Gene-edited CD38/CD45-CAR-NK cells for leukemia treatment and non-toxic conditioning

Prof. Dr. Boris Fehse
Research Dept. Cell & Gene Therapy, Dept. of Stem Cell Transplantation
University Medical Center Hamburg-Eppendorf

Background: Immunotherapies using genetically modified T cells carrying chimeric antigen receptors (CARs) have revolutionized the treatment of certain types of blood cancers. CARs recognise specific molecules (antigens) on cancer cells and lead to their destruction. In addition to T cells, natural killer (NK) cells have also been used for CAR therapies. Acute myeloid leukaemia (AML) is a form of blood cancer with a poor prognosis, which mainly affects older adults. Stem cell transplantation (SCT) is the only potentially curative treatment for high-risk AML, but it requires a toxic high-dose therapy. CAR-based therapies generally cause fewer severe side effects than SCT. However, CAR-T cells have not been successful in treating AML so far due to the lack of suitable target antigens and the rapid progression of the disease.

Strategy: Our solution to this problem is based on two new approaches. First, our CAR cells target two antigens, CD45 and CD38, at the same time, which are commonly found on most blood cells and especially on myeloid cancer cells. Second, we plan to use CAR-NK cells from healthy donors, which will be readily ("off-the-shelf") available as needed.

Preliminary data: We have demonstrated that both CD38 and CD45 can be efficiently removed from the CAR effector cells using a gene-editing tool for their "knockout". This is essential to prevent fratricide (i.e. that the CAR-NK cells attack each other). Importantly, CAR-NK cells with the double knockout have been found to be highly effective in eliminating cancer cells.

Goal: In this project, we intend to further develop our technology to prepare it for future clinical use. Our main goal is to create a simple method for the efficient production of CAR-NK cells with a double knockout of CD38 and CD45 and two CARs targeting CD38 and CD45.