

REVIEW

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Boron delivery agents for neutron capture therapy of cancer

Rolf F. Barth^{1*}, Peng Mi² and Weilian Yang^{1,3}

Abstract

Boron neutron capture therapy (BNCT) is a binary radiotherapeutic modality based on the nuclear capture and fission reactions that occur when the stable isotope, boron-10, is irradiated with neutrons to produce high energy alpha particles. This review will focus on tumor-targeting boron delivery agents that are an essential component of this binary system. Two low molecular weight boron-containing drugs currently are being used clinically, boronophenylalanine (BPA) and sodium borocaptate (BSH). Although they are far from being ideal, their therapeutic efficacy has been demonstrated in patients with high grade gliomas, recurrent tumors of the head and neck region, and a much smaller number with cutaneous and extra-cutaneous melanomas. Because of their limitations, great effort has been expended over the past 40 years to develop new boron delivery agents that have more favorable biodistribution and uptake for clinical use. These include boron-containing porphyrins, amino acids, polyamines, nucleosides, peptides, monoclonal antibodies, liposomes, nanoparticles of various types, boron cluster compounds and co-polymers. Currently, however, none of these have reached the stage where there is enough convincing data to warrant clinical biodistribution studies. Therefore, at present the best way to further improve the clinical efficacy of BNCT would be to optimize the dosing paradigms and delivery of BPA and BSH, either alone or in combination, with the hope that future research will identify new and better boron delivery agents for clinical use.

Keywords: Boron delivery agents, Neutron capture therapy, Brain tumors, Head and neck cancer, Melanoma

Background

Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when the stable isotope boron-10 (^{10}B) is irradiated with either low-energy (0.025 eV) thermal neutrons or, for clinical studies, epithermal neutrons (10,000 eV), which become thermalized as they penetrate tissue. This results in the production of high-linear energy transfer (LET) alpha (α) particles (^4He) and recoiling lithium-7 (^7Li) nuclei (Fig. 1a). In order to be successful, $\sim 20 \mu\text{g/g}$ of ^{10}B per weight of tumor must be selectively delivered to the tumor cells ($\sim 10^9$ atoms/cell), and enough neutrons must be absorbed by them to sustain a lethal $^{10}\text{B}(n, \alpha)^7\text{Li}$ capture reaction [1]. Since α particles have very short path-lengths (5–9 μm) their destructive effects are limited to

boron-containing cells (Fig. 1b). In theory, α particles can selectively destroy tumor cells and spare adjacent normal cells. Clinical interest in BNCT has focused primarily on high grade gliomas [2–5], patients with recurrent tumors of the head and neck region [6–13] who have failed conventional therapy, and a much smaller number of patients with cutaneous [14–17] or extra-cutaneous [18] melanomas. Because BNCT primarily is a biologically, rather than a physically, targeted type of particle radiation therapy, it should be possible to selectively destroy tumor cells infiltrating normal tissue. The requirement, however, is that sufficient amounts of ^{10}B and thermal neutrons are delivered to the site of the tumor. Up until 2014, the source of these neutrons has been specially designed nuclear reactors, but recently a number of companies in Japan [19] and the United States [20] have fabricated accelerator-based neutron sources, several of which are either being or will be evaluated in Phase I/II clinical trials.

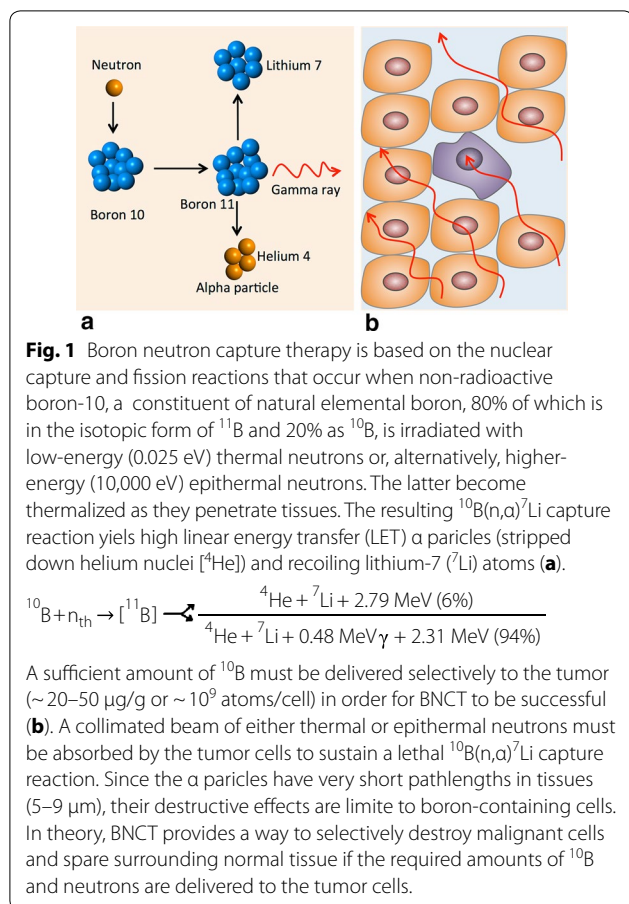
In this review, we will focus on the two drugs that have been used clinically for BNCT and their limitations, as

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well as a variety of low and high molecular weight boron delivery agents that have been evaluated in vitro and in experimental animal tumor models, but have not been evaluated clinically. Interested readers are referred to several more comprehensive reviews for more detailed information relating to boron delivery agents [21–24].

General requirements for boron delivery agents

The most important requirements for a BNCT delivery agent are: (1) low intrinsic toxicity; (2) high tumor uptake ($\sim 20\text{--}50 \mu\text{g } ^{10}\text{B}$) and low normal tissue uptake, ideally with a tumor:normal tissue and tumor:blood boron concentration ratios of $>3:1$; and (3) relatively rapid clearance from blood and normal tissues, and persistence in tumor for at least several hours during neutron irradiations. Approximately 50 years ago, research on the development of boron-containing delivery agents for BNCT began in the laboratory of Albert Soloway and his co-workers at the Massachusetts General Hospital in Boston. A large number of low molecular weight boron compounds were synthesized, from which the first second-generation compound emerged, a polyhedral borane anion, first synthesized by Miller et al. [25],

sodium mercaptoundecahydro-*closo*-dodecaborate ($\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$), commonly known as sodium borocaptate or BSH [26]. BSH first was used clinically by Hatanaka [2, 27] and Nakagawa [3] in Japan, and by Sauerwein and his research team in Europe [28, 29] in a Phase I/II clinical trial in Petten, The Netherlands, to treat patients with high grade gliomas.

