Therapeutic cancer vaccines are designed to program a patient’s own immune system to recognize and eliminate tumor cells. We sought to harness gene-modified tumor cells as a vaccine platform and developed cancer vaccines composed of breast cancer cells expressing GM-CSF (SV-BR-1-GM). We have recently reported favorable clinical outcomes in patient populations that match SV-BR-1-GM at one or more HLA alleles. Mechanistically, 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 (1). Building upon these observations, we hypothesized that tumor cells, in addition to providing tumor antigens, can also directly stimulate the immune system.

**OBJECTIVES**

In response to the demand for innovative immunotherapeutic strategies for advanced solid tumors, BriaCell Therapeutics is pioneering the development of a groundbreaking whole tumor cell vaccine therapeutic. This vaccine is designed to operate through two synergistic mechanisms: 1) facilitating the cross-presentation of cancer cell antigens by donor T-cells, and 2) directly activating the immune system. To achieve our objective, we will create a series of breast, prostate, melanoma, and lung cell lines with heightened immunogenicity through the following genetic modifications:

1. Expression of costimulatory molecules (CD80, CD86, 4-1BB-L,CD40) and immunomodulatory cytokines (GM-CSF, IFNα, IL-12 and IL-7). This modification aims to improve the cell's ability to present antigens and activate the host immune system.

2. Expression of an extended repertoire of HLA alleles to generate semi-allogeneic cell lines that will match the whole population at least at one HLA allele. This approach is intended to stimulate the host immune response to recognize tumor-associated antigens within the context of syngeneic MHC-I or II molecules with other allo-HLA molecules serving as a molecular adjuvant by activating the immune system (Fig. 2).

**METHODS**

- We engineered Bria-OTS cell lines from various cancer types, including breast cancer (SV-BR-1), prostate cancer (PC3), melanoma (SK-MEL-24), lung cancer (NCI-H222), and liver cancer (HCC-T1). These selections were based on their expression of a distinct 22-gene immune signature, initially characterized in SV-BR-1 cells.

- To enhance these tumor cell's antigen presentation capabilities and immune system stimulation, we genetically modified them to express co-stimulatory molecules and immunomodulatory cytokines. These modified cells were named antigen presenting tumor cell (APTC) (see Fig. 3).

- To create a semi-allogeneic cell therapy with broad applicability, we expanded the repertoire of HLA alleles expressed by SV-BR-1. Population analysis suggests that four cell lines, each carrying two HLA-A and two HLA-DRB3/4 alleles, should offer at least a single match in 99% of the population. This is critical, a 98% match at Class I HLA-A alleles and a 98% match at Class II HLA-DRB3/4 alleles (see Fig. 3).

- Functional validation: 1. Modified lymphocyte reaction assay (mMLR)

**RESULTS**

We are in the process of creating 'off-the-shelf' personalized cell-based therapeutic cancer vaccines designed to elicit potent immune responses against various solid tumors. The Bria-OTS cell line collection will offer the following key features:

1. Multi-modal mechanisms of Action: Bria-OTS cell lines have been engineered to trigger robust immune responses and deliver clinical efficacy through diverse mechanisms. These mechanisms include adaptive responses involving T-cells and innate responses involving dendritic cells and NK cells.

2. Precision Therapy: Bria-OTS cell lines will be precisely matched to individual patients based on their HLA antigens, encompassing over 99% of the U.S. population. This personalized approach ensures optimal compatibility and effectiveness.

3. Enhanced Safety: In contrast to current chemotherapeutic and hormone-based treatments, these are often associated with severe and potentially life-threatening adverse events. Bria-OTS offers improved safety profiles.

4. Rapid, Cost-Effective Treatment: Our 'off-the-shelf' cell line eliminates the need for personalized manufacturing, allowing for immediate administration following patient HLA genotyping. This streamlined process offers efficient and cost-effective treatment options.

References


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