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Leukemia-associated antigen reactive T-cells in ATIR101, a recipient-specific allodepleted T-cell product to reduce relapse rates and GVHD after haplo-HSCT

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Graft-versus-leukemia (GvL) relies on donor T-cells killing host leukemia cells post-transplant. T-cells preferentially recognizing leukemia cells are well documented but their clinical relevance remains challenged because thymic selection prevents high-affinity interactions of T-cells and antigens presented in self-HLA.

ATIR101, a personalized T-cell immunotherapeutic selectively depleted of HLA-haplotype mismatched T-cells, provides a unique platform to study leukemia-reactive T-cells because high-affinity interactions with leukemia antigens displayed in the mismatched haplotype may occur in contrast to antigens expressed in the matched haplotype, and interfering T-cells that react to the mismatched HLA-molecules have been eliminated.

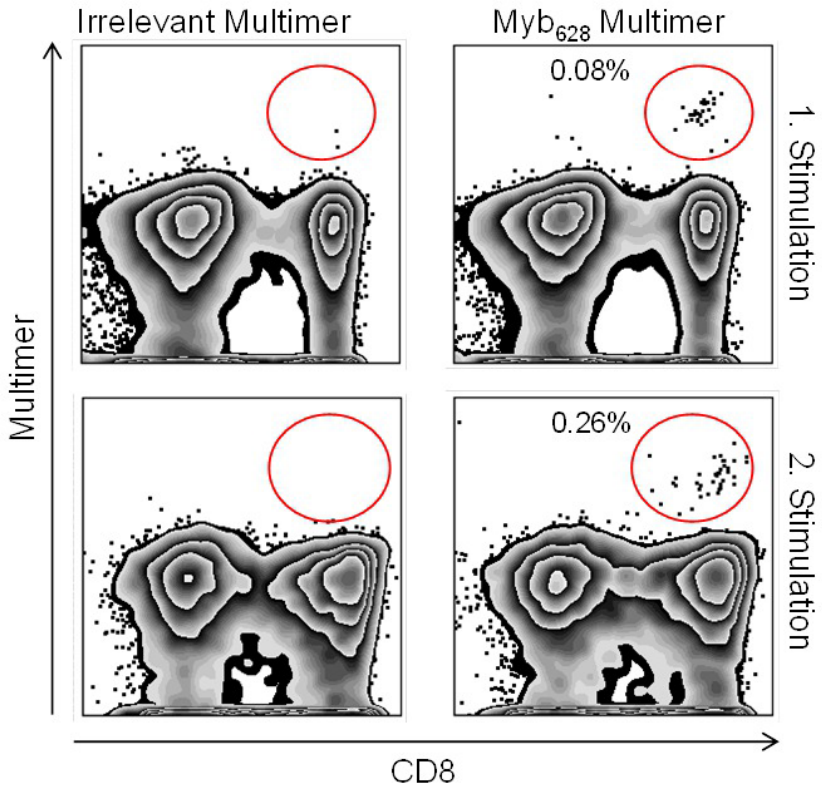
Two out of the first 10 ATIR101 batches manufactured in clinical phase 2 study NCT01794299 expressed a mismatched haplotype able of expressing a leukemia-associated antigen (LAA); these batches were screened for LAA-reactive T-cells.

Because the frequency of LAA-reactive T-cells is expected to be very low, we used peptide-MHC monomers presenting LAAs and established a stimulation platform with artificial APCs (aAPC) consisting of streptavidin coated microspheres loaded with biotinylated anti-CD28 antibodies and respective biotinylated peptide HLA-monomers.

In one batch, LAA-specific T-cells were detected: ATIR101 cells were stimulated with Myb_{628}/HLA-B44 aAPCs and specific T-cell expansion was assessed after one or two rounds of stimulation; an irrelevant HLA-B44 multimer was used as negative control. CD8+ T-cells with specific reactivity against Myb_{628} expressed in HLA-B44 were detected (figure 1).

These data show that T-cells recognizing LAAs expressed in the mismatched HLA-haplotype are retained in ATIR101 from which T-cells responding to the antigen-presenting foreign HLA-molecule have been eliminated. Conceivably, these cells would be expected to contribute to the GvL-effect of ATIR101.

Figure 1:


Irrelevant Multimer
Myb628 Multimer
0.08%
0.26%
1. Stimulation
2. Stimulation
Multimer
CD8