A second boron compound, first synthesized by Snyder et al. in 1958 [30], was introduced by Mishima and co-workers in Japan, a boron-containing amino acid (L)-4-dihydroxy-borylphenylalanine, known as boronophenylalanine or BPA [14, 15, 31]. Based on the assumption that BPA would preferentially be taken up by melanin-synthesizing cells, it initially was used to treat several patients with cutaneous melanomas by injecting it perilesionally [14, 15, 31]. Experimental data of Coderre et al. [32] at the Brookhaven National Laboratory in the United States demonstrated that BPA also was taken up by other histologic types of tumors, including a rat brain tumor, the 9L gliosarcoma. Based on this observation, BPA, as a fructose complex (BPA-F) which significantly increased its water solubility [33], very quickly entered into clinical use for the treatment of patients with high grade gliomas. A number of clinical trials were initiated, first in the United States [34, 35] and subsequently in Finland [36, 37], Sweden [38, 39] and Japan [4, 5, 40–42], and these demonstrated that BPA was therapeutically more effective than BSH. It subsequently became the drug of choice for clinical BNCT of patients with high grade gliomas [2–5] and recurrent tumors of the head and neck region [6–13, 43]. Interested readers are referred to two recent reviews that discuss the clinical results obtained using BNCT to treat brain and head and neck tumors [44, 45].

The major problem with both BSH and BPA is the significant variability in tumor uptake, especially in brain tumors. This was clearly demonstrated by Goodman et al. [46] in a biodistribution and pharmacokinetic study involving 20 patients with high grade gliomas. Tumor boron concentrations varied both within different regions of the tumor, as well as among patients who received the same dose of BSH. Similar variability was reported by Koivunoro et al. [47] in a group of 98 patients with gliomas who received BPA-F, although the blood and estimated normal brain boron concentrations were in a much narrower range. This variability in the tumor uptake of BPA and BSH most likely was due to the marked and complex intratumoral histologic, genomic, and epigenomic heterogeneity within high grade gliomas [48], as well as intertumoral variability from one patient to another. Experimental animal studies carried out by Barth and Yang and their co-workers using the F98 rat glioma model revealed similar variability in tumor boron concentration for both BSH and BPA in glioma-bearing

rats. This suggested that the broad range in mean survival time (MST) following BNCT was a consequence of the variability in tumor uptake and microdistribution [49–52]. Similar variability also has been described in a nude rat model for neutron capture therapy of intracerebral melanoma [53].

Third-generation boron delivery agents

Since neither BSH nor BPA adequately fulfills the criteria indicated in the preceding section on general requirements, there has been a pressing need to develop new boron delivery agents. With the development of improved synthetic techniques and an increased awareness of the requisite biochemical properties, a number of new boron delivery agents have emerged. The major challenge for their development has been the requirement for selective tumor cell targeting and the delivery of therapeutic concentrations of boron with minimal normal tissue uptake and retention. The effective killing of glioblastoma cells in the presence of normal brain tissue represents an even greater challenge than for malignancies at other anatomic sites. This is due to an additional biological impediment, the blood–brain barrier (BBB) [54, 55], which effectively excludes agents with molecular weights greater than 200 Da, and the highly infiltrative properties of glioma cells and their genomic heterogeneity.

Recent efforts to improve the selectivity of boron delivery agents has involved incorporating them into tumor-targeting moieties, such as unnatural amino acids, polyamines, peptides, proteins, antibodies, nucleosides, sugars, porphyrins, liposomes and nanoparticles [44]. A partial list of third generation boron delivery agents of low and high molecular weight is summarized in Table 1 and shown in Fig. 2. Among the low molecular weight boron delivery agents are boronated natural amino acids

