On- and off-target genotoxicity of CRISPR-Cas9 in T cells: Bridging research to phase I trials

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Cytomegalovirus (CMV) infections pose a serious risk to patients with weakened immune systems. While antiviral drugs help, they do not fully prevent CMV reactivation, leaving high-risk patients vulnerable to severe complications. Thus, the project aims to develop a novel T-cell therapy that can restore functional CMV immunity and thereby prevent CMV reactivation. To achieve this, the scientists are using CRISPR-Cas9 gene editing to engineer donor T-cells with a CMV-specific T-cell receptor (TCR), enabling the engineered cells to specifically recognize and kill CMV-infected cells. This method, known as 'orthotopic TCR replacement' (OTR), allows precise insertion of the TCR into the T-cell genome, making the engineered cells both safer and more effective compared to previous approaches for patient treatment. Before advancing to clinical trials, it is crucial to assess the safety of this gene-editing process. The project CRISBridge will use state-of-the-art techniques to examine potential risks, such as unwanted genetic modifications in specific genes or large structural changes in the cells' DNA. These analyses will provide the necessary data to define the safety profile of the product for regulatory approval and help pave the way for a first-in-human Phase I clinical trial. CRISBridge has the potential to offer a better treatment for immunocompromised patients, reducing CMV-related complications and improving overall survival.