Partnering to Fight a Dangerous Cancer in Brain Fluid

With a grant from Global Lung Cancer Impact Challenge, University of Colorado experts will explore a way to treat leptomeningeal disease.

May 25, 2026 By University of Colorado Cancer Center and Mark Harden

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When cancer spreads to membranes and fluid surrounding the brain and spinal cord – a complication known as leptomeningeal disease – the outlook is grim. Patients typically survive only a few months, even with treatment.

People with leptomeningeal disease badly need better therapies. Yet they are seldom included in clinical trials of new treatments because of concerns about their limited survival potential and other factors, resulting in a lack of high-quality evidence to guide new therapies.

Now, two University of Colorado Anschutz Cancer Center members are joining forces to investigate a new way to treat leptomeningeal disease stemming from a form of lung cancer.

The collaborators are Tejas Patil, MD, assistant professor of medicine in the CU Anschutz Division of Medical Oncology and a thoracic oncology specialist; and Peter Fecci, MD, PhD, who joined CU Anschutz last year as chair of the Department of Neurosurgery and whose research focus is solid tumor immunology, most typically as it applies in brain tumors.

Their project is backed by a two-year, $400,000 grant from the Global Lung Cancer Impact Challenge, a philanthropic initiative supporting research into both lung cancer and leptomeningeal disease.

Their goal is to develop an effective cellular therapy for leptomeningeal disease – therapies involving CAR T-cell technology, a form of personalized immunotherapy that harnesses a patient's own T cells, a key part of the body's immune system, to fight cancer.

"One of the key metrics for this grant is to try to address an unmet need, and to support a high-risk, high-reward approach to come up with a novel therapy," says Patil. "I'm very excited to be working with Dr. Fecci and his team to deliver on this."

"Even though our group's research usually focuses on brain tumors, we've stumbled upon a platform that may also be especially effective in certain lung cancers," Fecci says. "Fortunately,

this may also include leptomeningeal disease, which is a tremendous problem with few therapeutic options. Partnering with Dr. Patil is a fantastic opportunity to spark the type of cross-pollination and collaboration between disciplines that sometimes can really drive advances."

Engineering T cells

Leptomeningeal disease – also known as leptomeningeal carcinomatosis – can be caused by most solid tumors, but it most often originates with metastatic breast cancer, lung cancer, and melanoma. It affects 5% to 10% of solid tumor patients.

Leptomeningeal disease occurs when cancer spreads from its original site to the cerebrospinal fluid and the leptomeninges layers that surround the brain. The cancer typically spreads through the bloodstream or travels along nerves, or it invades directly from a tumor in the brain or spine.

Patil and Fecci's project seeks ways to target leptomeningeal disease in patients with non-small-cell lung cancer, the most common type of lung cancer.

In CAR T-cell therapy, T cells are extracted from a patient's own body, and then they are given a synthetic receptor that attaches to specific proteins on the surface of cancer cells, becoming chimeric antigen receptor (CAR) T cells. They are then infused back into the patient so they can attach themselves to cancer cells and kill them.

Unlike cancer drugs that have to be administered repeatedly, CAR T cells can expand and persist in the body for long periods, providing an ongoing immune shield against recurring cancer.

D2C7 and TIM4 BLT

Patil, Fecci, and their colleagues are exploring the use of CAR T cells engineered to target a protein that's produced in large amounts in cancers with epidermal growth factor receptor (EGFR) alterations – genetic changes that drive cancer growth – but not as much in healthy cells. A kind of CAR T cell called D2C7 will target EGFR only on cancer cells.

But a small percentage of cancer cells lack EGFR, so they can evade D2C7 treatment and grow back. So the Patil-Fecci team proposes to engineer D2C7 CAR T cells to secrete a molecule called TIM4 BLT that can grab hold of another molecule, phosphatidylserine, that leaks to the surface of cancer cells, especially after radiation treatment. The researchers see that as a potential way to make CAR T-cell therapy more effective against EGFR-negative cancer cells.

The forthcoming project will evaluate the safety and effectiveness of this approach to fighting leptomeningeal disease, using animal models. The study will evaluate whether the therapy works best if it's delivered into the brain, into the cerebrospinal fluid, or through the bloodstream, and it will also assess whether administering therapy before the CAR T-cell therapy makes treatment more effective. If successful, the project could lead to human clinical trials.

"It's a very technical, intensive project," Patil says. "We have very little data on whether this immunotherapy strategy would work in the cerebrospinal fluid. But the cool thing is we're looking

at a treatment modality for a population with a huge unmet need. I'm excited to get started on this."

The CRESTONE trial

The new project comes on the heels of an international clinical trial led by Patil, called CRESTONE, involving the use of an antibody drug called seribantumab to treat the rare occurrence of multiple cancer types driven by a genetic abnormality called an NRG1 fusion that causes uncontrolled cell growth. These fusions show up across many solid tumor types, most commonly lung cancer. Seribantumab blocks a protein called HER3 that gets stimulated by NRG1 fusions to help trigger tumor growth.

The phase II trial enrolled 54 patients at multiple sites in the United States and overseas. Most of them had advanced non-small cell lung cancer, with eight other tumor types represented.

Of the 54, 29 were evaluated to assess seribantumab's efficacy. In that group, 35% had their tumors shrink meaningfully through treatment with seribantumab, including two patients whose cancer disappeared completely, and another 44% had their tumors remain stable in size. These responses were seen across multiple cancer types and across many different NRG1 fusion variants. The drug also was generally well tolerated by the patients.

"These results support the antitumor activity and safety of seribantumab in patients with advanced solid tumors harboring NRG1 fusions," the study concluded.

Patil cautions that the trial was terminated early by the sponsor for business reasons, not due to poor results, so the sample size was smaller than planned. But he says the study "contributed evidence that targeting HER3 is a rational strategy to deal with NRG1 fusions."

The trial results were reported recently in the journal JCO Precision Oncology.

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