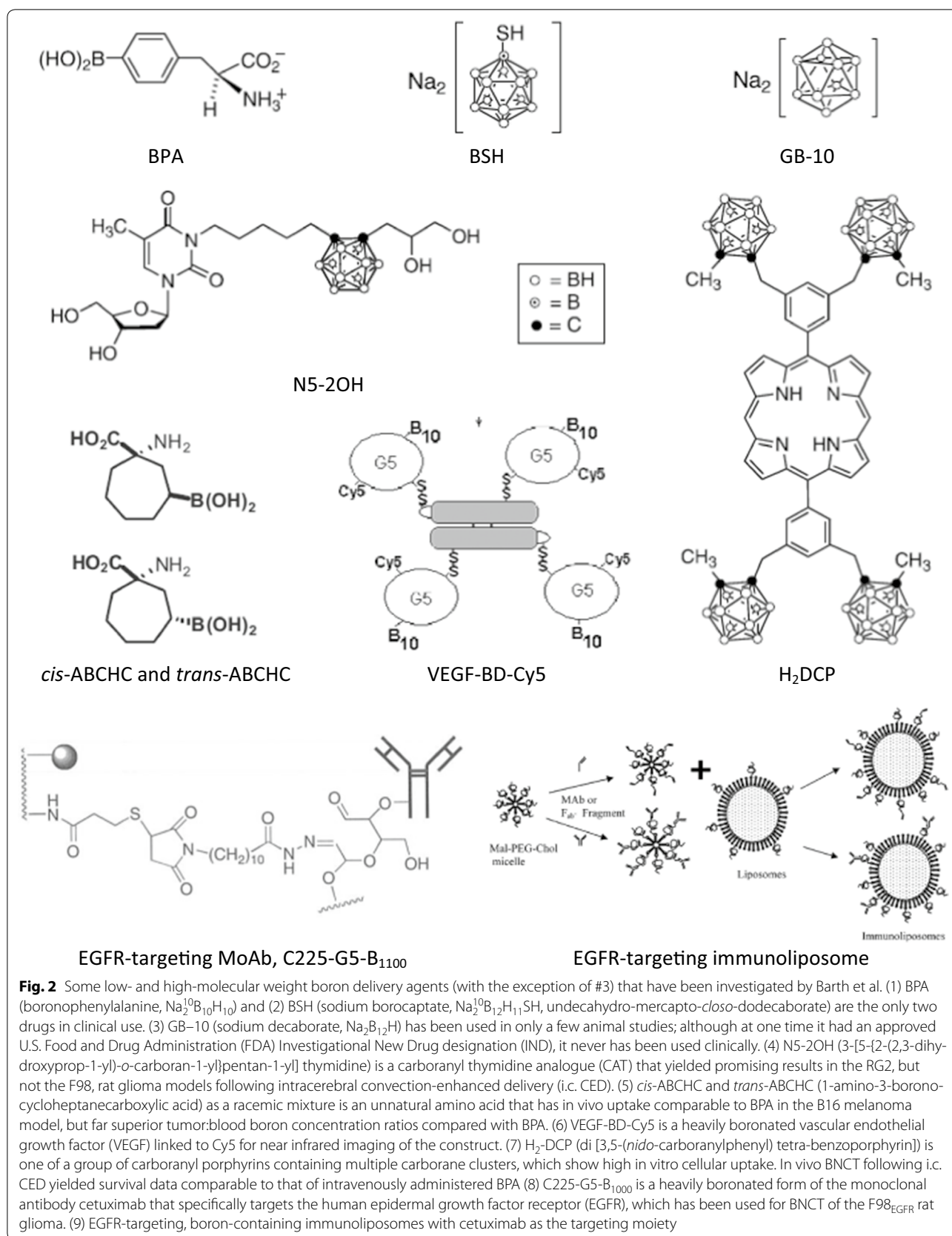
(i.e. BPA derivatives with higher percentage of boron by weight), as well as boronated derivatives of other amino acids such as aspartic acid, tyrosine, cysteine, methionine and serine [56–58]. Boron-containing unnatural amino acids also have been investigated because of their higher metabolic stability compared with the natural ones. The boronated derivatives of 1-aminocyclobutane-1-carboxylic acid (ABCHC) and 1-amino-3-boronocyclopentanecarboxylic acid (ABCPC) are examples of such compounds [57–60] (Fig. 2). Higher tumor and tumor:brain boron concentration ratios were obtained with ABCPC, but the tumor:blood ratios were comparable to that of BPA [61]. Unfortunately, no further animal studies have been carried out at the time of this writing on this promising class of compounds. Boron-containing linear and cyclic peptides conjugated to sodium borocaptate have been investigated because they are usually non-immunogenic, easy to synthesize, and often show low toxicity and high tissue penetrating properties [62]. Of particular interest are peptide ligands for over-expressed receptors on tumor cells, such as the vascular endothelial growth factor receptor (VEGFR) [63] (Fig. 2), somatostatin receptors and the epidermal growth factor receptor (EGFR and EGFR_{VIII}) [64–66] (Figs. 2, 3). However, the major problem relating to VEGF as a targeting moiety is that it would require repeated applications of BNCT to be effective. EGFR on the other hand is variably expressed on glioma cells either in its wildtype form or its mutant variant, EGFR_{VIII}.

Boron-containing purines, pyrimidines, thymidines, nucleosides and nucleotides also have been investigated as BNCT delivery agents, in particular 3-carboranyl thymidine analogues (3CTAs), which specifically target thymidine kinase-1 (TK1)-expressing tumor cells [67–69]. For example, in vitro studies of the thymidine derivative

Table 1 Examples of new low- and high-molecular weight boron delivery agents currently under evaluation

Boric acid [139]	Boronated VEGF [64]
Boron-containing immunoliposomes [101, 103] and liposomes [90, 91, 93, 94, 102, 104, 105]	Boronated unnatural amino acids [57, 61–64]
Boron-containing Lipiodol [143–145]	Boron-containing nanoparticles [140–142]
Boron nitride nanotubes [147–149]	Carboranyl nucleosides [70, 146]
Boronated co-polymers [85, 86]	Carboranyl porphyrazines [139]
Boronated cyclic peptides [62]	Carboranyl thymidine analogues [70–72]
Boronated DNA intercalators [77]	Decaborone (GB10) [131, 143]
Boronated EGF [82, 83] and anti-EGFR MoAbs [67–69, 150]	Dodecaborate cluster lipids and cholesterol derivatives [144]
Boronated polyamines [147, 151]	Dodecahydro-closo-dodecaborate clusters [144]
Boronated porphyrins [74–78]	Linear and cyclic peptides [65]
Boronated sugars [152]	Polyanionic polymers [86]
	Transferrin-polyethylene glycol liposomes [140]

