AN OFF-THE-SHELF PERSONALIZED CELLULAR APPROACH TO IMMUNOTHERAPY FOR THE TREATMENT OF ADVANCED SOLID TUMORS


Background BriaCell is developing off-the-shelf personalized cellular immunotherapies based on our most advanced lead candidate—SV-BR-1-GM, which is in Phase I/IIa clinical trial in patients with metastatic or locally recurrent breast cancer. SV-BR-1-GM is a breast cancer cell line with features of an antigen presenting cell (APC) which has been stably transfected with the CSF2 gene encoding GM-CSF (SV-BR1-GM). We have recently reported favorable clinical outcomes in patient populations that match SV-BR-1-GM at one or more HLA alleles. This clinical observation, together with the fact that SV-BR-1-GM cells can directly activate CD4+ T-cells in an antigen-specific HLA-restricted manner, as demonstrated by an in vitro antigen presentation assay, lead us to hypothesize that SV-BR-1-GM can function as an APC. We propose a therapeutic approach in which a patient will be treated with a cell line expressing HLA class I and II molecules matched to their genotype. Also, to further enhance direct antigen presentation to T-cells, the parent SV-BR-1 cells were genetically modified to express co-stimulatory molecules and additional immune-modulatory cytokines.

Methods Using CRISPR/Cas9 technology we have inactivated several endogenous HLA-A and HLA-DRB alleles present in five cancer cell lines (SV-BR-1, PC-3, LNCaP, SK-MEL-24, and NCI-H2228). Cells with inactivated HLA-A/DRB genes were transduced with lentiviral based vectors expressing selected cytokines and costimulatory molecules (GM-CSF, INFα, CD80, CD86, IL-12, IL-7, HLA-DRA, and 4-1BBL). Next, unique combinations of HLA-A and HLA-DRB3/4/5 alleles were transduced into the cells using lentiviral based vectors to generate a collection of cell lines that will match over 99% of the patient population for at least one HLA allele. Expression and functionality of the stimulatory molecules and transgenic HLA alleles was established using flow cytometry and cell-based assays.

Results Four cell lines (for each tumor type) that secreted GM-CSF, IFNα, IL12, IL7 and expressed CD80, CD86, 4-1BBL, and different combinations of both Class I and Class II HLA alleles were selected. Using cell-based assays – including mixed lymphocyte reaction assays – we demonstrated that the generated cells stimulate naïve T-cells.

Conclusions We have successfully generated “off the shelf” personalized cell-based therapeutic cancer vaccines that induce potent T-cell responses. These modified cancer cell lines will be used in clinical studies designed to first evaluate the safety of intradermal inoculation with the irradiated cells and later combined with other agents to augment the immune response.

REFERENCE