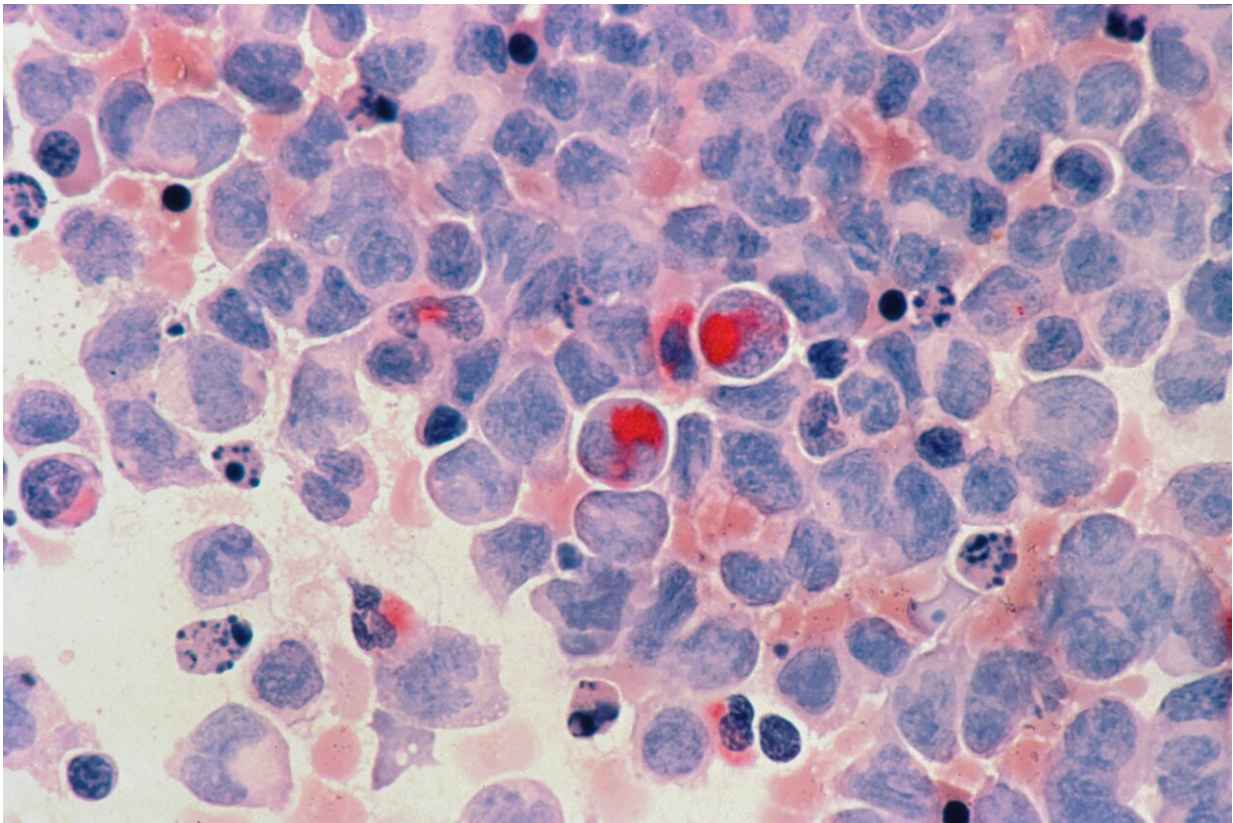


Targeting RAS proteins may prevent relapse in acute myeloid leukemia

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Acute myelocytic leukemia (AML). Credit: Unsplash/CC0 Public Domain

Relapses in a common form of leukemia may be preventable following new research that has identified how the cancer develops resistance to first line treatments.

The research [published](#) in *iScience* by researchers from the University of Birmingham, the Institute of Cancer Research (ICR), Newcastle University, the Princess Maxima Center of Pediatric oncology and the University of Virginia identified changes in a mutated form of acute myeloid leukemia (AML) samples from patients who relapsed after receiving FLT3 inhibitor treatment.

The team found that the resistant cancer had up-regulated multiple other signaling pathways to overcome the drug's action, and that the genetic change was able to be replicated in lab tests.

These experiments revealed that by targeting RAS family proteins, using a small molecule inhibitor developed from a chemical library screen using the paratope of an inhibitory intracellular antibody by Terry Rabbitts' team at the Weatherall Institute of Molecular Medicine University of Oxford and the ICR, increased signaling no longer rescued the cells from cell death.

The team identified that the transcription factors AP-1 and RUNX1 were at the heart of mediating [drug resistance](#). The two factors cooperate and bind to their [target genes](#) together, but only in the presence of growth factor signaling. The drugs targeting FLT3 rewire the cell, resulting in the upregulation of other signaling pathway associated genes, which then restored AP-1 and RUNX1 binding.

Drugging RAS, which is a key component in multiple signaling pathways, prevented this restoration of RUNX1 binding, and therefore signaling from growth factors no longer rescued the [cancer cells](#) from death.

Professor Constanze Bonifer from the Institute of Cancer and Genomic Sciences at the University of Birmingham, who has just taken up a position at the University of Melbourne, and is one of the senior authors

of the paper said,

"The pharmaceutical industry had high hopes that drugs targeting aberrant growth factor receptors such as the FLT3-ITD would prevent people from relapse. However, cancer cells are smart, and rewire their growth control machinery to use other [growth factors](#) present in the body. Targeting RAS family members prevents the cancer from rewiring and using different signaling pathways to escape cell death."

Targeting RAS blocks rewiring

The [small molecule inhibitors](#) used to target RAS in this study were developed using intracellular antibody technology. This technology involves screening a large number of antibody fragments to identify those which bind to the target protein in cells and prevent their protein-protein interactions.

Small molecule inhibitors can be screened from chemical libraries that interact with the parts of the target protein where these antibody fragments bind (the paratope). Due to the unparalleled natural specificity of these antibody fragments, this technology (called Antibody derived or Abd technology) can be used to target difficult to drug proteins and identify new parts of the protein which can be targeted to prevent [protein-protein interactions](#).

Professor Terry Rabbitts from the Institute of Cancer Research who developed these drugs said, "The strength of the Antibody-derived technology approach is that intracellular antibodies can be selected to essentially any protein. In turn, their specific binding sites can be employed to select [chemical compounds](#) for drug discovery against hard to drug proteins.

"Mutant RAS was considered undruggable, but the Abd technology

facilitated the development of the RAS-binding compounds used in the current study of cancer cell re-wiring. And technology will allow development of a new generation of drugs to hard-to-drug and intrinsically disordered proteins."

AML with a FLT3-ITD mutation occurs in nearly 30% of all patients and is a highly aggressive disease with a poor prognosis. This genetic change causes the expression of a mutant growth factor receptor which is always active and therefore cancer cells expressing it grow uncontrollably. While inhibitors which specifically target the FLT3 protein are now in use in the clinic, patients treated with these inhibitors frequently relapse.

More information: Daniel J.L. Coleman et al, Pharmacological inhibition of RAS overcomes FLT3 inhibitor resistance in FLT3-ITD+ AML through AP-1 and RUNX1, *iScience* (2024). [DOI: 10.1016/j.isci.2024.109576](https://doi.org/10.1016/j.isci.2024.109576)

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