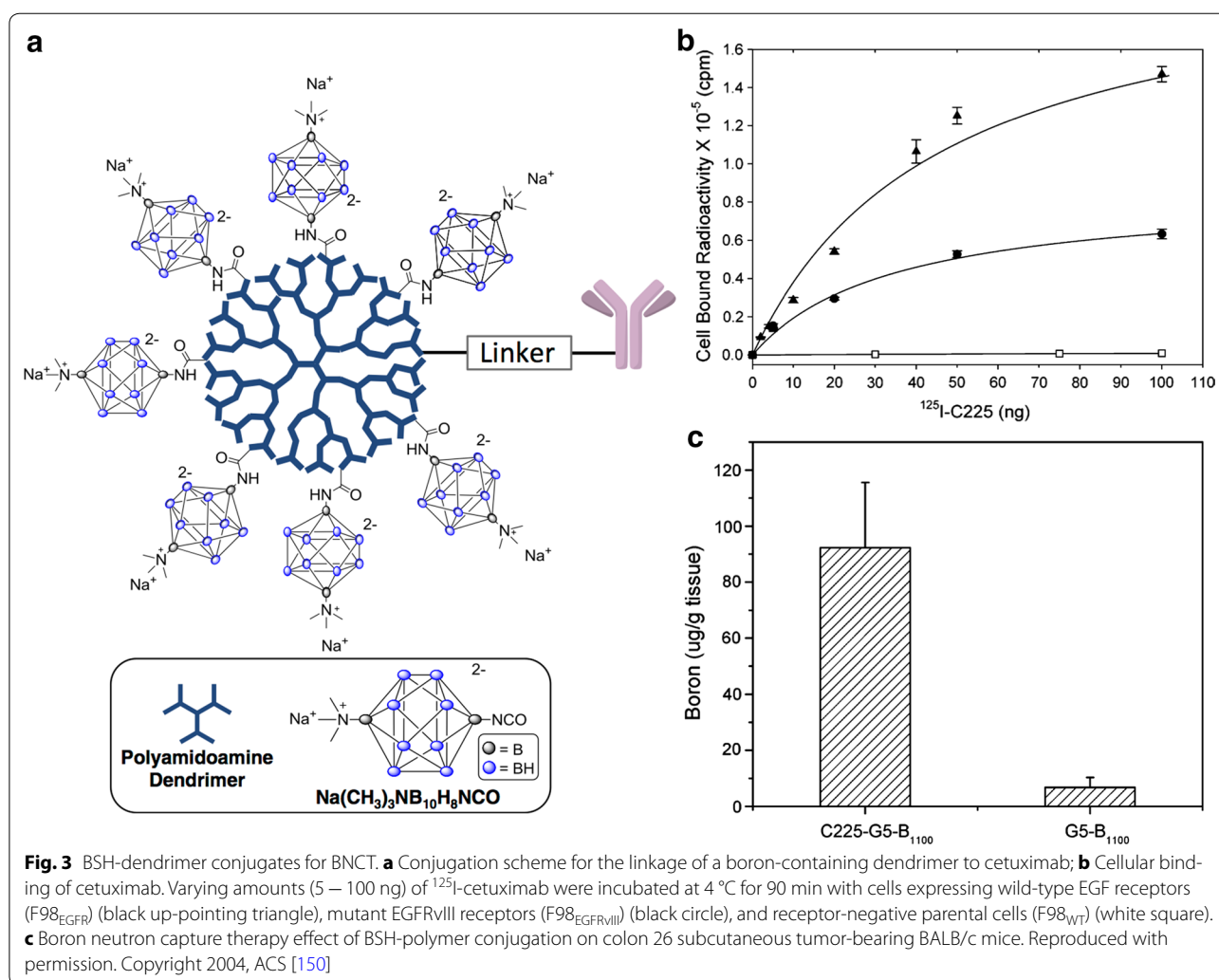
The delivery agents are listed alphabetically and not in any order indicating their potential usefulness for BNCT. None of these agents have been evaluated clinically. BNCT boron neutron capture therapy, EGF epidermal growth factor, EGFR epidermal growth factor receptor, MoAbs monoclonal antibodies, VEGF vascular endothelial growth factor



designated N5-2OH (Fig. 2) demonstrated selective tumor uptake, a high rate of phosphorylation and low toxicity [67], which led to in vivo biodistribution and BNCT studies in brain tumor-bearing rats. Convection enhanced delivery (CED), by which therapeutic agents are delivered directly to the brain and completely bypass the BBB [70], has been an effective way to deliver some boron compounds [68, 71] and high molecular weight bioconjugates to brain tumor-bearing rats [64–66]. CED of N5-2OH to rats bearing intracerebral RG2 gliomas was effective for the selective delivery of therapeutic concentrations of boron to tumors with very high tumor:brain and tumor:blood ratios and without any concomitant toxicity [68]. Following BNCT, a significant prolongation in the MST of tumor-bearing rats was observed [68]. However, similar studies carried out using the almost identical F98 rat glioma, which also expressed amplified TK1, only produced a modest increase in MST

[72], suggesting that N5-2OH may not be as effective as a boron delivery agent as was originally thought [68].

Boron-containing porphyrin derivatives (porphyrins, chlorins, bacteriochlorins, tetrabenzoporphyrins, and phthalocyanines) have been studied extensively due to their low toxicity and natural affinity for tumors [73–75]. Examples of such compounds are BOPP [75], CuTCPP [21], and H₂DCP [71] (Fig. 2). Porphyrin derivatives have been shown to deliver therapeutic amounts of boron to tumor bearing mice and rats, but as reported by Kawabata et al., this may not be localized in tumor cells [71]. In vivo biodistribution studies, carried out 24 h following intracerebral administration by means of CED to F98 glioma bearing rats, revealed unusually high tumor boron concentrations (~100 µg/g). Surprisingly, the MST 5-6 weeks following tumor cell implantation were very similar to those obtained using BPA, which attained much lower boron concentrations. Histologic



examination of the brains of rats that received the boronoporphyrin compounds, followed by BNCT, revealed that they were localized in macrophages rather than tumor cells, thereby providing an explanation for the much lower than expected MST [71]. Further synthetic studies will be required to design porphyrin compounds that would have decreased affinity for macrophages and increased tumor cell uptake.

Other boron-containing DNA binding molecules, including alkylating agents, DNA intercalators, minor-groove binders and polyamines, have been investigated [76]. For example, derivatives of aziridines, acridines, phenanthridines, various Pt(II) complexes and carbonyl polyamines have been described [22–24]. These compounds sometimes show low tumor selectivity and significant toxicity, in part due to their multiple cationic charges and/or ability for binding to DNA of normal cells. Boron-containing sugars, including derivatives of glucose, mannose, ribose, galactose, maltose and lactose, also have been investigated [77]. This class of molecules usually have low toxicity, but also unfortunately low tumor uptake, in part due to their hydrophilicity and rapid clearance from tissues.

