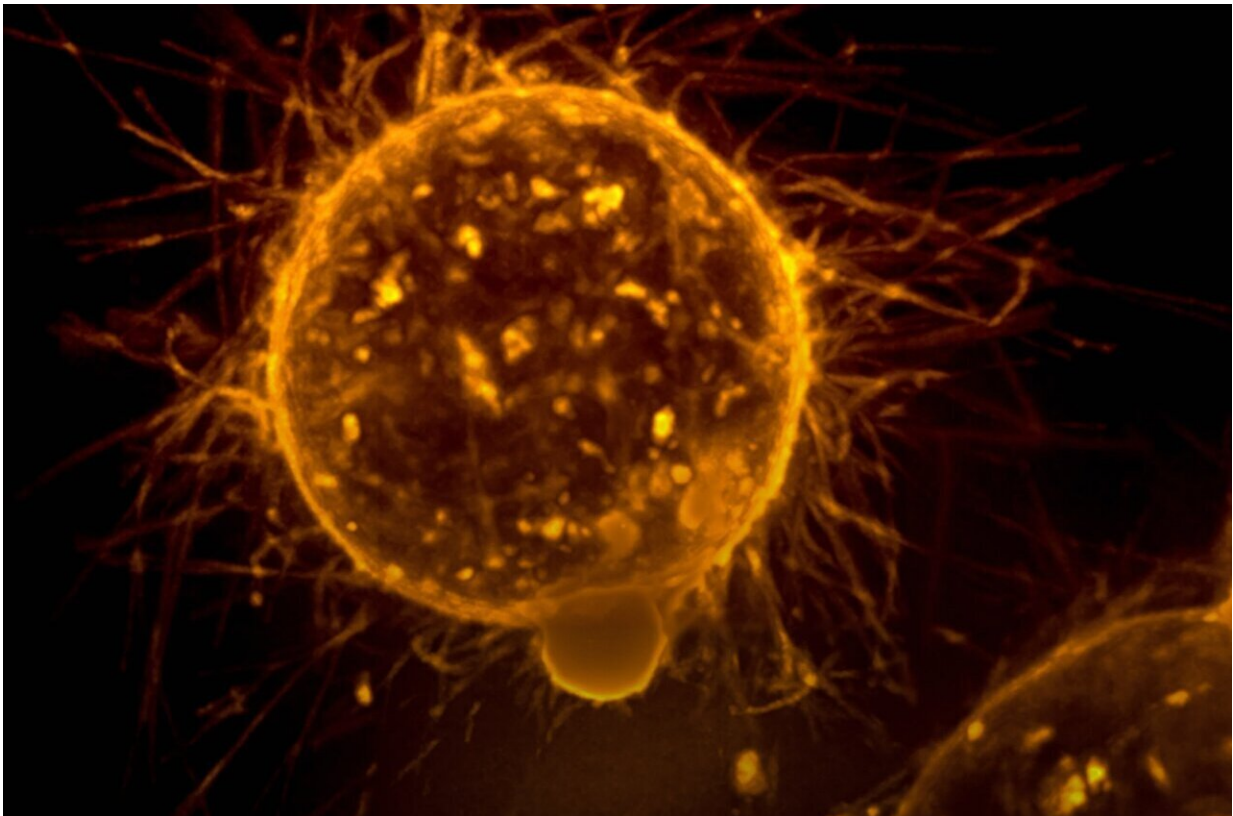


New hope for treatment of infant cancer that has puzzled researchers for decades

March 14 2022



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New research has begun to unravel the mystery of why a particular form of leukemia in infants has defied efforts to improve outcomes, despite significant improvements in treating older children. Scientists from the

Wellcome Sanger Institute, Great Ormond Street Hospital, Newcastle University and their collaborators found subtle differences in the cell type that causes B acute lymphoblastic leukemia (B-ALL) that may help to explain why some cases are more severe than others.

