TARGETING A NOVEL SHARED TUMOR-SPECIFIC ANTIGEN WITH T CELL RECEPTOR TRANSDUCE T CELLS FOR THE TREATMENT OF OVARIAN CANCER

¹Justyna Ogonek*, ¹Tiziana Franceschetti, ¹Andreas Acs, ¹Alexander Schmidt, ¹Alexandra Kuhlenkamp, ²Krystel Vincent, ²Claude Perreault, ¹Barbara Loesch, ¹Adriana Turqueti Neves, ¹Slavoljub Milosevic, ¹Dolores Schendel, ¹Daniel Sommermeyer. ¹Medigene Immunotherapies GmbH, Planegg-Martinsried, Germany; ²Université de Montréal, Montreal, Canada

Background Transgenic T cell receptor (TCR)-based T cell therapies are a powerful treatment for cancer. However, one of the greatest remaining challenges is the successful identification of tumor-specific antigens (TSAs) that are shared between patients and tumor entities and elicit strong T cell responses. The non-coding region of the genome has become a promising source of such novel TSAs. Previously, we have identified ten immunogenic shared TSAs, derived from the translation in canonical and non-canonical reading frames of non-mutated non-coding genomic regions like introns, intergenic regions and 5'-untranslated regions. In the following process, we identified several TCRs specific for these TSAs. Here we aimed at the validation of two TSA-specific TCRs in a model of ovarian cancer-derived organoids.

Methods Freshly collected ovarian tumor and normal ovarian tissue expressing the HLA of interest were mechanically disrupted, enzymatically digested and cryopreserved. Expression of the TSA of interest in the primary tumor tissue was confirmed with RNA sequencing and mass spectrometry. Thawed single cell suspensions were used to generate tumor organoids and 2D-growing normal ovarian cell lines. To validate the generated cell lines, the presence or absence of two previously identified tumor-specific mutations was investigated by targeted Sanger sequencing in the genome of the tumor organoids, normal cell lines and primary tissues. Two TSA-specific TCRs were retrovirally transduced into CD8+ T cells of three healthy donors. Expanded TSA-specific CD8+T cells were co-cultured 24 hours with single cell suspensions of IFN- γ pre-stimulated, tumor organoids or the 2D-growing normal ovarian cell line. IFN- γ ELISA was used to assess activation of TSA-specific T cells upon co-culture.

Results The TSA of interest was detected both at the transcriptomic and proteomic level in the primary ovarian tumor tissue. Using frozen single cell suspensions of this tumor and corresponding normal tissue, tumor organoids and 2D-growing normal cell lines were successfully established and their integrity was confirmed. Both TSA-specific TCRs were efficiently expressed on CD8+ T cells from three donors. TCR-transgenic T cells showed activation upon co-culture with tumor organoids without recognition of normal ovarian cell lines. Normal cells were only recognized after loading with the specific target peptide.

Conclusions In conclusion, the high relevance of two TCRs identified to be specific for a novel shared tumor-specific antigen was confirmed in a model of ovarian cancer organoids. The findings support further development of these TCRs for cancer immunotherapy and implementation of tumor organoids as a relevant tool for the characterization of TSA-specific TCRs.

Ethics Approval 'The tumor and normal tissue samples were purchased at a Biobank, collected in compliance with all applicable EU regulations and were pseudonymized.'

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.189>