Among the high molecular weight boron delivery agents, monoclonal antibodies (MoAbs), polymers, dendrimers, liposomes and nanoparticles have been the most intensively studied. MoAbs are a very promising class of tumor-targeting agents due to their high specificity for molecular targets such as EGFR and EGFR_{VIII} [65, 66] and the ligands EGF [78] and VEGF [63]. Extensive studies have been carried out by Barth, Wu and Yang and their co-workers using a heavily boronated precision dendrimer with five dendritic generations that has been linked by means of heterobifunctional reagents to the EGFR targeting MoAb cetuximab (ErbixTM) [65], the EGFR_{VIII} targeting MoAb L8A4 [64] or EGF [79] itself (Fig. 3). These bioconjugates were administered intracerebrally by means of CED to rats bearing receptor positive F98 gliomas that have been transfected with the human gene encoding EGFR or EGFR_{VIII} (F98_{EGFR} or F98_{EGFR_{VIII}}) [64–66, 79, 80]. The best survival data were obtained in F98_{EGFR} glioma bearing rats when these bioconjugates were combined with intravenous administration of BPA, yielding a two to threefold increase in MST compared to irradiated controls [64–66, 80]. However, these bioconjugates would have been ineffective against F98 wildtype tumors (F98_{WT}), which do not express amplified EGFR. If similar studies had been carried out in rats bearing composite tumors consisting of F98_{EGFR} and F98_{WT}, we would predict only a modest increase in MST.

Finally, as recently reported by Sun et al. [81], it is noteworthy that a MoAb directed against the stem cell marker CD133, which frequently is expressed on glioma cells,

could be used to deliver a heavily boronated dendrimer to specifically target this cell population, both in vitro and in vivo. A significantly longer survival time was seen in BALB/c mice bearing intracerebral CD133 + SU2 glioma cells compared to that of CD133 – SU2 cells. These results suggest that further studies using CD133 targeting, boron containing bioconjugates are warranted to evaluate their potential.

Polymers are alternative carriers for boron compounds, and linkage to them could improve the solubility and pharmacokinetics of these compounds by increasing their circulation half-life and tumor accumulation [82]. BPA is a hydrophobic boron compound, whose cellular uptake is dependent upon the L-amino acid transporter system [83], and conjugation to polymers might also increase its solubility as had complexation with fructose [33]. For example, boronated cationic copolymers, composed of different ratios of acrylamide, N-acryloyl-3-aminophenylboronic acid and N-acryloyl-diaminoethane (the cationic moiety), have been synthesized as delivery agents for boronic acids (Fig. 4) [84]. The molecular weight of the resulting tri-block polymer ranged from 9.98 to 10.21 kDa, which resulted in 14–21 µg/g of boron per gram tumor with an increased cationic monomer ratio in tumor versus normal peri-colonic tissue following intravenous injection of boronic polymers. However, cationic polymers can trigger serious side effects in vivo, such as the induction of cell necrosis via impairment of Na⁺/K⁺-ATPase, thereby resulting in an inflammatory response [85]. Therefore, some polyanionic polymers have been evaluated, such as PEGylated-polyglutamic acid, which has been synthesized by conjugating BSH via a disulfide bond [86]. BSH is hydrophilic and has a higher boron content than BPA, but lower tumor uptake and retention due to its negative charge and low molecular weight. Cellular uptake was significantly improved by conjugating BSH with PEGylated-polyglutamic acid (PEG-*b*-P(Glu-BSH)), which increased tumor cell uptake within 1 h and resulted in a five-fold increase in the tumor boron concentration compared to that of BSH at 24 h [86, 87]. PEG-*b*-P(Glu-BSH), was administered intravenously to BALB/c mice bearing subcutaneous implants of the Colon-26 (C26) carcinoma cell line. This resulted in 70–90 µg of B¹⁰ per g tumor after a single intravenous injection at the dose of 50 mg/kg with a tumor:blood ratio of 20:1. In vivo BNCT was carried out 24 h after intravenous injection of PEG-*b*-P(Glu-BSH) to tumor-bearing mice, indicating enough ¹⁰B was delivered to eradicate the tumor. Based on these studies it was concluded that Glu-BSH appeared to be superior to BSH, as evidenced by increased tumor:normal tissue ratios and an improved tumor:blood ratio. However, high uptake in non-target organs [88] and questions relating to their

