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Folate Functionalized Boron Nitride Nanotubes and their Selective Uptake by Glioblastoma Multiforme Cells: Implications for their Use as Boron Carriers in Clinical Boron Neutron Capture Therapy

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Abstract Boron neutron capture therapy (BNCT) is increasingly being used in the treatment of several aggressive cancers, including cerebral glioblastoma multiforme. The main requirement for this therapy is selective targeting of tumor cells by sufficient quantities of ^{10}B atoms required for their capture/irradiation with low-energy thermal neutrons. The low content of boron targeting species in glioblastoma multiforme accounts for the difficulty in selective targeting of this very malignant cerebral tumor by this radiation modality. In the present study, we have used for the first time boron nitride nanotubes as carriers of boron atoms to overcome this problem and enhance the selective targeting and ablative efficacy of BNCT for these tumors. Following their dispersion in aqueous solution by noncovalent coating with biocompatible poly-L-lysine solutions, boron nitride nanotubes were functionalized with a fluorescent probe (quantum dots) to enable their tracking and with folic acid as selective tumor targeting ligand. Initial in vitro studies have confirmed substantive and selective uptake of these nanovectors by glioblastoma multiforme cells, an observation which confirms their potential clinical application for BNCT therapy for these malignant cerebral tumors.

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Introduction

High-grade glioblastoma multiforme is uniformly fatal and largely unresponsive to all available treatments. Patients with these tumors usually survive for <1 year from the time of first diagnosis. Conventional surgical excision, generally limited to the main tumor mass, does not remove the microscopic foci of neoplastic cells that invade the surrounding normal brain substance beyond the main tumor mass, and are responsible for the inevitable tumor recurrence [1]. Conventional radiotherapy cannot ablate completely these tumors [2], since this would require unacceptably high radiation doses that result in severe brain damage [3]. Boron neutron capture therapy (BNCT) is a binary modality therapy that has the potential for effective treatment of many forms of cancers, including cerebral glioblastoma multiforme brain and melanomas [4–6]. BNCT is based on the neutron capture reaction, $^{10}B(n, \alpha)^{7}Li$, where a ^{10}B atom captures a low-energy thermal neutron and spontaneously decays to produce the linear recoiling particles ^{4}He (α particle) and ^{7}Li. In tissues, these particles have short penetration ranges, approximately the width of a single cell (5 μm for ^{7}Li and 9 μm for ^{4}He). As the average linear energy transfer is high (^{7}Li, 162 keV/μm; ^{4}He, 196 keV/μm), this results in densely ionizing radiation restricted to the track of each particle [7, 8]. Thus, the essential requirement for effective BNCT is selective targeting of tumor cells with sufficient quantities of ^{10}B atoms (15–30 μg/g or more) and their irradiation with low-energy thermal neutrons. In theory, BNCT is potentially capable of killing individual cancer cells while sparing the healthy normal parenchyma. Consequently,