Long-sought genetic model of common infant leukemia described

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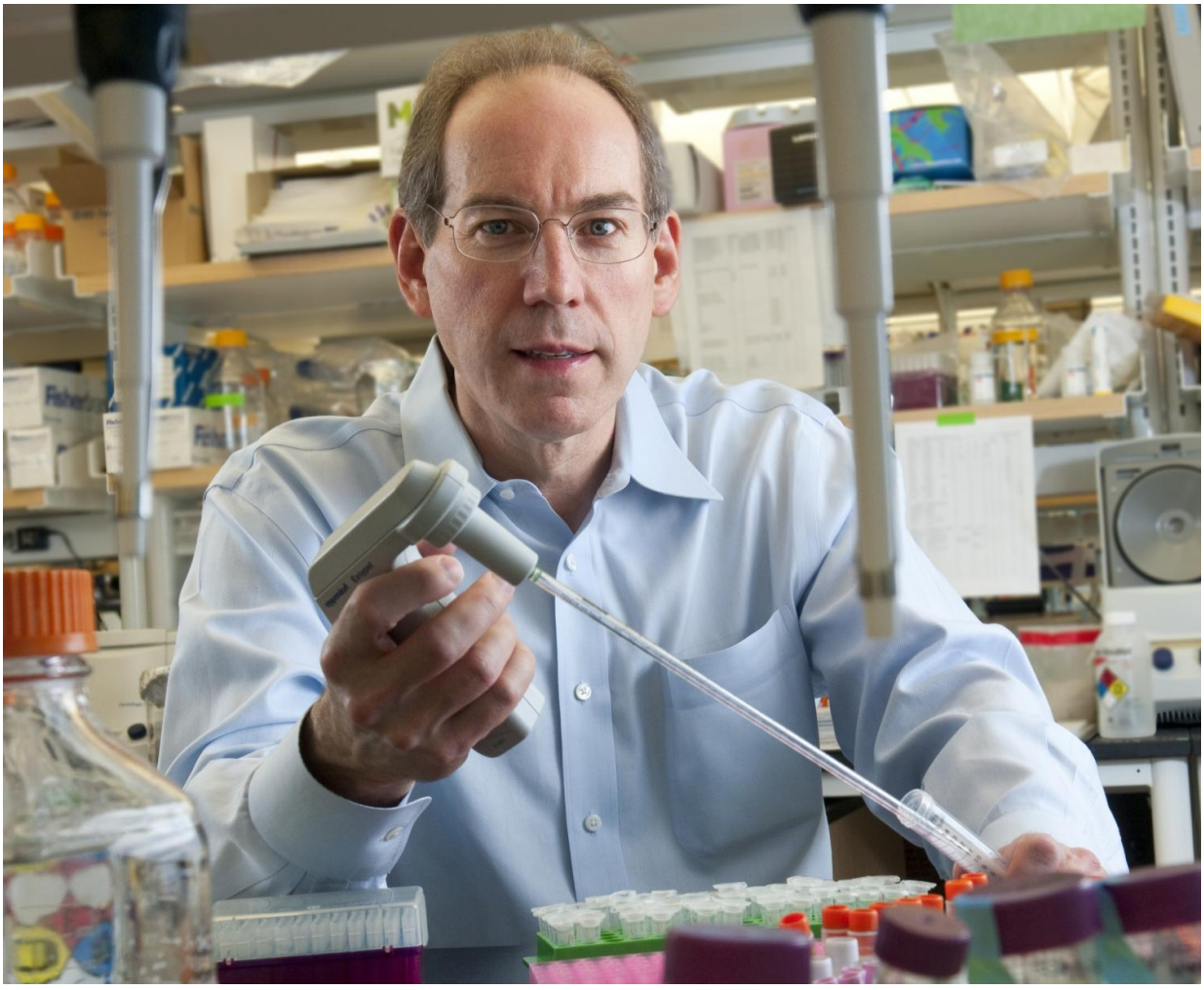

Michael Thirman, MD, Associate Professor of Medicine at the University of Chicago, in his laboratory. Credit: The University of Chicago Medicine

After nearly two decades of unsuccessful attempts, researchers from the University of Chicago Medicine and the Cincinnati Children's Hospital Medical Center have created the first mouse model for the most common form of infant leukemia. Their discovery, published in the Nov. 14, 2016, issue of *Cancer Cell*, could hasten development and testing of new drug therapies.