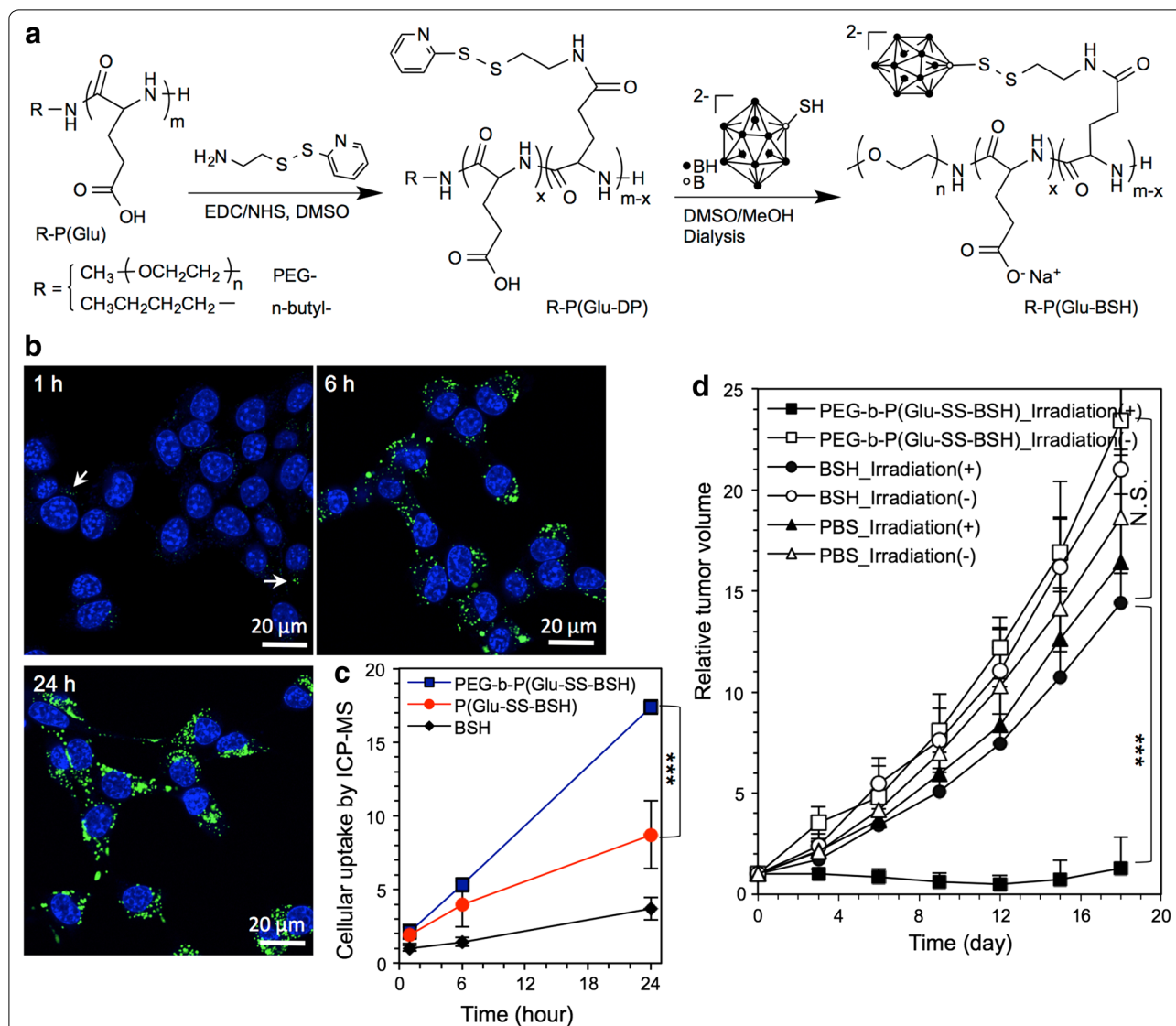


Fig. 4 BSH-polymer conjugates for tumor BNCT. **a** Synthetic scheme of BSH-polymer conjugates [PEG-*b*-P(Glu-SS-BSH) and P(Glu-SS-BSH)]; **b** Time-lapsed cellular uptake of PEG-*b*-P(Glu-SS-BSH) by C26 cancer cells was investigated by confocal laser scanning microscopy (CLSM). Both PEG-*b*-P(Glu-SS-BSH) and P(Glu-SS-BSH) were labeled with Alexa488 (green color), and their dose was 20 $\mu g/mL$ on a BSH basis, while the nuclei were stained with Hoechst (blue color). **c** Relative cellular uptake of BSH, PEG-*b*-P(Glu-SS-BSH) and P(Glu-SS-BSH) was measured by inductively coupled plasma mass spectrometry (ICP-MS). The C26 cancer cells were exposed to BSH, PEG-*b*-P(Glu-SS-BSH) and P(Glu-SS-BSH) for 1, 6 and 24 h ($n = 3$), at a dose of 100 $\mu g/mL$ on a BSH basis, while the results were measured by ICP-MS and normalized by comparing with the cellular uptake of BSH at 1 h. The data are expressed as the mean \pm SD, *** $P < 0.001$. **d** Tumor growth ratio of C26 subcutaneous tumors in BALB/c mice that were irradiated with thermal neutrons ($1.6\text{--}2.2 \times 10^{12}$ neutron/cm²) at Kyoto University Reactor (KUR) for 1 h after intravenous injection of phosphate buffered saline (PBS), BSH, and BSH-polymer conjugates for 24 h at a dose of 100 mg/kg on a BSH basis. Reproduced with permission. Copyright 2017, Elsevier [86]

ability to traverse the BBB must be evaluated before biodistribution studies in larger animals are initiated. Recently, functionalized dodecaborate has been linked to albumin and, following intravenous administration, it was effective in achieving tumor targeting and enhanced efficacy against subcutaneous implants of the murine C26 colon carcinoma [89]. This suggested that it might be

useful as a delivery agent for extracranial tumors such as head and neck cancer and melanomas.

Liposomes, which are vesicles containing an aqueous volume entirely enclosed by a lipid bilayer [90], have been extensively studied, for more than 35 years as potential boron delivery agents [86, 91–98]. The compound $Na_3[1-(2'-B_{10}H_9)-2-NH_3B_{10}H_8]$ has been incorporated into the core of liposomes (Fig. 5) and this subsequently

was followed by two in vivo studies in mice bearing the EMT6 mammary tumor. The tumor boron concentration in the latter was $\sim 40 \mu\text{g/g}$ at 54 h after a single intravenous injection, after which it gradually decreased [98, 99]. In both studies [97, 98], following BNCT there was slower tumor growth compared to that of the control groups. Boron compounds such as these also can be conjugated to lipids to form boron-loaded liposomes with boron concentrations of 150 ppm. Their in vitro tumoricidal effects also have been demonstrated following neutron irradiation [97].

Targeting moieties such as MoAbs [92], antibodies directed against carcinoembryonic antigens (CEA) [100], transferrin [101], and EGFR [102] also have been introduced on the surface of liposomes to specifically target tumor cells. These immunoliposomes could deliver low molecular weight hydrophobic agents such as BSH that have been incorporated into their lipid bilayers [102, 103], and liposomes can transport large numbers of boron-containing molecules intracellularly, resulting in high tumor boron uptake [104]. Liposomes also have been extensively investigated as delivery agents for a variety of polyhedral boron anions and these studies are described in detail elsewhere [105]. High tumor boron concentrations were attained in vitro when polyhedral boron anions were encapsulated in tumor-selective unilamellar liposomes, and their in vivo therapeutic efficacy has been demonstrated in EMT6 tumor bearing mice [93]. Linkage of boron-containing liposomes to the MoAb cetuximab (C225 or ErbituxTM) resulted in specific in vitro molecular targeting of EGFR expressing F98_{EGFR} glioma cells [102]. Boron-containing lipids bearing covalently-bound boron clusters also have been described [105, 106]. These nanoparticles showed no leakage of the encapsulated boron compounds and had the capability of delivering high tumor payloads of boron in mice bearing subcutaneous gliomas and increased survival times following BNCT [106, 107]. However, their large size and high molecular weight would preclude their passage across the BBB in rodents bearing intracranial tumors unless there was disruption of the BBB. This could be accomplished by such methods as the intra-carotid infusion of a hyperosmotic solution of mannitol [49–52], focused ultrasound [108, 109], or direct intratumoral administration by means of CED [64, 110]. Despite all of their potential advantages, boron containing liposomes have yet to be evaluated in animals other than rodents, and their clinical use as boron delivery agents is still to be determined [86, 111].

