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Nanomedicine & Nanotechnology Open Access
ISSN: 2574-187X

Overcoming Malignant Glioma Therapeutic Challenges: Nanocarrier-Mediated Delivery of Immune Checkpoint Blockers via Nasal Route

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Editorial
Volume 8 Issue 3
Received Date: August 25, 2023
Published Date: September 06, 2023
DOI: 10.23880/nnoa-16000249

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Keywords: Immunotherapy; Nanomedicine; Bilosomes; Brain Cancer

Abbreviations: BBB: Blood Brain Barrier; TGF-β: Transforming Growth Factor β; CTL: Cytotoxic T Lymphocyte.

Editorial

Malignant glioma represents a prevailing malignancy within both paediatric and adult populations, necessitating advanced therapeutic interventions. Traditional therapeutic avenues encompassing surgical resection, radiotherapy, and chemotherapy have yielded unsatisfactory clinical outcomes [1]. The infiltrative nature intrinsic to brain tumours impedes comprehensive eradication *via* surgical intervention, while the impervious blood-brain barrier (BBB) significantly diminishes drug penetration, thereby undermining therapeutic efficacy.

Under physiological circumstances, the brain tissue is endowed with immune privilege state owing to the lack of conventional lymphatic drainage routes to lymph nodes and the unique anatomical attributes, including the BBB [2]. This condition partially shields the brain from immune surveillance, perpetuating the survival of antigenically aberrant brain cells. Despite these factors, immune surveillance persists, and upon tumour detection, an immune response is triggered. Nonetheless, this intrinsic antitumor immune response remains insufficient to eliminate rapidly proliferating brain cancer cells. Malignant gliomas are known to express potent immune suppressive agents, including transforming growth factor β (TGF-β), which suppress T-cell proliferation while augmenting apoptotic tendencies [3].

The efficacy of endogenous immune responses in eliminating established tumours remains infrequent, primarily due to the suppressive tumour microenvironment. Consequently, brain cancer immunotherapy requires effective strategies to overcome the immune-inhibitory elements and enhance immune responses against malignant cells. In the context of solid tumours, the activation of T-cells facilitates a robust immune response, thanks to their distinct attributes including heightened specificity, potent cytotoxicity, and durable immunological memory. Furthermore, activated cytotoxic T-cells (CTLs) have demonstrated the capacity to traverse the BBB [2]. However, the efficiency of activated CTLs in eradicating established tumours is significantly compromised by tumour-induced immune suppression, mediated through immune checkpoint molecules and other pathways. Despite the pivotal role of immune checkpoint molecules in regulating immune response induction, they can profoundly suppress immune activation. Notably, the interaction between the immune checkpoint molecule such as Programmed cell death protein-1 (PD-1) and its ligand PD-L1, expressed by T cells and cancer cells respectively, has been associated with marked suppression of CTL cytotoxicity [4]. Consequently, the blockade of immune checkpoint interactions using monoclonal antibodies has emerged as

a promising immune-based therapeutic intervention. The appeal of cancer immune-based therapeutic approaches is underscored by their therapeutic efficacy, safety, and enduring effects. However, overcoming tumour-induced immune suppression necessitates the implementation of fortified strategies.

Capitalising on their distinctive features, the development of novel nano-sized carriers has elicited escalating interest over recent decades. These interests have rendered the incorporation of nanocarriers into various biomedical domains, including drug delivery, immunotherapy, disease diagnosis, and regenerative medicine inevitable [5,6]. Bilosomes, a promising vesicular nano-sized delivery system composed of self-assembled bile salts and surfactants, have demonstrated the capacity to transport therapeutic agents to brain sites following nasal administration [7,8]. In this context, bilosomal delivery of immune checkpoint blockers *via* the nasal route presents a compelling strategy for the efficient therapeutic management of glioma. This approach could not only effectively target CTLs and the brain tumour microenvironment but also offer a patient-friendly and non-invasive administration route.

The significant advantages exhibited by nanomaterials in preclinical studies have posed key questions about their translational potential to clinical applications. Challenges such as scalability, biocompatibility, long-term safety, and regulatory approval stand as major hurdles in transitioning nanomedicines from laboratory bench to clinical bedside. Consequently, a comprehensive re-evaluation of current nanomedicine research themes is imperative to surmount these obstacles and facilitate successful clinical integration.

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