

Methods for developing engineered T-cells for immunotherapy that are both non-alloreactive and resistant to immunosuppressive drugs. The present invention relates to methods for modifying T-cells by inactivating both genes encoding target for an immunosuppressive agent and T-cell receptor, in particular genes encoding CD52 and TCR. This method involves the use of specific rare cutting endonucleases, in particular TALE-nucleases (TAL effector endonuclease) and polynucleotides encoding such poly-peptides, to precisely target a selection of key genes in T-cells, which are available from donors or from culture of primary cells. The invention opens the way to standard and affordable adoptive immunotherapy strategies for treating cancer and viral infections.