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Novel aptamer-based targeted agents for boron neutron capture therapy

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Motivation and Aim: Glioblastoma is the most frequent malignant brain tumor which still remains incurable due to its rapid growth, invasive nature, and resistance to conventional therapies. Boron neutron capture therapy (BNCT) represents a promising radiotherapeutic approach to the treatment of malignant tumors in general and glioblastoma in particular [1]. Successful BNCT needs a boron-containing therapeutic agent for addressed delivery of ^{10}B isotope inside cancer cells, and a source of epithermal neutrons to irradiate and kill boron-containing targets. Polyhedral boranes, namely boron clusters, are very attractive for the purposes of BNCT since they combine high boron content with relative metabolic inertness and low toxicity. Otherwise, cell-specific nucleic acid aptamers seem to be prospective candidates for carrying ^{10}B to tumor cells. Here, we aimed to evaluate the potential of aptamers specific to human glioblastoma cells as boron delivery agents for BNCT.

Methods and Algorithms: The study was carried out using the human glioblastoma cell line U-87 MG as target cells and normal human fibroblasts hFF8 as controls. We formed a set of fluorescently labeled 2'-F-RNA and DNA aptamers that were reported to internalize into the U-87 MG human glioblastoma cells. Their cell penetration was assessed by confocal microscopy. The *closo*-dodecaborate residue was attached to the 5'-end of the aptamer through the click reaction between the 5'-alkyne-modified aptamer and azide-containing derivative of *closo*-dodecaborate [2]. Cell toxicity of aptamer conjugates was examined by the MTT test. Model BNCT experiments *in vitro* were performed on the Tandem-BNCT neutron source (Budker Institute of Nuclear Physics, Novosibirsk, Russia). Their results were assessed by two independent methods: real-time cell analysis and clonogenic assay.

Results: Two 2'-F-RNA aptamers demonstrated specific internalization into glioblastoma U-87 MG glioblastoma cells and entered cell nuclei. *Closo*-dodecaborate conjugates of the aptamers possessed low cell toxicity and showed the same intracellular localization as the parent aptamers. A pre-treatment of the cells by boron-containing aptamer conjugates resulted in the specific decrease of tumor cells viability after neutron irradiation. The effect was comparable to that of ^{10}B-boronophenylalanine taken as a control.

Conclusion: We demonstrated for the first time the specific inhibition of cancer cell proliferation in model BNCT experiments with 2'-F-RNA aptamers loaded by the *closo*-dodecaborate. Taking into account their target specificity, ease of synthesis and a wide

range of chemical approaches for high boron-loading, aptamers represent a very promising basis for engineering novel BNCT agents.

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