Re-engineering Cancer Vaccines: Bria-OTS+ Integrates Innate and Adaptive Immunity for Broad and Persistent Anti-Tumor Responses

BriaCell

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Miguel Lopez-Lago[1], Pravin Kesarwani[1], Vikas Bhardwaj[1], Xiaoyi Zheng[1], Ying Liu[1], Sagarika Pachhal[1], George Woodfield[1], Patience Cournoo[1], Renee Cortez[1], Charles L. Wiseman[1], William V. Williams[1]

[1]*BriaCell Therapeutics Corp. Philadelphia, PA*

BACKGROUND AND OBJECTIVES

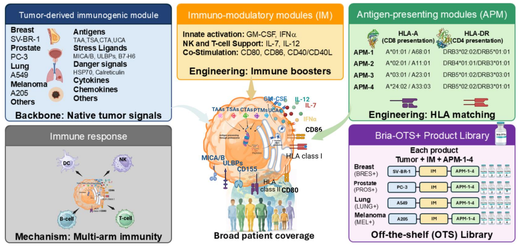
BACKGROUND

Many cancers remain resistant to immunotherapy due to tumor heterogeneity, immune evasion, and insufficient activation of coordinated immune responses. While allogeneic tumor cell vaccines provide an off-the-shelf source of diverse tumor antigens, their clinical efficacy has been limited by weak immunogenicity and incomplete engagement of both innate and adaptive immune pathways. Bria-OTS+ is a genetically engineered, multi-modal allogeneic tumor cell vaccine platform designed to overcome these limitations. By integrating antigenic breadth with immune-stimulatory cytokines, co-stimulatory signals, and multi-HLA presentation, Bria-OTS$^+$ enhances antigen presentation and drives coordinated activation of dendritic cells, T cells, NK cells, and other immune effectors.

OBJECTIVE

To validate Bria-OTS+ as a modular, immune-activating platform capable of inducing broad, durable, and functionally coordinated anti-tumor immune responses.

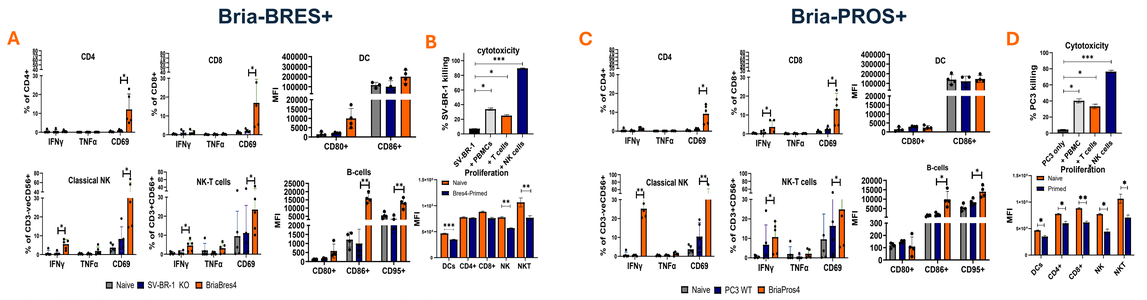
METHODS



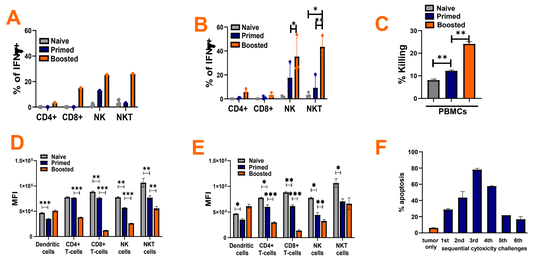
Modular Engineering of Bria-OTS$^+$ Cell Lines: Integrating Tumor immunogenetic factors, Immune Modulators, and HLA Diversity: *Bria-OTS$^+$ is built from three functional modules that together create a modular, immune-educating vaccine platform. The Tumor-derived Antigen Modules (TAM) provide a broad repertoire of tumor-associated and stress-induced antigens to ensure antigenic diversity. The Immuno-modulatory 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 (1–3 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 (2-5 days)**, allowing expansion and maturation of activated T cells and other immune populations; (3) **Boosting (1–3 days)**, where a second exposure to Bria-OTS+ cells further enhances immune activation and expands tumor-specific T cell populations; and (4) **Effector phase (1-2 days)**, 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+ Primes 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.*



