Redefining Cancer Vaccines: Bria-OTS+ Integrates Trained Innate Immunity and Adaptive Memory to Overcome Immune Resistance

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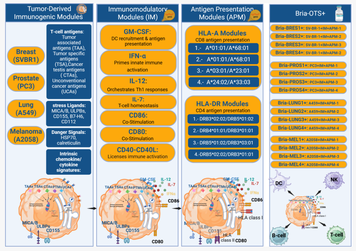
BACKGROUND AND OBJECTIVES

Despite significant advances in immuno-oncology, many cancers remain resistant to treatment due to tumor heterogeneity, immune evasion, and insufficient immune activation. Allogeneic tumor cell vaccines offer a promising off-the-shelf strategy by presenting a broad repertoire of tumor-associated antigens; however, their clinical impact has been limited by weak immunogenicity and suboptimal activation of immune effector pathways.

Bria-OTS+ is a novel, genetically engineered allogeneic tumor cell vaccine platform designed to overcome these limitations. It is genetically modified to express immune-stimulatory cytokines, co-stimulatory molecules, and a diverse library of HLA alleles to enhance antigen presentation and immune engagement. This multi-modal approach drives coordinated activation of dendritic cells, T cells, B cells, NK cells, and NKT cells, supporting both personalized and off-the-shelf immunotherapy applications.

Bria-OTS+ represents a next-generation cancer vaccine that integrates classical adaptive immune memory with innate immune training. This reflects a paradigm shift in vaccine design, from focusing solely on adaptive immunity to actively engaging and educating both innate and adaptive compartments. By activating these immune pathways, Bria-OTS+ functions as a modular, immune-educating platform capable of overcoming resistance and inducing durable anti-tumor responses.

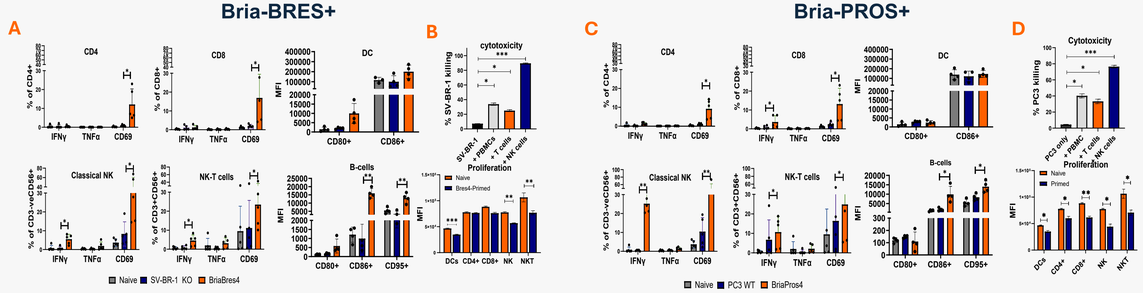
METHODS



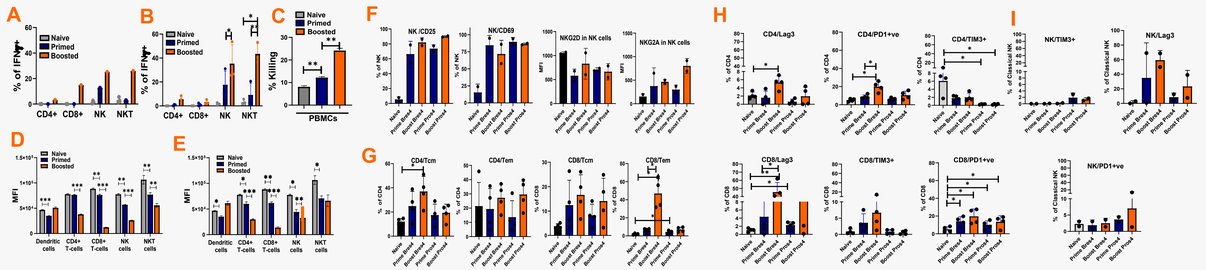
Modular Engineering of Bria-OTS⁺ Cell Lines: Integrating Tumor immunogenetic factors, Immune Modulators, and HLA Diversity: *Bria-OTS⁺ is built from three functional modules that together create a modular, immune-educating vaccine platform. The Tumor-derived Antigen Modules (TAM) provide a broad repertoire of tumor-associated and stress-induced antigens to ensure antigenic diversity. The Immunomodulatory Modules (IM) recruit, prime, and activate immune effectors. The Antigen-Presentation Modules (APM) introduce diverse HLA-A and HLA-DRB3/4/5 alleles, enabling semi-allogeneic antigen display and optimized T-cell recognition. Four pre-manufactured Bria-OTS⁺ cell lines, each carrying two HLA-A and two HLA-DRB3/4/5 alleles, together provide > 99 % predicted HLA matching across populations, personalizing the cell lines thus enabling broad patient applicability and coordinated activation of dendritic, T, B, and NK cells*

