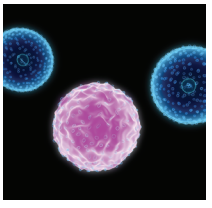
Clinical Trials

Major finding: NY-ESO-1 TCR-engineered T cells show antigen-specific clinical activity in advanced multiple myeloma.

Clinical relevance: *Ex vivo*–expanded T cells traffic to and durably persist in the marrow and are well tolerated.

Impact: Efforts to increase the survival and function of engineered T cells may further improve myeloma treatment.

AFFINITY-ENHANCED TCR-ENGINEERED T CELLS INDUCE ANTIMYELOMA RESPONSES



Adoptive transfer of autologous tumor-reactive T cells has been investigated as a strategy to augment clinical responses to autologous stem cell transplantation (ASCT) in patients with multiple myeloma. The immunogenic cancer-testis antigen NY-ESO-1 is expressed in a large percentage of advanced myelomas and is associated with poor prognosis, prompting Rapoport, Stadtmauer, Binder-Scholl, and colleagues to assess the safety and antitumor activity of NY-ESO-1– and LAGE-1–specific TCR-engineered T cells in multiple myeloma in a phase I/II trial. *Ex vivo*–expanded autologous engineered T cells were administered to twenty patients with advanced antigen-positive myeloma two days after ASCT. Engineered T cells were detected in the marrow, which represents the primary tumor site, and exhibited cytotoxic functionality and long-term persistence that inversely correlated with NY-ESO-1 expression. Autologous engineered T cells were well tolerated and did not induce severe cytokine release syndrome or treatment-related fatalities. Furthermore, infused engineered T cells mediated durable antigen-specific antimyeloma activity, resulting in decreased expression of NY-ESO-1 and LAGE-1 in all patients and reduced numbers of CD138-positive myeloma cells. Fourteen (70%) of 20 patients achieved a near-complete or complete response, four patients experienced a partial response, and one patient had stable disease; median progression-free survival was 19.1 months and median overall survival was 32.1 months. Of note, tumor progression was associated with antigen escape in two cases and loss of modified T cells in the blood in eight cases. These findings suggest that NY-ESO-1–specific TCR-engineered T cells may result in enhanced and more durable clinical responses in antigen-positive multiple myeloma, and support efforts to further increase persistence and antigen spreading. ■

Rapoport AP, Stadtmauer EA, Binder-Scholl GK, Goloubeva O, Vogl DT, Lacey SF, et al. NY-ESO-1–specific TCR–engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med 2015;21:914–21.

Lymphoma

Major finding: *DDX3X* loss-of-function mutations contribute to natural killer/T-cell lymphoma (NKTCL) pathogenesis.

Approach: Somatic mutations in NKTCL were identified by whole-exome sequencing and confirmed by targeted sequencing.

Impact: Mutations in *DDX3X* and *TP53* are associated with poor clinical outcome in patients with NKTCL.

DDX3X IS THE MOST FREQUENTLY MUTATED GENE IN NATURAL KILLER/T-CELL LYMPHOMA

Natural killer/T-cell lymphoma (NKTCL) is an aggressive subtype of non-Hodgkin lymphoma that has poor prognosis and no available targeted therapy. Mutations in *TP53*, *NRAS*, and genes in the JAK–STAT pathway have been identified in NKTCL, but the role of these and other as-yet-unidentified driver mutations in the molecular pathogenesis of NKTCL has not been fully elucidated. To identify additional genetic alterations that may drive NKTCL tumorigenesis, Jiang and colleagues performed whole-exome sequencing of matched tumor and normal samples from 25 patients with NKTCL and identified mutations in 795 genes that were predicted to alter protein function. Based on the presence of recurrent mutations predicted to modulate functions and relevance to oncogenesis, 26 of the 795 genes were selected for validation in 80 patients with NKTCL. The RNA helicase gene DEAD box helicase 3, X-linked (*DDX3X*), mutated in 21 (20%) of 105 patients, was found to be the most frequently mutated gene. In addition, mutations in six other members of the same RNA helicase family as well as known tumor suppressors (*TP53*), the JAK–STAT pathway (*STAT3*), and epigenetic modifiers (*MLL2*) were also identified. There was little overlap between *DDX3X* mutations and *TP53* mutations. Most of the identified alterations in *DDX3X* affected conserved amino acids in the ATP-binding helicase and the C-terminal helicase domains, and several of these mutations exhibited decreased RNA unwinding activity *in vitro*. Furthermore, wild-type DDX3X exerted a suppressive effect on cell-cycle progression and activation of the NF-κB and MAPK pathways, which was lost upon mutation of *DDX3X*. Kaplan-Meier analysis of prognostic data for 95 patients with NKTCL showed that high-risk NKTCL patients with mutant *DDX3X* and/or mutant *TP53* had significantly worse prognosis compared with patients lacking mutations in both *DDX3X* and *TP53*. Together, these results identify *DDX3X* loss-of-function mutations in NKTCL and demonstrate their role in NKTCL pathogenesis. ■

Jiang L, Gu ZH, Yan ZX, Zhao X, Xie YY, Zhang ZG, et al. Exome sequencing identifies somatic mutations of DDX3X *in natural killer/T-cell lymphoma. Nat Genet 2015 Jul 20 [Epub ahead of print].*