientific barrier, and researchers hope it opens the door to a new class of cancer treatments - viruses genetically designed to ignore healthy cells and penetrate tumor cells to destroy them. Given the nature of the replicating virus being used, there is a possibility patients could experience some improvement even though the trial is focusing on toxicity.

The new treatment is the product of an unusual collaboration with medical powerhouse M.D. Anderson Cancer Center at the University of Texas, and UAB is leading the way with the first human trial.

Researchers have taken extraordinary steps to ensure the safety of this viral therapy. Like gene therapists nationwide, they are still working in the shadow of Jesse Gelsinger's death in 1999. Gelsinger, 18, died after being injected with a genetically altered adenovirus at the University of Pennsylvania.

Cancer collaboration:

The adenovirus that provides the foundation for the new treatment was created by scientists at M.D. Anderson led by Dr. Juan Feuyo. In its natural form, an adenovirus causes common colds, but Feuyo's team transformed it into a conditionally replicative adenovirus - commonly called a CRA.

In other words, it was designed to home in on cells in gliomas, or brain tumors, and then kill the cells while reproducing to kill still more cancer cells. But the treatment needed improvement.

Typically viruses work by latching onto receptors in cells and then penetrating them. Once inside, they hijack the cell's DNA, use it to reproduce and eventually kill the cell. But researchers at UAB led by Yancey Gillespie found that receptors on cancer cells have a deficiency that keeps viruses from latching onto them.

M.D. Anderson researchers needed a way to circumvent that defense, and UAB's Gene Therapy Center had scientists on staff with vast knowledge about the adenovirus. Two of those scientists, Igor Dimitriev and Victor Krasnykh, were recruited from Russia, where they worked on basic research that was applied to the former Soviet Union's germ warfare program. Ramon Alemany, who now heads a cancer gene therapy group in Barcelona, Spain, also worked with the adenovirus team at UAB.

The UAB researchers added a peptide, a molecule, to the virus that allowed it to bypass the usual receptor on the cancer cell and take an alternative route to penetrate it. Lab tests showed that the enhanced adenovirus infected cancer cells at an impressive rate.

"All we did was subtly modify the binding properties, but we dramatically improved its potency," Curiel said.

Safety issues:

As the project evolved, scientists became excited about the possibilities for Delta-24-RGD, but they also

were concerned about whether it was safe for patients.

"The fundamental biology of the virus is altered, and you're turning it loose in people," Curiel said.

Curiel and Alvarez began working closely with the FDA to find ways to ensure the safety of Delta-24-RGD. Federal officials have been particularly sensitive about gene therapy experiments since the highly publicized death of Gelsinger in Pennsylvania eight years ago.

So UAB called upon Southern Research Institute and Auburn University School of Veterinary Medicine to bolster the effort.

Southern Research has long been known for its ability to test new drugs for toxicity, and it has achieved a designation as one of two National Gene Vector Lab Toxicology Centers. So it was called upon to run specialized toxicology tests.

But the safety data was still incomplete because the human adenovirus does not replicate in mice, which are typically used to test drugs for toxicity before making the jump to humans, Curiel said.

To overcome that problem, scientists at UAB designed another virus based on the same scientific principals used to create Delta-24-RGD, but adapted for testing in dogs with cancer. Veterinarians at Auburn successfully performed those safety trials, and results are being prepared for publication, Curiel said.

Also, UAB tested the adenovirus in the lab with human liver tissue samples, Curiel said.

The FDA looked at the safety data and approved Delta-24-RGD for trial at UAB. NIH and UAB's safety committee, an institutional review board, have also approved the trials.

Meanwhile, M.D. Anderson also is working toward approval for trials of Delta-24-RGD in gliomas. UAB is about three months ahead of M.D. Anderson in the process, Curiel said.

"We started at the same time as M.D. Anderson, and with all of their power and all of their money, we got done far in advance of them," he said.

In addition, the Free University of Amsterdam in the Netherlands is planning trials of the adenovirus against gliomas at about the same time M.D. Anderson starts its trials, Curiel said.

Through the lengthy process, Curiel said, UAB received enthusiastic financial support from the NIH. It has been awarded \$2.5 million over the past five years through a variety of grants intended to speed critical research, and it recently gained another grant to field an imaging system to track Delta-24-RGD in the next human trial.

The new system will use a PET scanner to observe the action of Delta-24-RGD as it attacks cancer cells. The system was developed by a UAB team led by researcher Long Le, who came to this country as a Vietnamese boat person. The researchers developed the system by attaching fluorescent and enzymatic proteins to the Delta-24-RGD, which makes the adenovirus show up as a glow under the scanner.

All in all, about 30 people at UAB have been involved in Delta-24-RGD research, Curiel said. Many experts didn't see much hope for the project five years ago when it started, but hard work and persistence changed that, Curiel said.

"Many in the field would have seen this as a non-starter, from a safety standpoint or conceptual standpoint," he said. "It's taken us forever to do this."

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