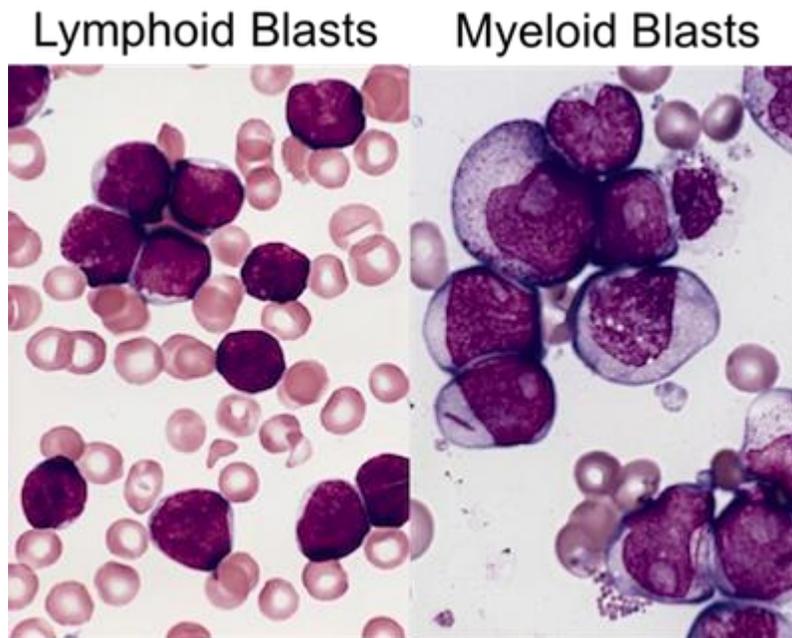


Unique cancer arising after anti-CD19 CAR-T cell therapy

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Representative micrographs demonstrate the phenotypic difference between lymphoid and myeloid cancer cells. After anti-CD19 CAR-T cell therapy all patients achieved remission of B-cell ALL; however, in two cases patients relapsed with myeloid malignancies.

Immunotherapy represents a new wave of cancer therapies that are just entering clinics or currently in trial. This approach to cancer treatment re-trains a patient's immune system to recognize and destroy tumor cells. While this can be achieved in multiple ways, chimeric antigen receptor (CAR)-T cell therapy has recently demonstrated high success for B cell malignancies. In this approach, patient T cells are harvested and genetically modified to recognize and destroy any cell expressing CD19. CD19 is expressed on B cells, both healthy and cancer alike. While healthy B cells are collateral damage, this therapy ablates cancer cells. Trials using this approach have been over 90% effective at achieving stable remission in patients suffering from B cell malignancies who failed to respond to any conventional therapy. Scientists in the Clinical Research Division at Fred Hutch have been on the forefront of CAR-T cell therapy – from pre-clinical development through the current patient trials. In any clinical trial non-responding or resistant patients emerge; however, Dr. Cameron Turtle and colleagues in the Riddell lab report in their recent publication in *Blood*, on an exceedingly unique pair of cases that did not achieve sustained remission. Two patients enrolled in the anti-CD19 CAR-T cell trial were cured of B cell ALL, however, immediately following remission they acquired an AML-like cancer.

No single drug will work in every patient. When it comes to cancer each tumor has its own molecular background, moreover a patient's unique biochemistry may further alter a therapy's effectiveness. Thus when a therapy is effective in some patients but not others it is important to understand what was different between these two groups. In a [pair of very successful clinical trials](#) for anti-CD19 CAR-T cell therapy 27 out of 29 patients reached a sustained remission, yet to continue improving cancer treatment these researchers are working to understand why two patients did not achieve that remission. It is difficult to draw conclusions from only two patients; however, there were a number of striking similarities in these cases. Due to the mechanism of the therapy, only patients with B cell specific leukemia were enrolled in the trials, yet not all B cell leukemia have the same underlying molecular lesions. The cancers in seven patients on the trials contained the MLL rearrangement. The mixed lineage leukemia (MLL) gene encodes a histone methyltransferase that is important for hematopoietic development. In some instances a large chromosomal rearrangement near the MLL gene deregulates its activity. All seven of the MLL rearranged cases achieved remission, however, two of this group quickly relapsed, but seemingly with a new cancer. As hematopoietic stem cells differentiate they split into two major classes, lymphoid and myeloid. This is the difference between lymphoid (CLL/ALL) and myeloid leukemia (AML/CML), they arise from the partially differentiated cell lineages. In both cases of remission the patients were initially diagnosed with ALL, based on both microscopic pathology and cell type specific protein expression. Upon relapse the cancer cells were no longer expressing the CD19 marker targeted by the CAR-T cells, but also expressed markers consistent with a myeloid cancer (CD56, CD13, and CD64).

This result begs the question, how did this different cancer type arise? With only two cases it is difficult to say, but the authors present two possible mechanisms. The first hypothesis is that a lymphoid cancer cell was able to reprogram itself into the myeloid type. In fully differentiated normal cells this sort of re-differentiation does not happen, but leukemic cells adopt an immature phenotype somewhere between stem cells and fully differentiated ones, thus such a transition may be possible. In fact, there have been rare reports of such a switch after intensive chemotherapy. One of the cases in this study supports such a model. Researchers analyzed the genetic mutations in the ALL and AML-like cells, both contained the MLL rearrangement and mutation within another oncogene, IGH. These shared features suggest they arose from a common cell, consistent with type switching. Another hypothesis is that while the ALL cells dominated the patients blood, rare myeloid cells existed but at lower proliferation rates. After anti-CD19 therapy removed the ALL cells this allowed the outgrowth of the rare AML-like population. This hypothesis was supported by the second case; in that patient both lymphoid and myeloid cells contained the MLL rearrangement, yet differed in the mutational status of IGH.

While it is difficult to draw many conclusions from these early findings, these researchers suggest that patients with MLL-B-ALL may need closer observation and study during CAR-T cell therapy.

[Gardner R, Wu D, Cherian S, Fang M, Hanafi LA, Finney O, Smithers H, Jensen MC, Riddell SR, Maloney DG, Turtle CJ.](#) (2016). Acquisition of a CD19 negative myeloid phenotype allows immune escape of MLL-rearranged B-ALL from CD19 CAR-T cell therapy. *Blood*. 124(20):2406-10.

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