Pro-B acute lymphoblastic leukemia (ALL) with the (4;11) translocation is responsible for about 70 percent of infant and 10 percent of both childhood and adult acute lymphoblastic leukemias. The new mouse model replicates the human genetic flaw that causes this disease, making it much easier to study.

This subtype of leukemia results from a genetic fusion t(4;11), known as a translocation. This combines parts of two separate genes. One of those genes, MLL (short for mixed-lineage leukemia), comes from chromosome 11. The other fragment, AF4 (short for ALL fused gene) from chromosome 4. The hybrid MLL-AF4 gene results in leukemia.

Children and adults with this disease produce vast numbers of dysfunctional blood cells, which eventually crowd out functional cells. MLL-AF4 leukemia has a dismal prognosis, among the worst of any subset of acute leukemia.

"For 20 years, scientists have repeatedly tried and consistently failed to make a model of MLL-AF4 Pro-B acute lymphoblastic leukemia," said Michael Thirman, MD, Associate Professor of Medicine at the University of Chicago. "Even though we understood the basic genetic flaw, no one had been able create a mouse model that mimicked the human disease, which is crucial for evaluating potential therapies."

That frustrated many researchers, who shifted their focus to test alternative hypotheses on the causes of this leukemia or refocused their

laboratories to study different aspects of this disease.

Thirman's team, including longtime colleague Roger Luo, PhD, began working on this problem "years ago," he said, and stayed with it. They quickly identified two hurdles.

The first was a problem with the retrovirus that scientists used to insert the leukemia-causing gene into mouse cells. That gene, acquired from leukemia patients, consisted of a human gene fragment from MLL linked to the human fragment from AF4.

"We soon discovered that the virus wasn't working," Thirman explained. "We knew that certain parts of human DNA can decrease viral titers. So we switched from the human version of AF4 to the mouse version, Af4, which is slightly different. This increased viral titers 30 fold."

That worked, but it led to hurdle two. The mice injected with virus transporting MLL-Af4 developed leukemia, but it was the wrong kind. They developed acute myeloid instead of acute lymphoblastic leukemia. "Despite the use of lymphoid conditions," the study authors wrote, "no lymphoid leukemia was observed."

Next, they collaborated with James Mulloy, PhD, at Cincinnati Children's Hospital Medical Center, whose graduate student Shan Lin inserted the fused MLL-Af4 gene into human CD34 cells, derived from cord or peripheral blood from volunteer donors. They transferred those cells to mice with immune systems that permit the growth of human cells . This time, the mice developed Pro-B ALL, identical to the leukemia found in humans.

"The model worked perfectly," Thirman said. Within 22 weeks, all of the mice developed exactly the same type of leukemia as observed in patients.

Expression of MLL-Af4 in human cells "recapitulates the pro-B ALL observed in patient with t(4:11) as shown by immunophenotype, chromatin targeting of the fusion, nuclear complex formation, and gene expression signatures," the authors wrote. "It mimics the disease found in humans both phenotypically and molecularly."

"The differences in the type of leukemia that developed using mouse versus human cells were striking," said Mulloy. "Researchers need to consider these differences carefully when choosing which model to use to mimic human disease. The available evidence now indicates that the approaches are not equivalent."

They conclude that "our MLL-Af4 model will be a valuable tool to study this most prevalent MLL-fusion leukemia with such a poor prognosis."

However, there is more work to be done. "MLL fusion disease is not a single genetic entity," the authors note. "Each has its own genetic and biological features associated with particular fusion partners." This highlights the need for "more models specific to each fusion. Our MLL-Af4 model will be a valuable tool."

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