NEOANTIGEN-SPECIFIC TCR-T CELLS TARGETING SHARED HOTSPOT MUTATIONS FOR ADOPTIVE CELL THERAPY IN COMMON EPITHELIAL CANCERS


Background EGFR, KRAS and TP53 have frequent somatic hotspot mutations giving rise to biologically relevant amino acid substitutions in EGFR, KRAS and p53 proteins, respectively, that can be processed and presented on the cell surface by human leukocyte antigen (HLA) molecules as neoantigens to T cells through their T-cell receptor (TCR). These mutations are critical for the cancer cell and are absent in normal tissue; thus, these shared neoantigens are attractive and likely safe targets. Given the complexity of different neoantigen/HLA combinations needed to effectively target a large patient population, a TCR library approach is warranted and can be used “off-the-shelf” for any patient with matching somatic hotspot mutation and HLA restriction. Sleeping Beauty transposition is the most advanced non-viral gene transfer technology for TCR-T cells and is appealing for TCR libraries given its low cost, speed, and flexibility.

Methods In this study, Sleeping Beauty transposons were constructed with TCRs targeting EGFR, KRAS and p53 neoantigens restricted by either or both HLA Class-I and HLA Class-II molecules. Donor T cells from peripheral blood were co-electroporated with TCR transposon and Sleeping Beauty transposase and grown in vitro to clinical scale quantities (>10⁹ TCR-T cells) with high expression (>60%) of the introduced neoantigen-specific TCRs.

Results The specificity of TCRs to neoantigens was confirmed in TCR-T cell co-cultures with antigen-presenting cells pulsed with peptides, which demonstrated interferon-γ secretion and/or up-regulation of 41BB on the TCR-T cell surface in response to the neoantigen with high avidity (<1 ng/mL for some TCRs) and negligible recognition of wild type peptides. Furthermore, TCR-T cells lysed tumor cells with endogenous expression of the somatic mutation and HLA restriction element but did not recognize tumor cells lacking either somatic mutation or HLA restriction element, indicating that the targeted neoantigens are normally displayed on the tumor cell at sufficient levels for elimination by TCR-T cells. Ziopharm has a cleared corporate-sponsored IND for a Phase 1/2 clinical trial, being conducted in collaboration with MD Anderson Cancer Center, in which patients with matching somatic hotspot mutation and HLA restriction will be identified, genes encoding suitable neoantigen-specific TCR will be inserted into their autologous T cells from peripheral blood by Sleeping Beauty transposition, and TCR-T cells will be adoptively transferred for the treatment of bile duct, colon, lung, pancreas and gynecological cancers.

Conclusions Ziopharm’s library TCR-T cell program has the potential to result in safe, durable, objective clinical regressions of cancer at a commercial scale.

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