In vitro vaccination assay using Bria-OTS+ cells*. Bria-OTS+ cells, are co-cultured with peripheral blood mononuclear cells (PBMCs) in an* ***in vitro vaccination*** *assay to induce an anti-tumor immune response. The activation protocol consists of four sequential phases: (1)* ***Priming (2–3 days)****, where PBMCs initially interact with Bria-OTS+ cells, leading to cytokine release (primarily IFNγ, IL-2), proliferation, and activation of immune cells; (2)* ***Resting (5–7 days)****, allowing expansion and maturation of activated T cells and other immune populations; (3)* ***Boosting (2–3 days)****, where a second exposure to Bria-OTS+ cells further enhances immune activation and expands tumor-specific T cell populations; and (4)* ***Effector phase (24 hours)****, where cytotoxic activity against target tumor cells is assessed through cell killing assays. Throughout the process, immune activation is characterized by cytokine release, proliferation, and cellular activation markers. The final effector phase evaluates the cytotoxic potential of the activated immune cells, primarily CD8+ T cells and NK cells, against target tumor cells.*

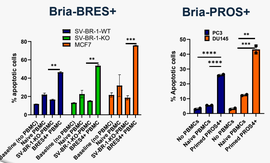
RESULTS



Bria-OTS+ Potency: ***Bria-OTS+ Prime Broad Innate and Adaptive Immune Activation:*** *PBMCs were co-cultured with Bria-OTS+cells during the priming phase (3 days) of the in vitro vaccination assay. Bria-BRES4+(A–B) and Bria-PROS4+ (C–D) induced strong early activation marked by IFN-γ/TNF-α production and CD69 upregulation across CD4⁺, CD8⁺, NK, and NK-T cells. Dendritic and B cells exhibited increased CD80/CD86 expression, indicating enhanced antigen-presenting potential. Primed PBMCs showed elevated proliferation and cytotoxic activity against parental tumor targets, confirming the potency of Bria-OTS+ in initiating robust innate and adaptive immune responses..*

