to drive angiogenesis and resist therapies, have been identified. BTSCs often drive tumorigenesis by elevating angiogenic factor production. Recognition that angiogenesis is a pathologic hallmark of glioblastoma multiforme (GBM) (**Figure 1A**) and that antiangiogenic agents demonstrate efficacy in GBM animal models led to clinical testing of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), in patients with recurrence. The U.S. Food and Drug Administration (FDA) approved the use of bevacizumab for recurrent glioblastomas in 2009. It was associated with 6-month progression-free survival rates of 36.0%; however, the majority of recurrent GBMs progress after an average of 4 months of treatment. As bevacizumab may target BTSCs by disrupting a perivascular niche and neutralizing secreted VEGF, this drug represents the first FDA-approved anti-BTSC therapy.

Although additional methods of targeting VEGF are also being explored, antagonism of VEGF signaling is not sufficient to prevent tumor progression. In a well-designed research paper published in *Proceedings of the National Academy of Sciences of the United States of America*, Soda et al. reveal a new paradigm for glioblastoma angiogenesis whose main contribution is transdifferentiation of glioblastoma cells into endothelial cells (tumor-derived endothelial cells [TDECs]) (3). They have found that these cells lack VEGF receptors and constitute 20% of the tumor endothelial population. This is a plausible explanation for the resistance of TDECs to antiangiogenesis treatment (2, 3).

However, if there is a transdifferentiation of GBM cells into TDECs, which are the signaling molecules in this context? In the same paper, the authors suggested that hypoxia-inducible factor 1 (HIF-1) is an important enhancer of TDEC differentiation of tumor cells (3). So, could the HIF-1 be a new target? Within this context, Hamsa et al. described the antiangiogenic activity of berberine (**Figure 1B**), a naturally occurring isoquinoline alkaloid present in a number of important medicinal plants (1). They have demonstrated that drastically elevated expressions of HIF and VEGF by tumor cells under hypoxic conditions were decreased after treatment with berberine. Does this suggest a new era in the treatment of glioblastoma? Medicinal plant properties versus GBM?

It should be emphasized that the mechanisms that determine intrinsic resistance of subsets of glioblastomas to antiangiogenic therapy, as well as the mechanisms that develop during follow-up that allow the tumor to eventually progress after an initial response, are extremely important. Elucidating the intermediates in this cell differentiation, the angiocrine modulators between tumor cells and endothelial cells open new trends in the management of the most common and malignant brain tumor. Researchers must open their minds to all therapeutic possibilities.

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Prospects in Boron Neutron Capture Therapy of Brain Tumors

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The concept of boron neutron capture therapy (BNCT) was proposed after both the discovery of the neutron by James Chadwick in 1932 and the work of Maurice Goldhaber concerning the unusual capacity of the boron-10 (^{10}B) isotope to capture large thermal neutrons (**Figure 1**).

The peculiarity of the neutron capture reaction is that radiated high-energy alpha particles have high linear energy transfer and a range of about 5 to 9 microns, which is comparable to cell size (**Figure 2**). Therefore, 80% of the nuclear reaction energy is released inside the cell that contains the neutron-trapping boron.

Enlargement of the transmembrane ionic gradient, the ability to detect ionized boron, and boron-10 delivery remain problematic with BNCT. The expedience and availability of boron-containing compounds and agents for selective delivery to the specimen with the help of boron nitride nanotubes, monoclonal antibodies, liposomal delivery, and immunoliposomal conjugation with endothelial growth factor and

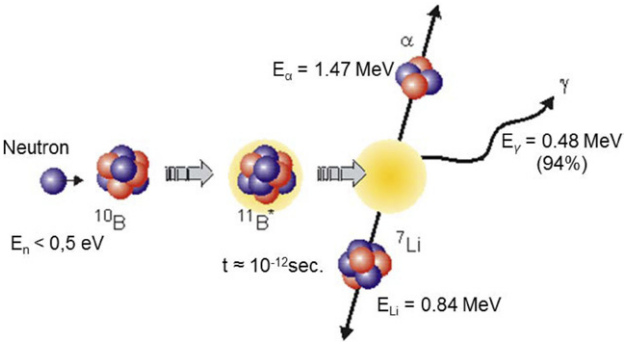

Figure 1. The nuclear reaction of boron neutron capture therapy. The boron-10 (^{10}B) nucleus captures the thermal neutron and emits the lithium-7 (^{7}Li) ion and an alpha-particle in opposite directions.

vascular endothelial growth factor receptors are being actively studied. Pharmacological investigations of boron drugs continue to be of fundamental importance. Characteristics of their accumulation in the tissues, distribution in the tumors of different histological structures, and stages are also subjects of research.

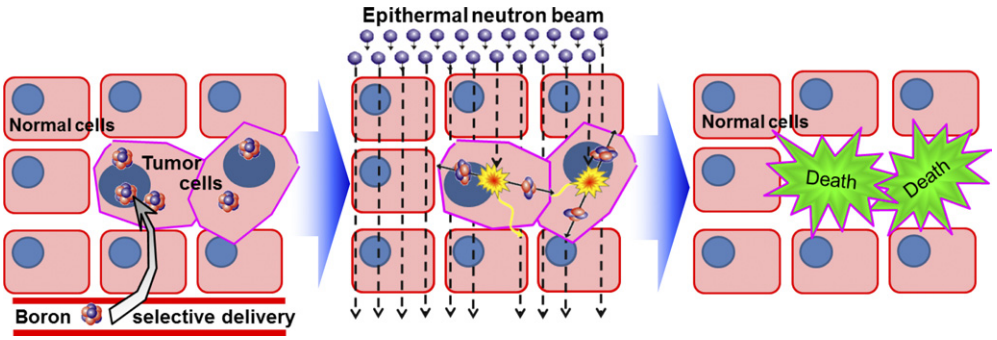

Figure 2. The scheme of boron neutron therapy.

The current priority in BNCT investigation is the analysis of the ultimate and nonlinear effects of neutrons on tissues. Epithermal neutrons possess high values of linear energy transfer and relative biological effectiveness. In regard to tumor damage, this decreases dependence on cell cycle phase and oxygen saturation value, and reduces the probability of reparation of sublethal defects. Thermal neutrons ($E_n < 0.5$ eV) have low penetrating power. Conversely, epithermal neutrons ($0.5 \text{ eV} < E_n < 10$ keV) pass deep into the tissue, where they become thermal. The theoretical advantage of the epithermal beam lies in its ability to irradiate tumor cells that are located deep or some distance from the main tumor site.

New clinical indications and criteria for selection of patients that may benefit from BNCT are being investigated. To date, disseminated melanomas and multifactorial glioblastomas are considered to be conditions generally accepted for BNCT.

For a long time, BNCT remained an experimental treatment because there were no autonomous sources of epithermal neutrons with high-quality beams.

At the Institute of Nuclear Physics, Novosibirsk, Russia, a device capable of producing epithermal neutrons specialized for clinical application was created. It is based on the tandem accelerator with vacuum isolation and near-threshold regimen of neutron emission in the lithium-7 (^{7}Li) (p,n) beryllium-7 (^{7}Be) reaction.

This invention opens new possibilities in the development of neutron capture therapy. The device created in Novosibirsk can be mounted in any oncology clinic. The innovative near-threshold regimen of neutron emission noticeably simplifies the requirements regarding device placement and maintains safety standards. A homogeneous beam of epithermal neutrons was obtained for the first time. The BNCT aspects are being actively studied on the glioblastoma cell model.

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