Discovery pinpoints cause of two types of leukemia, providing insights into new treatment approach

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(Medical Xpress)—Patients with two forms of leukemia, who currently have no viable treatment options, may benefit from existing drugs developed for different types of cancer, according to a study conducted by researchers at the Knight Cancer Institute at Oregon Health & Science University (OHSU).

The study, published in the May 9 edition of the *New England Journal of Medicine*, isolated the molecular mutation that causes chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML) in some patients. That mutation, occurring in a gene called colony stimulating factor 3 receptor (CSF3R), initiates a chain reaction involving other gene families known as SRC, JAK, and TNK2, which subsequently drives these diseases.

This discovery is promising for patients as it will aid in diagnosing these cancers, which are currently difficult for physicians to distinguish from other leukemias. More importantly, the study results suggest that these patients could be helped by existing FDA-approved drugs designed to inhibit the chain reactions impacting JAK and SRC/TNK2, though clinical trials are needed.

"Our ability to rapidly pinpoint a new cancer-driving mutation demonstrates the power of integrating improved genome sequencing technology. It will accelerate our ability to tailor treatments to

individuals and each research victory gives us more insight into the nature of this complex disease," said Jeffrey W. Tyner, Ph.D., an assistant professor with the OHSU Knight Cancer Institute and Cell & Developmental Biology Department, whose lab led the research. "What distinguished this research was our method for matching voluminous amounts of gene sequencing data with drug sensitivity data to quickly deduce which mutations were relevant in causing disease and this allows us to make a difference for patients who don't currently have good therapeutic options."

Tyner and the other researchers who conducted this study used a combination of tests not yet commonly deployed together for research on primary specimens collected from cancer patients. They performed gene sequencing on specimens from 27 patients, creating a profile of the possible genetic causes of these diseases. This enabled them to highlight the important mutations that were common among CNL and aCML patients. As they gathered information on potentially relevant mutations, they simultaneously tested how fresh samples of patients' cancer cells responded to different drugs. This enabled the scientists to link drug efficacy to CSF3R gene mutations.

The two-pronged study approach provided researchers with the ability to quickly home in on and verify a root cause of these rare forms of leukemia. Of the 27 patients in the study, 16, or about 59 percent, had the CSF3R mutation.

"This approach allows us to rapidly discover mutations that are fundamental to cancer growth and identify drugs that might be used to combat them," said Julia Maxson, Ph.D., of the OHSU Knight Cancer Institute, who was first author on the study. "Our findings are not only promising for the treatment of patients with CNL and aCML but also validate our approach to identify new drug targets in cancer."

In fact, during the study period, a CNL patient was treated with the FDA-approved drug ruxolitinib, which inhibits the cancer cell growth initiated by the CSF3R mutation. This treatment resulted in a dramatic improvement in the patient's condition.

CNL and aCML impact several hundred patients in the United States each year. Patients afflicted with these conditions typically live only two to three years. These forms of cancer have also been difficult to diagnose because there wasn't enough known about their genetic drivers. Knowing that they are defined by mutations in CSF3R provides physicians with a means to confirm a diagnosis. Tests for this mutation are already available; the OHSU Knight Diagnostic Laboratories' GeneTrails panel for leukemias has the capability to check for this mutation.

In an editorial that accompanies the study in the *New England Journal of Medicine*, Jerald Radich, M.D., of the Fred Hutchinson Cancer Research Center in Seattle, wrote that the approach is "an example of what genetically informed treatment may look like in the near future." Radich continued: "This is how we will beat cancer, one gene, one disease at a time."

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