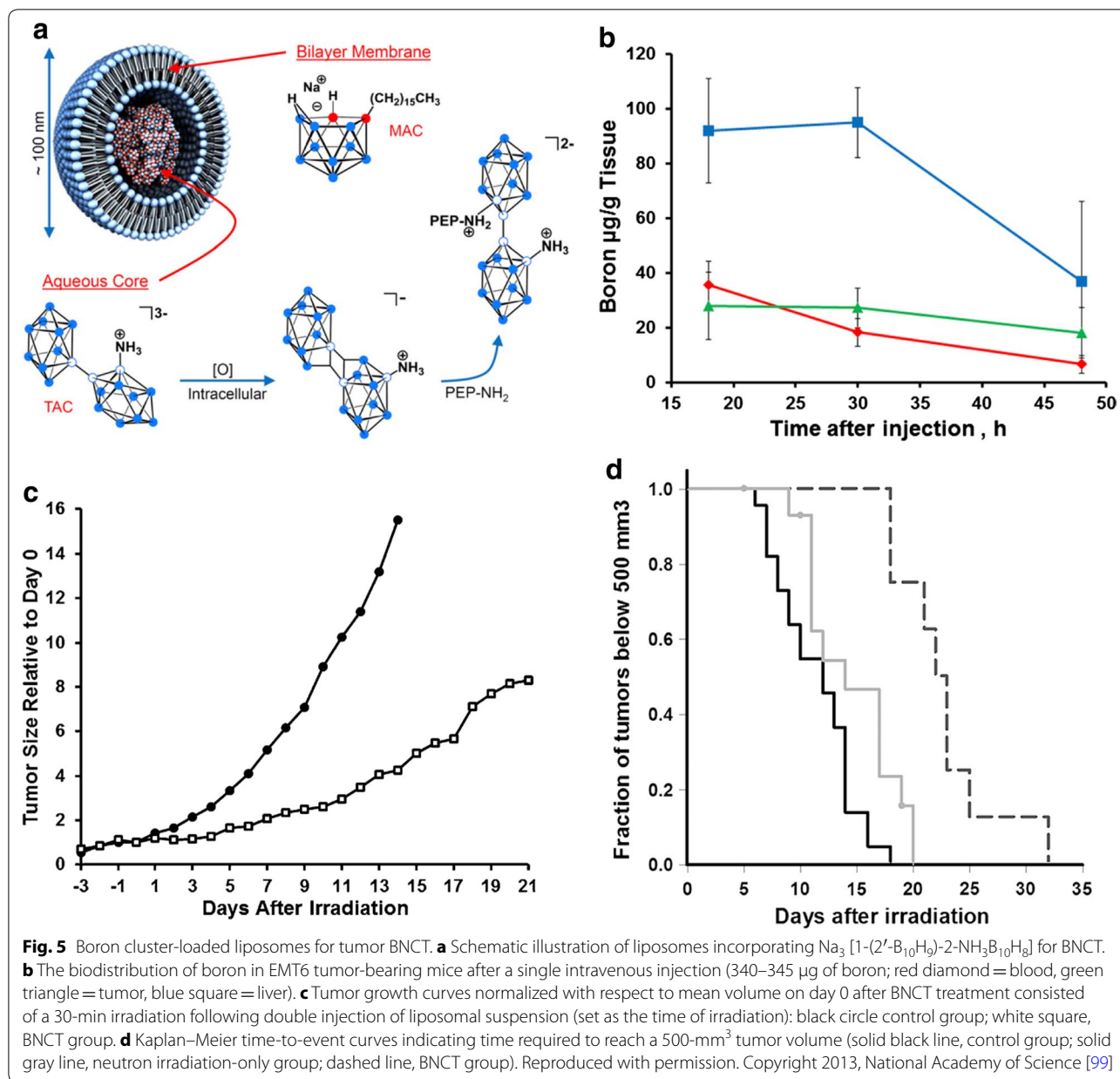
Polymeric nanoparticles have been evaluated for drug delivery to metastatic tumors [112] and as potential delivery agents for gadolinium neutron capture therapy (Gd-NCT) [113–115]. Boron-containing micelles were shown to have improved stability, blood circulation time,

and tumor accumulation [116]. Recently, boron clusters containing redox nanoparticles have been developed, which have reactive oxygen species scavenging ability, high therapeutic efficacy and minimal side effects (Fig. 6) [117]. They were formed by static interaction of the positively charged BSH-conjugated polymers with the positively charged polymers with redox-responsive groups. These nanoparticles had an extended circulation time in blood and increased uptake in C26 tumors with over 5% of the injected dose per gram tumor at 48 h. They effectively suppressed the tumor growth following BNCT when administered at a dose of 15 mg/kg. In addition, these micelles also could be decorated with folic acid on their surface to increase tumor-specific targeting [118, 119] and achieve higher intracellular boron concentrations [120].

Ending on a positive note, the single most practical major advance in the development of boron delivery agents has been described by Kabalka et al. [121, 122] and Imahori et al. [123, 124]. They have labeled BPA with fluorine-18 for positron emission tomography (PET) in order to determine the tumor uptake of BPA and thereby improve treatment planning [124]. It should be pointed out, however, that PET is usually performed prior to surgical resection of the primary tumor in the case of high grade gliomas, and therefore the imaging data may not reflect the uptake of ¹⁸F-BPA by residual or recurrent tumor that would be treated by means of BNCT. Nevertheless, ¹⁸F-BPA PET at least provides some data on the macroscopic uptake of BPA but not on the cellular uptake by individual or clusters of tumor cells, which are too small to be identified by any real time imaging techniques. At present, cellular and subcellular localization of boron can be determined by means of secondary ion mass spectrometry [125–127] or alpha track autoradiography [128] which would allow more accurate dosimetry, but unfortunately these techniques cannot be carried out in real time. Finally, boron compounds also have been conjugated to diethylene-triamine-penta-acetic acid gadolinium (III) dihydrogen (Gd-DTPA) to form a potential theranostic system (Gd/B-NPs) with β -cyclodextrin [129] for tumor localization by MRI and the determination of boron concentrations [130].