The study, published today in *Nature Medicine*, focused on the majority of infant B-ALL cases caused by changes to the KMT2A gene. The findings provide a number of promising drug targets, raising hopes that effective treatments for infant B-ALL may be developed in the future.

Acute lymphoblastic leukemia (ALL) can take various forms, depending on the cell type involved. These cancers occur when [cells](#) malfunction as they develop from [hematopoietic stem cells](#) to mature [blood cells](#). In the case of B-ALL, disease arises from a type of immune cell called B lymphocytes, more commonly known as B cells.

B-ALL in children was once a universally fatal disease that is now curable in the majority of cases. An exception is B-ALL in children below one year of age, where [treatment](#) is successful in less than 50 percent of cases, with no significant improvement in the last two decades. Treatments that are proven in tackling other forms of leukemia, such as [bone marrow transplants](#), have proved ineffective against infant B-ALL. It is currently treated with strong chemotherapy, which can be hard for the patient to endure even if they are cured.

In this paper, researchers set out to study KMT2A-rearranged infant B-ALL by comparing [cancer cells](#) to normal human blood cells. Gene expression data from 1,665 childhood leukemia cases was referenced against single-cell mRNA data from around 60,000 normal fetal bone marrow cells.

Analysis found that infant B-ALL exhibited distinct cellular signals with a notable contribution from early lymphocyte precursors (ELPs), an

immature immune cell type that normally develops into B cells.

Dr. Laura Jardine, a first author of the study from Newcastle University, said: "Leukaemias are usually classified by the cell type involved, and in the case of B [acute lymphoblastic leukemia](#) (B-ALL) we talk about B cell progenitors. But our analysis of this disease has shown that this is actually an early lymphocyte precursor leukemia".

As well as being able to distinguish ELP cells from other types of B cell, the researchers found that the closer an ELP cell was to becoming a mature B cell, the better the outcome for the patient.

Dr. Jack Bartram, a senior author of the study from Great Ormond Street Hospital, said: "As part of this study, we think that we have unpicked why B acute lymphoblastic leukemia (B-ALL) is more responsive to treatment in some children, but why it's not so successful for infants. Cancers with more 'mature' early lymphocyte precursors (ELPs) have characteristics that seem to respond better to treatment. These more mature cells are more common in B-ALL in older children but sadly not for our younger patients, meaning the treatment is less effective. The challenge now is to develop our understanding and confirm these suspicions so that we can improve treatments for all patients."

To further investigate the molecular landscape of KMT2A-rearranged infant B-ALL, researchers compared gene expression profiles of the cancer to that of normal ELP cells. Unlike normal ELP cells, those involved in cancer had molecular features of different cell types, suggesting a malfunction in the normal process of differentiation. Multiple biological pathways and markers were identified in these hybrid ELP cells that could make promising targets for new therapies.

Dr. Sam Behjati, a senior author of the study from the Wellcome Sanger

Institute, said: "Though it is too early to draw definitive conclusions about why B acute lymphoblastic [leukemia](#) (B-ALL) has much poorer outcomes in infants than in [older children](#), this study offers compelling evidence that the maturity of the cells involved is a key factor. As well as generating new drug targets, these data will allow us to observe how the 'cell type' of certain cancers corresponds to patient outcomes, allowing us to better assess disease severity and determine the best course of treatment."

More information: Simon Bomken, Single-cell transcriptomics reveals a distinct developmental state of KMT2A-rearranged infant B-cell acute lymphoblastic leukemia, *Nature Medicine* (2022). [DOI: 10.1038/s41591-022-01720-7](#).
www.nature.com/articles/s41591-022-01720-7

Provided by Wellcome Trust Sanger Institute

Citation: New hope for treatment of infant cancer that has puzzled researchers for decades (2022, March 14) retrieved 30 January 2024 from <https://medicalxpress.com/news/2022-03-treatment-infant-cancer-puzzled-decades.html>

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