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Towards carborane-functionalised structures for the treatment of brain cancer

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Teaser: *The development of carborane derivatives with high cancer-cell targeting specificity is key to these materials fulfilling their promise as the clinical BNCT agents of the future.*

Highlights

- BNCT has long been considered a promising technique for the treatment of brain tumours.
- The carboranes represent a most promising class of BNCT agents.
- Progress in the molecular design of carborane-based agents is reviewed.

Boron neutron capture therapy (BNCT) is a promising targeted chemoradiotherapeutic technique for the management of invasive brain tumors, such as glioblastoma multiforme (GBM). A prerequisite for effective BNCT is the selective targeting of tumour cells with ^{10}B-rich therapeutic moieties. To this end, polyhedral boranes, especially carboranes, have received considerable attention because they combine a high boron content with relative low toxicity and metabolic inertness. Here, we review progress in the molecular design of recently investigated carborane derivatives in light of the widely accepted performance requirements for effective BNCT.

The principles of boron neutron capture therapy

BNCT is a two-step targeted chemoradiotherapeutic technique that involves the selective delivery of ^{10}B-rich agents to cancer cells for the purpose of their selective destruction through subsequent irradiation with low-energy neutrons, which initiate highly localised nuclear fission reactions that do not damage surrounding tissue (Figure 1). Integral to successful BNCT is the selective uptake of a therapeutic dose of the boron-containing agent by cancer cells. At a neutron fluence (see Glossary) of 10^{12} neutrons/cm^2, and ignoring the microdistribution of the drug, this is calculated at 30 mg of ^{10}B/g of tumour (approximately 10^9 atoms of ^{10}B per cell) [1]. To minimise damage to the vascular endothelial cells and white matter, the tumour:blood and tumour:surrounding tissue concentration ratios must both be higher than 3:1 [2]. Monte Carlo simulations have shown that boron accumulated within the cell nucleus has little effect on neighboring cells and it is more effective in inducing cell death (*ca*. 2.5×) than the same amount of boron distributed uniformly within the entire cell [3]. This suggests that the mechanism of neutron bombardment-initiated damage is determined by the intracellular location occupied by the boronated agent. Similarly, calculations have shown that boron localised at the cell surface has a *ca*. 10% lower killing effect than an equimolar quantity of boron that is uniformly distributed within the entire cell [3]. Irradiation of the localised boronated agent with a beam of thermal neutrons leads to each ^{10}B atom capturing a neutron to form ^{11}B*, which in turn undergoes nuclear fission to release the energy that induces localised tumour cell necrosis. Consequently, the nuclear reaction of ^{10}B can effect the selective destruction of malignant tumour cells without compromising the surrounding healthy tissue. The probability of a nuclide capturing a neutron is enumerated by the 'neutron-capture cross section' (σ_{th}, measured in barns; 1b = 10^{-24} cm^2). Offering a good compromise between toxicity and stability, ^{10}B is characterised by σ_{th} = 3838 b [4]. Compared with X-ray methods, the use of neutron beams is preferred for treatments involving hypoxic cells [5] because the oxygen enhancement ratio (the ratio of radiation doses required to effect the same rate of cell death under oxic as under hypoxic conditions) of neutrons is 1.6, which is lower than that of X-rays (2.5–3.0).