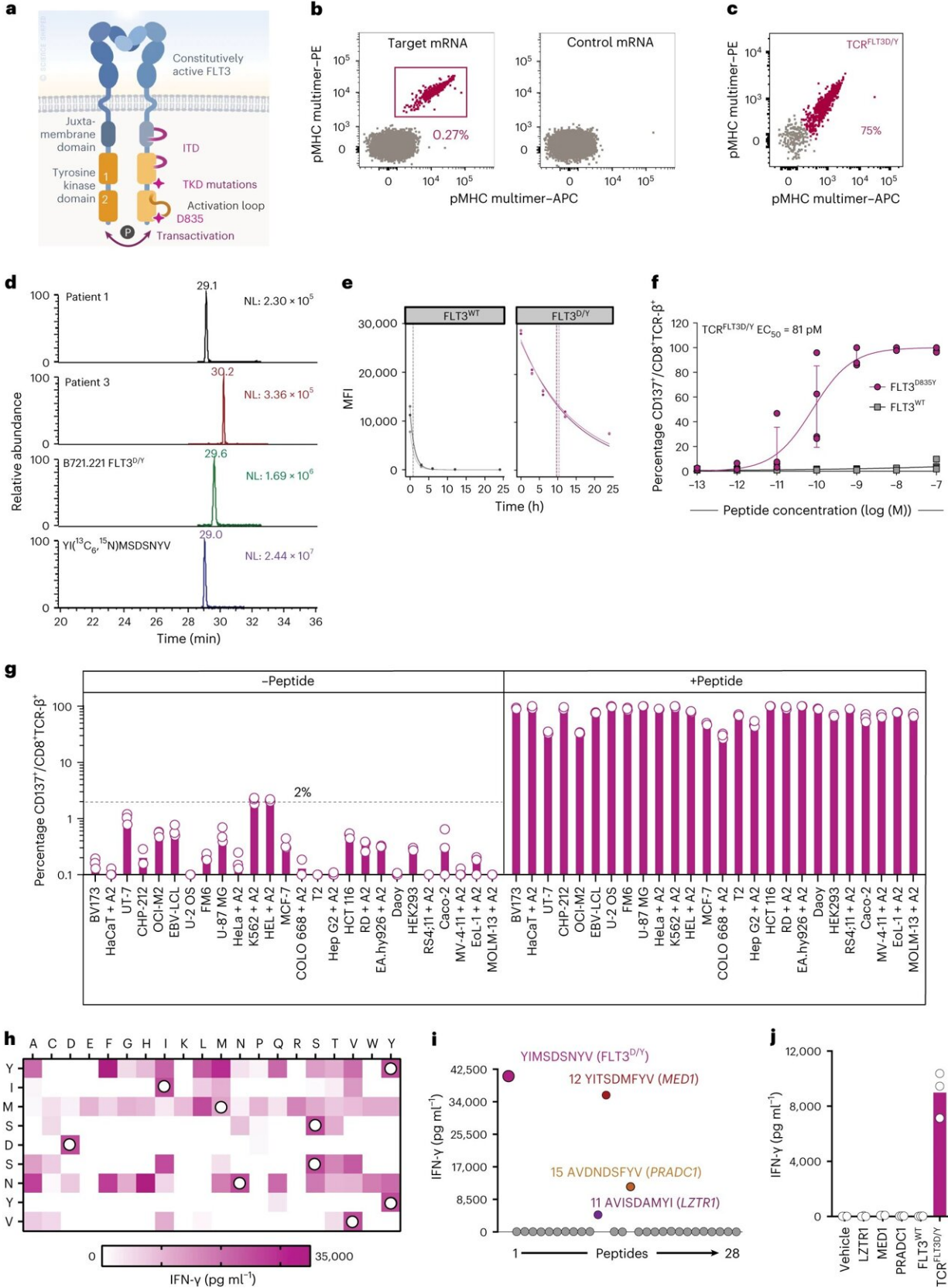


A possible new treatment for acute myeloid leukemia

October 2 2023



$\text{TCR}^{\text{FLT3D/Y}}$ cells specifically recognize mutated peptide with high sensitivity in an HLA-A2-restricted manner and do not show off-target reactivity. **a**, Schematic illustration of FLT3. TKD, tyrosine kinase domain. **b**, Naive CD8^+ T cells co-cultured with autologous HLA-A2⁺ mRNA-transfected moDCs stained with $\text{FLT3}^{\text{D/Y}}$ pMHC multimers. **c**, CD8^+ T cells transduced to express $\text{TCR}^{\text{FLT3D/Y}}$ stained with $\text{FLT3}^{\text{D/Y}}$ pMHC multimers (Gating strategy in Extended Data Fig. 3b). **d**, Parallel reaction-monitoring analysis, targeting the $\text{FLT3}^{\text{D835Y}}$ peptide ($m/z = 1,091.4389^{1+}$) in primary AML cells from two patient samples and the B721.221 cell line transduced to express $\text{FLT3}^{\text{D835Y}}$ and HLA-A2. NL = normalization level. **e**, Off-rates for FLT3^{WT} or $\text{FLT3}^{\text{D/Y}}$ peptide binding to HLA-A2 measured by flow cytometry. Vertical lines indicate calculated half-lives in each experiment. Dots represent mean fluorescence intensity (MFI) values of intact pMHC complexes on fluorescent particles at the indicated time points (h) (one replicate per experiment, $n = 3$ independent experiments). **f**, Activation of $\text{TCR}^{\text{FLT3D/Y}}$ cells (CD137^+) co-incubated with peptide-pulsed K562 cells. Data points are from $n = 4$ donors transduced to express TCR in $n = 3$ independent experiments, with each circle representing the mean of three technical replicates per donor, shown as mean \pm s.e.m. **g**, Activation of CD8^+ $\text{TCR}^{\text{FLT3D/Y}}$ cells co-incubated with HLA-A2⁺ cell lines with or without $\text{FLT3}^{\text{D/Y}}$ peptide. Results are from one experiment representative of $n = 4$ (BV173, CHP-212, EBV-LCL, K562, Daoy, RS4;11), $n = 3$ (HaCaT, U-2 OS, FM6, U-87 MG, HeLa, MV-4-11, EoL-1, MOLM-13) or, for the remaining cell lines, $n = 2$ independent experiments using different T cell donors; data points represent $n = 3$ technical replicates. The suffix + A2 denotes that cell lines were transduced with HLA-A*02:01, whereas remaining cell lines naturally express it. Connecting lines in **f** and bars in **g** show mean. The dashed line in **g** shows the highest level of activation by cell lines alone. **h–j**, IFN- γ produced by $\text{TCR}^{\text{FLT3D/Y}}$ cells co-incubated with K562 cells loaded with peptides from the mimotope library (**h**) or pulsed with the peptides that were predicted as potentially cross-reactive from the in silico search (**i**) or transfected with mRNA constructs encoding 30–32-mer peptides with the candidate cross-reactive peptide inducing reactivity (shown in **i**) in the middle, flanked by its naturally occurring sequence, or transfected with mRNA encoding the $\text{FLT3}^{\text{D/Y}}$ epitope or FLT3^{WT} (**j**). White circles in **h**, amino acids of the $\text{FLT3}^{\text{D/Y}}$ peptide. Positive reaction for IFN- γ , 5,000–35,000 pg ml⁻¹. LZTR1, leucine zipper-like post-translational regulator 1; MED1, mediator complex subunit 1; PRADC1, protease-associated domain-containing protein 1. Data in **h–j** are from one of n

= 2 independent experiments, and individual data points represent one (h,i) or three (j) technical replicates. Credit: *Nature Cancer* (2023). DOI: 10.1038/s43018-023-00642-8

New research has identified a novel immunotherapy for acute myeloid leukemia. The [study](#), published in *Nature Cancer*, describes a T-cell receptor that recognizes a mutation shared between a subgroup of patients with the disease. The results provide hope for new and effective treatment using T cells equipped with the therapeutic T cell receptor, "programmed" to kill the leukemia cells.

