Early-career Investigator Aims to Transform Leukemia Treatment With a Novel Approach to CAR T-cell Therapy

Working with Gates Institute, Mathew Angelos is pioneering University of Colorado Anschutz's first entirely home-grown CAR T-cell trial.

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Mathew Angelos, MD, PhD, a new assistant professor of hematology at the University of Colorado School of Medicine, is part of a wave of promising early-career physician-investigators. With a focus on bringing cutting-edge treatments from the lab to the clinic, Angelos is exploring the potential of CAR T-cell therapy to revolutionize the treatment of acute myeloid leukemia (AML) and other hematologic cancers. His ongoing research using CD64 as a target in CAR T-cell therapy is a novel and promising approach that stands to make a meaningful impact in leukemia treatment. In a recent interview, he shared his journey into hematology/oncology, the promise of CAR T-cell therapy, and his ambitions for translational research as a CU Cancer Center member and Gates Institute member investigator developing a trial at CU Anschutz.

Angelos' passion for hematology and oncology began during his post-baccalaureate research program at the National Cancer Institute. His mentor, a physician-scientist, inspired him by seamlessly integrating laboratory findings into early-phase clinical trials. This experience sparked Angelos' interest in the intersection of science and patient care, setting him on the path toward a dual MD/PhD degree at the University of Minnesota. During his PhD, Angelos focused on hematopoietic stem cells, becoming increasingly intrigued by gene therapy's potential to treat blood cancers. His fascination grew further during his residency and fellowship at the University of Pennsylvania, where the burgeoning field of cellular therapies solidified his interest in leukemia research. He found the rapid progression of leukemia cases to be both a challenge and an opportunity for innovative therapies, like CAR T cells, to make a significant impact.

Pioneering a New Approach to AML Treatment

CAR T-cell therapy, a breakthrough treatment in blood cancers such as B-cell lymphomas and acute lymphoblastic leukemia (ALL), has garnered attention for its ability to induce deep remissions in patients who had previously exhausted other treatment options. However, Angelos

notes that translating this success to AML has proven difficult.

“Unlike other blood cancers, AML presents unique challenges for CAR T-cell therapy,” he explains. “The biggest issue is finding a suitable leukemia target that doesn’t cause toxicity to normal blood cells and other organ systems. We’ve experimented with markers like CD33 and CD123, but both led to bone marrow suppression and other toxic effects without reliably eradicating AML.”

Angelos’ research focuses on overcoming these challenges by developing rationally designed CAR T-cell therapies that are tailored to each patient’s unique AML biology. The goal is to then use CAR T cells at “the right place and the right time” to offer a more comprehensive and durable remission for AML patients.

Preparing for First-in-Human Trials

As Angelos prepares to move this research from the lab into the clinic, there are several key considerations. One of the most critical factors is selecting the right patients for the initial trials.

“We’ve seen in other CAR T-cell trials for AML that patients with very high disease burdens may not respond as well and are at higher risk for severe side effects, like cytokine release syndrome,” Angelos notes. “Learning from these earlier trials, we’re aiming to treat patients who have persistent disease after standard therapy, the patients that we know have a high likelihood of frank relapse that happens in a span of weeks, and by using strategies to reduce leukemia burden before CAR T-cell infusion.”

The first phase of the phase 1 clinical trial, aimed at establishing CAR T-cell safety and optimal CAR T-cell dosing, is expected to begin in mid-2025. This will mark a significant milestone in the development of a therapy that could offer new hope to AML patients who have run out of other treatment options.

Advancing Cancer Care Through Teamwork and Translational Research

Throughout his career, Angelos has been passionate about bridging the gap between bench research and bedside care. He believes that the key to success as a physician-scientist lies in collaboration.

“I’ve realized that being a principal investigator means being part of a larger, collaborative team that allows me to play a vital role in bringing research directly into clinical practice,” he explains.

Angelos attributes these opportunities to collaborative colleagues and predecessors who make his research possible, including Craig Jordan, PhD, a leukemia expert at CU Anschutz. Jordan and his laboratory identified CD64, a marker robustly expressed on leukemic stem cells in AML patients who had relapsed after standard treatment. This discovery laid the foundation for Eric Kohler, MD, PhD, in the Pediatric Bone Marrow Transplant Division at Children’s Hospital Colorado, and Haley

Simpson, MD, PhD, to engineer and validate a highly active CAR T-cell therapy that targets CD64 in both in vitro and in vivo models. The results so far have been extremely promising, with the CD64-specific CAR T cells inducing prolonged remissions in mice using aggressive AML models.

Transforming Leukemia Treatment Using Novel Molecular Target in Entirely Home-Grown CAR T-cell Trial at CU Anschutz

“Drs. Kohler’s and Simpson’s preclinical work has really laid the foundation to bring this to CAR T cell product to the clinic,” Angelos says. “This will be a first-in-human study, and it’s incredibly exciting. There isn’t even a pharmaceutical drug targeting CD64 right now, so this is truly novel work. We’re creating something from scratch here in Colorado that could fundamentally change how we treat myeloid diseases.”

As Angelos embarks on his new role at CU Anschutz, he’s excited about the opportunities to continue pushing the boundaries of cancer treatment through research. He’s eager to integrate his work on cellular and other immunotherapies into the clinic and hopes to inspire the next generation of physician-scientists along the way.

“Through CU Anschutz and the Gates Institute, I’ve found a community that’s dedicated to translational science, and I’m excited to be part of these efforts,” he says. “I was impressed by the comprehensive resources available at the Gates Institute to facilitate the regulatory and biomanufacturing processes needed to realize our research goals. This really is a rare find and establishes CU Anschutz as a leader among academic medical centers in the cellular therapies field.”

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