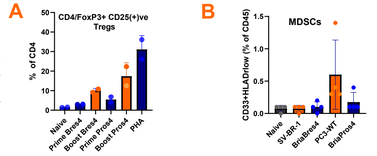
Bria-OTS+ induces durable functional persistence, recall capacity, and sustained cytotoxic activity *Bria-OTS+ priming generates immune cells with long-lasting functional competence, characterized by preserved effector function, enhanced recall responses, and sustained cytolytic activity across repeated challenges. **(A–B) Recall cytokine response.** IFN-γ secretion is increased upon recall stimulation in PBMCs primed with **(A) Bria-BRES+** and **(B) Bria-PROS+**, demonstrating persistence of effector function following initial priming. **(C) Cytotoxic recall activity.** Cytolytic responses are significantly enhanced after boosting, indicating retention and amplification of killing capacity upon secondary stimulation. **(D–E) Proliferative persistence.** Secondary stimulation induces greater proliferation than initial priming in **(D) Bria-BRES+** and **(E) Bria-PROS+**, consistent with sustained expansion potential and functional persistence. **(F) Serial killing capacity.** Bria-OTS+–primed immune cells maintain cytotoxic activity across multiple sequential tumor cell challenges, demonstrating durable killing capacity and resistance to functional exhaustion over repeated engagements.*

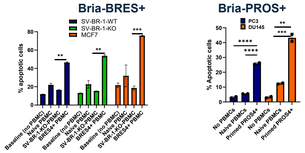
Conclusion: *Together, these findings show that Bria-OTS+ induces persistent, recallable immune responses with sustained proliferative and cytolytic capacity, supporting durable anti-tumor functionality over time.*

Minimal Induction of Immunosuppressive Cells by Bria-OTS+–Primed Immune Responses

*(A) Frequency and/or activity of **Tregs (CD4$^+$CD25$^+$FOXP3$^+$)** following co-culture with Bria-OTS+–primed PBMCs. A modest increase is observed, consistent with physiological immune regulation rather than dominant suppression (**n = 2 donors**). (B) Quantification of **MDSC populations** (e.g., CD11b$^+$CD33$^+$HLA-DR$^{low/-}$ subsets) shows no significant expansion or activation, indicating that Bria-OTS+ does not drive myeloid-mediated immunosuppression (**n = 5 donors**).Collectively, these data indicate that Bria-OTS+ induces robust immune activation **without concomitant expansion of dominant immunosuppressive mechanisms**, maintaining a favorable balance between effector and regulatory compartments.*

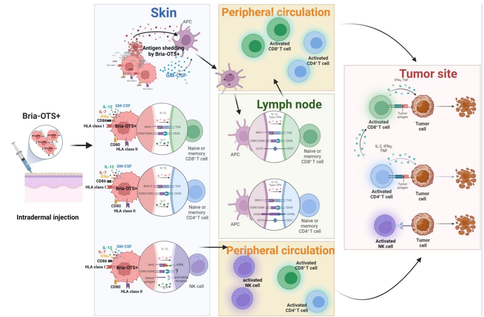
Conclusion *: Bria-OTS+ priming does not promote a strongly immunosuppressive environment, with limited effects on regulatory T cells (Tregs) and minimal activation of myeloid-derived suppressor cells (MDSCs).*





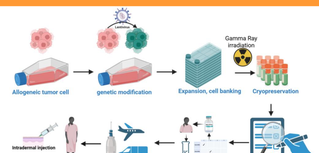
Broad Tumor Recognition Suggests Shared Antigen Coverage and Reduced Escape Risk: *PBMCs activated with Bria-BRES4+ or Bria-PROS+ cells exhibit cytotoxic activity against both homologous (SV-BR-1-WT, SV-BR-1-KO, PC3) and heterologous (MCF7, DU145) tumor targets. Target cell apoptosis was quantified after co-culture with naïve PBMCs or Bria-BRES4+/Bria-PROS4+ primed PBMCs. Both Bria-PROS4+ priming and 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+ defines a next-generation whole-cell vaccine platform that integrates antigen breadth, multi-lineage immune activation, and functional persistence to overcome key limitations of cancer immunotherapy.

- **Broad antigenic repertoire:** Simultaneous presentation of TAAs, TSAs, and unconventional cancer antigens (UCAs) enables coverage of tumor heterogeneity and reduces immune escape.
- **Multi-compartment immune activation:** Coordinated engagement of dendritic cells, T cells, NK cells, and NKT cells drives both adaptive priming and innate effector function.
- **NK-driven, HLA-independent activity complements HLA-restricted T-cell responses to maintain efficacy.:** Robust NK cell activation supports anti-tumor activity even in HLA-deficient or immune-evasive settings.
- **Functional persistence without exhaustion:** Primed immune cells retain recall capacity, proliferative potential, and serial killing activity, supporting durable anti-tumor responses.
- **Balanced immune modulation:** Limited activation of immunosuppressive populations (Tregs, MDSCs) suggests preservation of an overall effector-dominant immune state.
- **Translatable and scalable platform:** Modular HLA engineering enables broad population coverage, supporting both off-the-shelf and semi-personalized approaches with favorable manufacturability.