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IMMUNOTHERAPY

# Exploiting natural killers in AML

Patients with relapsed and/or refractory acute myeloid leukaemia (AML) have a poor prognosis; allogeneic stem-cell transplantation is potentially curative, but many patients are ineligible. A novel approach involving adoptive transfer of preactivated natural killer (NK) cells might enable the 'graft-versus-host' response to be harnessed without bone-marrow transplantation.

Todd Fehniger and co-workers showed that *ex vivo* stimulation with IL-12, IL-15, and IL-18 imbues NK cells with a 'memory-like' phenotype. These cells responded more robustly to, and more effectively killed, leukaemic blasts, both *in vitro* and in mouse xenograft models, compared with NK cells exposed to only low-dose IL-15.

Subsequently, the researchers conducted a first-in-human trial with memory-like NK cells in patients with AML. Fehniger summarizes the most-significant findings: "First, the administration of preactivated NK cells was safe at all dose levels tested, and we did not see any serious adverse events related to the NK cells. Second, we tracked the donor memory-like NK cells in the patients, and found that they proliferate, expand, and attack leukaemia cells more effectively than endogenous NK cells do. Finally, we observed complete remissions in four of nine (44%) patients treated, which is promising in these patients without effective standard therapies. By comparison, in other clinical trials with small cohorts, purified donor NK cells have resulted in complete remissions in only 7% of patients with AML."

The researchers plan to investigate this approach in a larger expansion cohort, as well as in combination with 'mini' transplantation or agents — cytokines, bispecific engagers, or inhibitors of NK-cell checkpoints — that might increase the effectiveness NK-cell therapy in AML and beyond.

Fehniger concludes, "this study takes a new, paradigm-changing observation in NK-cell biology, that of memory-like NK-cell function (which was made just a few years ago at the laboratory bench), and translates it into a promising new immunotherapy strategy."

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**ORIGINAL ARTICLE** Romee, R. *et al.* Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci. Transl. Med.* **8**, 357ra123 (2016)