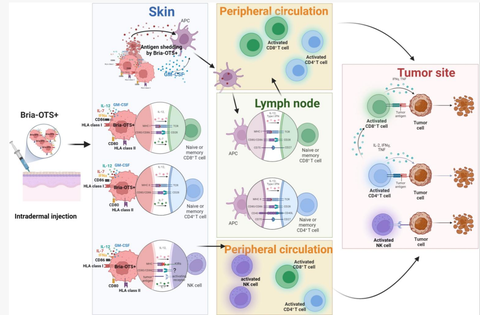


Bria-OTS+ Persistence: ***Recall Function, Memory Formation, and Functional Durability:*** *Bria-OTS+ primed immune cells exhibit durable recall capacity, memory-like reprogramming, and adaptive checkpoint modulation across T and NK compartments. (A–B) IFN-γ secretion is enhanced upon recall stimulation in both (A)* ***Bria-BRES+*** *and (B)* ***Bria-PROS+*** *primed PBMCs, demonstrating persistent effector functionality after priming. (C) Cytotoxic recall responses significantly increase after boosting, confirming retention of cytolytic competence. (D–E) Cellular proliferation is higher upon secondary stimulation than after initial priming with (D)* ***Bria-BRES+*** *and (E)* ***Bria-PROS+****, consistent with long-term proliferative memory and persistence. (F) NK cells show increased expression of* ***CD25****,* ***CD69****,* ***NKG2D****, and* ***NKG2A****, defining a memory-like, cytokine-responsive phenotype characteristic of trained NK immunity. (G) T cells exhibit a memory-like differentiation pattern following Bria-OTS+ stimulation, consistent with antigen-experienced, recall-capable phenotypes. (H) In CD4⁺ and CD8⁺ T cells, PD-1 and TIM-3 remain low while LAG-3 increases after boosting, consistent with controlled inhibitory signaling and a limited exhaustion/senescence signature rather than terminal dysfunction. (I) NK cells display a similar selective pattern of checkpoint expression, maintaining function potential despite repeated stimulation. Together, these findings demonstrate that Bria-OTS+ induces* ***persistent, recallable immune activation with memory-associated features and balanced checkpoint control****, supporting durable effector competence over time.*



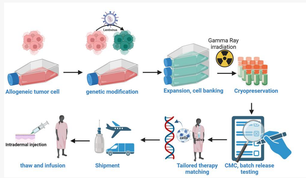
Bria-OTS+ Breadth: ***Broad Tumor Recognition Suggests Shared Antigen Coverage and Reduced Escape Risk:*** *PBMCs activated with Bria-BRES4+ or Bria-PROS+ cells exhibit cytotoxic activity against both homologous (SV-BR-1-WT, SV-BR-1-KO, PC3) and heterologous (MCF7, DU145) tumor targets. Target cell apoptosis was quantified after co-culture with naïve or Bria-BRES4+ or Bria-PROS4+ .Both Bria-PROS4+– or Bria-BRES4+ priming markedly increased killing across all targets, indicating recognition of shared tumor-associated antigens and stress ligands. These results support the clinical potential of Bria-OTS⁺ vaccines to elicit broad, cross-tumor immune responses and reduce the risk of antigen-escape variants.*

PROPOSED MECHANISM OF ACTION



Bria-OTS+ Proposed Mechanism of Action: *Bria-OTS, when injected intradermally, directly activates both naive and previously exposed (memory) T-cells, as well as natural killer (NK) cells. Concurrently, professional antigen-presenting cells (APCs) process the Bria-OTS+ antigens. These APCs then migrate to regional lymph nodes, where they prime T-cells against tumor antigens. The activated T-cells and NK cells subsequently travel to the tumor site, where they trigger a robust anti-tumor immune response.*

PATH TO CLINICAL APPLICATION



CONCLUSIONS

Bria-OTS⁺ demonstrates a multifaceted mechanism of action characterized by:

- **Broad antigenic coverage, expressing diverse Tumor-Associated Antigens (TAAs), Tumor specific Antigens (TSA) and Unconventional Cancer Antigens (UCAs). Smith C.C., Selitsky S.R., Chai S., Armistead P.M., Vincent B.G., Serody J.S. Alternative tumour-specific antigens. Nature Reviews Cancer. 2019;19(8): 509-525**
- **Comprehensive immune engagement, activating both adaptive and innate immune compartments.**
- **Enhanced tumor recognition and control, counteracting immune escape via Natural Killer (NK) cell activation, even in HLA-deficient contexts.**
- **Durable immune memory formation, supporting long-lasting anti-tumor protection upon boosting.**
- **Flexible applicability, suitable for both personalized and off-the-shelf vaccine formats with strong stability profiles.**
- **Streamlined clinical use, featuring a simplified administration process.**
- **Favorable safety expectations, with an anticipated low toxicity and good tolerability profile.**