

Novel strategies for targeted delivery of boron carbide nanoparticles to the tumor environment in boron neutron capture therapy

Summary

Boron neutron capture therapy (BNCT) is a type of targeted radiotherapy that involves the destruction of boron-containing cancer cells using a neutron beam. It represents an alternative treatment option for patients with tumors located in hard-to-reach areas and resistant to conventional therapies, such as gliomas, melanomas, as well as head and neck cancers. A key factor in the effectiveness of BNCT is the use of boron-containing compounds, whose role is the selective delivery of high concentrations of the boron-10 isotope (20–35 µg per gram of tumor) to cancer cells while remaining non-toxic to healthy tissues. Moreover, the ability of these compounds to cross the blood–brain barrier is crucial in the treatment of patients with brain tumors. A promising candidate for BNCT is boron carbide (B₄C) in the form of nanoparticles. However, to selectively deliver B₄C to the tumor environment, it is necessary to use carriers or surface modifications that enable this compound to interact specifically with tumor cells, limiting nonspecific effects on normal cells.

The aim of the research conducted as part of the doctoral dissertation was to develop two strategies for the targeted delivery of boron carbide nanoparticles to the tumor environment. The first approach involved functionalizing nanoparticles with antibodies against receptors overexpressed in cancer cells, such as the low-density lipoprotein receptor (LDLR) and the epidermal growth factor receptor (EGFR). The second strategy was based on the use of macrophages as cellular carriers of boron carbide nanoparticles. In this case, their natural abilities to phagocytose, cross the blood-brain barrier, as well as migrate and accumulate within the tumor environment were exploited. Both B₄C delivery strategies represent an original and innovative research trend that has not yet been described in the literature.

The doctoral dissertation consists of a series of five thematically related scientific publications: two review articles and three original research papers. The review article (Wróblewska et al. *Postep Hig Med Dosw*, 2021) summarizes the current state of knowledge on boron neutron capture therapy and progress in the design of compounds and carriers intended for this therapy. Particular attention was paid to boron-rich compounds, among which boron carbide nanoparticles demonstrate great potential. Examples of targeted surface modifications

of B₄C that improved the selectivity of compound delivery to the tumor microenvironment were also discussed.

The original research paper (Rudawska et al. *Int J Nanomed*, 2025) focused on assessing the efficacy of B₄C nanoparticles functionalized with anti-LDLR and anti-EGFR antibodies in the targeted delivery of boron to cancer cells. The obtained results confirmed the accumulation of high boron concentrations in cells expressing both receptors on their surface, with the B₄C anti-LDLR modification proving particularly effective.

The review article (Wróblewska et al. *Int J Nanomed*, 2023) provides an introduction to a second nanoparticle delivery strategy based on the use of macrophages as cellular carriers. This publication presents a detailed characterization of macrophages, discusses the "Trojan horse" strategy, and highlights the potential of macrophages as boron carriers in boron neutron capture therapy.

The collected knowledge allowed for conducting studies on the use of macrophages for the delivery of boron carbide nanoparticles, the results of which were presented in two original research papers (Wróblewska et al. *J Nanobiotechnology*, 2024; Rudawska et al. *bioRxiv*, 2026). Macrophages derived from cell lines and bone marrow cells exhibited a high ability to uptake two boron carbide preparations (B₄C 1 and B₄C 2). However, the smaller nanoparticles (B₄C 1) proved to be more promising due to their minimal impact on cell viability, mobility, and phenotype. Furthermore, bone marrow-derived macrophages loaded with B₄C 1 demonstrated the ability to cross an *in vitro* model of the blood-brain barrier toward a glioma environment.

Research conducted as part of the doctoral dissertation confirmed the effectiveness of delivering boron carbide nanoparticles to the tumor environment, both through targeted surface modification and via macrophage-mediated transport. Moreover, they provide a basis for further research and may be of great importance for the continued development of boron neutron capture therapy. Additionally, considering the unique role of macrophages in the immune response and the originality of the proposed therapeutic strategy, it may represent a novel form of radioimmunotherapy.