Acute myeloid leukemia (AML) is the most frequent form of leukemia in adults. The disease develops very rapidly, and has a very poor prognosis, with an average overall 5-year survival rate of 29% with standard therapy. Immunotherapy has led to significant advances in the treatment of several types of cancer in later years. However, there is currently no approved immunotherapy for AML except for [stem cell transplantation](#), which is a treatment with potentially life-threatening side effects.

The research group of Professor Johanna Olweus at the University of Oslo (UiO) and Oslo University Hospital (OUS), in collaboration with Professor Sten Eirik Jacobsen's and researcher Petter Woll's research groups at Karolinska Institutet (KI) in Stockholm, has now identified a possible target for the treatment of AML.

The researchers have provided important proof-of-concept that T-cell receptor (TCR) T cells targeted to mutations shared between patients, can be an attractive therapeutic option in AML. "This provides hope that we can develop a new and effective treatment for [acute myeloid leukemia](#), with likely relevance also for other cancer types," says

Professor Johanna Olweus.

Recent research has provided hope that immunotherapy can be targeted to mutations, as mutations are specific for cancer cells and are a necessary part of cancer development. However, the results have been discouraging so far.

"Almost all mutations are unique to the individual cancer tumor and patient, and targeted treatment must therefore be tailored to each individual patient. We also know that many mutations exist only in some [cancer](#) cells, which allows other [cancer cells](#) to escape treatment. In addition, only few mutations are recognized by the [immune cells](#), Professor Olweus explains.

However, certain rare mutations are shared between subgroups of patients. The authors of the study were interested in exploring the potential of utilizing such [mutations](#) as targets for immunotherapy. One gene that often is mutated in AML is FLT3, which can contribute to disease acceleration. Using technology developed in Olweus' group, postdoc Eirini Giannakopoulou and colleagues identified a T-cell receptor that recognizes the mutation. Giannakopoulou, first author of the study, describes the discovery as "finding a needle in a haystack."

The researchers' then demonstrated that the T-cell receptor was safe. Next, they showed that the T-cell receptor effectively eliminated leukemia cells in multiple disease-relevant models. Such data for TCR-T cells or CAR-T cells are rare in the field.

"Here, the expertise on AML models in the groups of Woll and Jacobsen was crucial. The animal studies in advanced models where leukemia cells from patients were transplanted into mice, were conducted at KI in collaboration between the groups," Olweus says.

The treatment proved to be highly effective in eliminating mutated [leukemia cells](#) in just two weeks. "An important finding was that we were able to show that TCR-T cells could also kill cells with characteristics of [leukemia](#) stem cells," says doctoral candidate Madeleine Lehander, second author and a central contributor to the study, and supervised by Woll and Jacobsen.

Numerous members of the UiO/OUS group and the KI groups are co-authors on the article, which Olweus describes as "a fantastic collaboration that has spanned many years, where the groups complement each other's expertise perfectly." This is the second major collaboration project between the groups—the first was published in *Nature Biotechnology* in 2022.

More information: Giannakopoulou, E. et al, A T cell receptor targeting a recurrent driver mutation in FLT3 mediates elimination of primary human acute myeloid leukemia in vivo, *Nature Cancer* (2023). [DOI: 10.1038/s43018-023-00642-8](https://doi.org/10.1038/s43018-023-00642-8)
www.nature.com/articles/s43018-023-00642-8

Provided by University of Oslo

Citation: A possible new treatment for acute myeloid leukemia (2023, October 2) retrieved 29 April 2024 from <https://medicalxpress.com/news/2023-10-treatment-acute-myeloid-leukemia.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--