PERSONALIZED CANCER IMMUNOTHERAPY THROUGH MINOR HISTOCOMPATIBILITY ANTIGEN TARGETING

Cédric Carli[1], Valérie Janelle[1], Julie Taillefer[1], Julie Orio[1] and Jean-Sébastien Delisle[1,2]

[1] Centre de recherche de l'Hôpital Maisonneuve-Rosemont, Montreal, Quebec, Canada.

[2] Division of Hematology-Oncology, Hôpital Maisonneuve-Rosemont and Department of Medicine, University of Montréal, Montreal, Quebec, Canada.

Allogenic hematopoietic cell transplantation (AHCT) can cure hematological malignancies refractory to cytotoxic therapy. The therapeutic potential of AHCT largely depends on the so-called graft-versus-leukemia (GVL) effect mediated by donor T cells recognizing mainly Minor histocompatibility antigens (MiHA) on the malignant cells. Our collaborators developed a method based on deep sequencing and high-throughput mass spectrometry to determine HLA*A0201 associated MiHA. Our objectives are to validate these novels MiHA and to develop a clinical grade-compliant method to reliably expand MiHA-specific CD8 T-cell lines.

To evaluate the immunogenicity of newly discovered MiHA, we adapted a previously published 10-day protocol based on immunomagnetic T-cell selection, peptide-loaded dendritic cells and cytokine-driven activation of antigen-specific T cells. We validated this approach using the MiHA HA-1 and generated a product composed of 65% CD8 T cells, 0.3% of which are multimer HLA-A2/HA-1 positive. Importantly, the IFNγ-ELISpot assay is sufficient to determine the antigen-specificity of the T cell line. Based on ELISpot assay, we show that two putative MiHA peptides are immunogenic. Examining the polyfunctionality by flow cytometry, we can estimate that at least 3.5% of CD8 T cells in the culture are antigen-specific for one of the two peptides newly identified.

Our clinical grade-compliant method to generate MiHA-specific T-cell lines hinges on a co-culture with peptide-pulsed dendritic cells and responder T cells, followed by an enrichment step using IFNγ capture and rapid expansion protocol. Our results using HA-1 as a model MiHA showed that IFNγ-secreting T cells enrichment after 3 dendritic cells stimulations followed by 12 days of rapid expansion led to a MiHA-specific T-cell product with no evident sign of culture-driven exhaustion.

Our results set the stage for a phase I clinical trial using HLA-A2 associated MiHA-specific T-cell lines for the treatment of high risk hematological malignancies.