T cell receptor gene therapy targeting mutant NPM1 on acute myeloid leukemia

Eva M. Argiro[1], Nadine E. Struckman[1], E. Onur Karakaslar[2,3,4], Georgia Koutsoumpli[1], Ian C.D. Johnston[5], Erik B. van den Akker[2,3,4], J.H. Frederik Falkenburg[1], Mirjam H.M. Heemskerk[1], Rosa de Groot[1], Constantijn J.M. Halkes[1], Marieke Griffioen[1].

1) Department of Hematology, Leiden University Medical Center, Leiden, Netherlands
2) Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands.
3) Pattern Recognition & Bioinformatics, Delft University of Technology, Delft, The Netherlands.
4) Leiden Center for Computational Oncology, Leiden University Medical Center, Leiden, The Netherlands.
5) Miltenyi Biotec B.V. & Co. KG, Bergisch Gladbach, Germany

ABSTRACT

Introduction
Acute myeloid leukemia (AML) is a life-threatening malignancy that requires further therapeutic improvement. One of the most common AML sub-entities is AML with mutant NPM1 (dNPM1-AML), in which a 4 base pair frameshift insertion occurs in the NPM1 gene. We previously reported on a T cell receptor (TCR) which, upon transfer to CD8 T cells, is able to target AML cells carrying this mutation by recognizing CLAVEEVSL, a 9-mer dNPM1-derived neoantigen presented by HLA-A*02:01. Since dNPM1-AML is a highly heterogeneous disease, highlighted by the recent identification of distinct dNPM1-AML subtypes by bulk transcriptomics, we here investigated the inter- and intra-patient heterogeneity in more detail and assessed the *in vitro* susceptibility of AML cells with different phenotypes to lysis by dNPM1-A2 TCR-engineered T cells.

Methods
A 28-color spectral flow cytometry-based antibody panel was used to phenotype dNPM1-AML cells and to assess lysis of different leukemic cell subsets in co-culture with dNPM1-A2 TCR-T cells.

Results
Different dNPM1-AML cells were identified, with early hematopoietic stem cell- or progenitor-like phenotypes or more mature monocyte- or dendritic cell-like phenotypes. Upon coculture with dNPM1-A2 TCR-engineered T cells, all subpopulations were efficiently lysed, albeit with different kinetics.

Conclusion
The results emphasize the potential of dNPM1-A2 TCR-T cells as a therapeutic strategy to treat patients with dNPM1-AML. This strategy is currently being evaluated in a first-in-human phase I/II clinical trial at the Leiden University Medical Center.