Conclusions

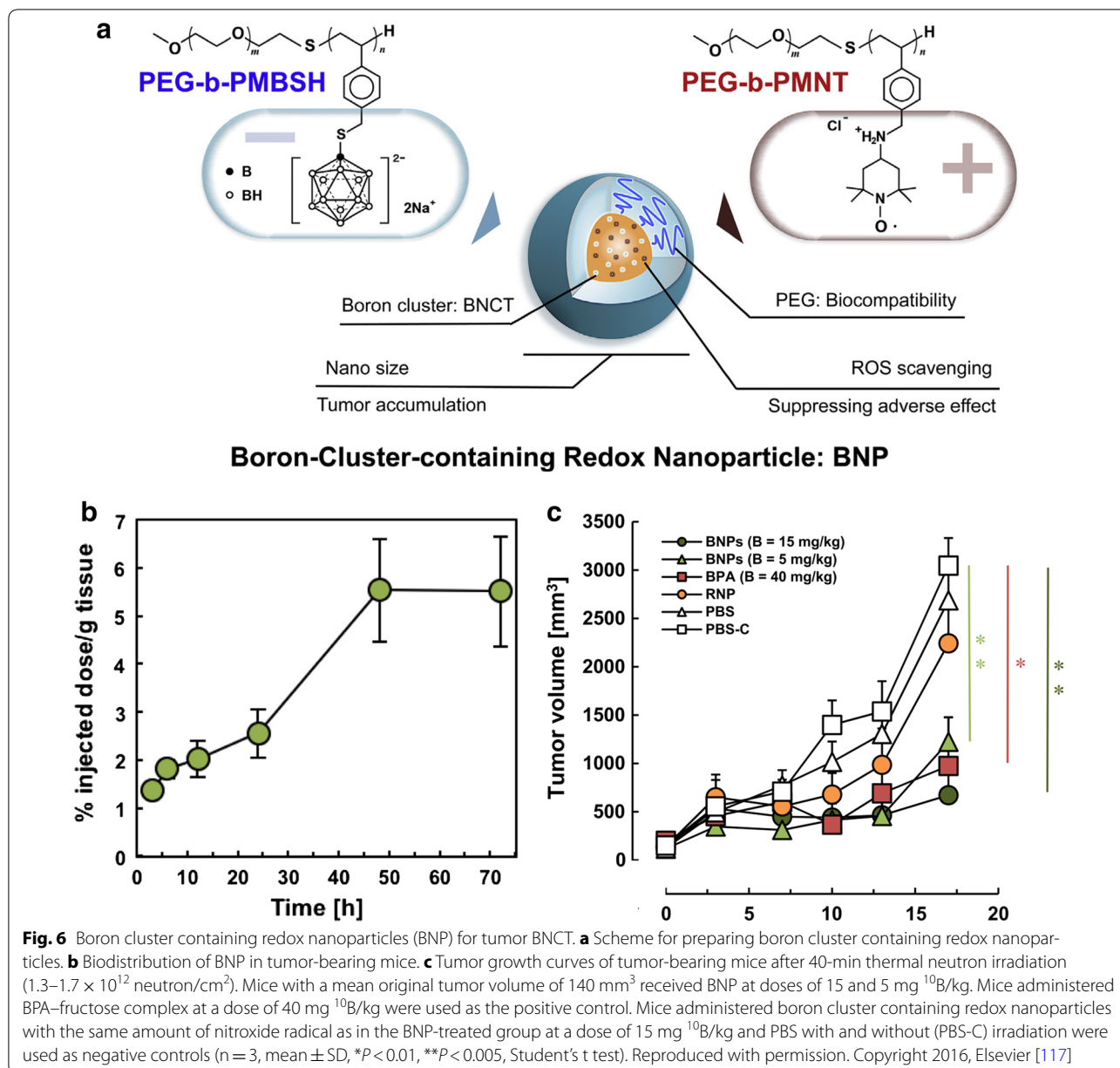
Why has it been so difficult to develop new boron delivery agents for BNCT? Clearly, it has not been for a lack of trying, as evidenced by the voluminous literature beginning in the 1970s on their design and synthesis, as summarized in a number of reviews [21–24]. However, there are still only two drugs in clinical use, BSH and BPA. Objectively, the challenges are much more difficult



than the design of chemotherapeutic or tumor imaging agents. Boron delivery agents must not only have tumor selectivity but also deliver amounts far in excess of that required for radiopharmaceuticals to detect tumors by radiodiagnostic modalities such as single photon emission computerized tomography and PET. In contrast to radiopharmaceuticals, these agents must deliver enough ^{10}B , presumptively to all tumor cells, in amounts sufficient to sustain a lethal $^{10}\text{B}(n,\alpha)$ Li capture reaction ($\sim 20\text{--}50 \mu\text{g}$ per g tumor or $\sim 10^9$ atoms per tumor cell). Furthermore, they must persist in these tumor cells for a sufficient amount of time, and simultaneously clear

from surrounding normal tissues to ideally attain a tumor:normal tissue ratio of 3–4:1.

Translating experimental animal data into a clinical biodistribution study represents a significant hurdle that must be overcome. *First*, and most importantly, as of the time of writing there has been a lack of convincing experimental animal data that would warrant the initiation of expensive clinical biodistribution studies for any of the boron delivery agents that we have described in this review. *Second*, there is a major challenge in going from laboratory synthesis to scale up synthesis in a Good Manufacturing Practices (GMP) facility before clinical studies



can be initiated. *Third*, these biodistribution studies would have no direct benefit to the patients participating in them other than the altruistic reason that might help other future patients with malignancies that would be treated by means of BNCT. *Fourth*, the issue of funding of such a Phase I clinical biodistribution studies represents a significant hurdle, at least in the United States, where at this time there is very little chance of getting funding from the government or the pharmaceutical industry and where an Investigative New Drug application would require very convincing experimental animal data, including toxicologic evaluation in at least one non-rodent animal species.

What, then, is the best course of action at the present time? *First* and foremost would be to optimize the dosing paradigms for BSH and BPA. Clinical data generated by the Swedish group [38, 39, 131] suggest that increasing the dose of BPA and the infusion time resulted in improved survival in patients with high grade gliomas who had been treated with BNCT. *Second*, methods should be explored to enhance the delivery of BSH and BPA, both in brain tumor patients and patients that have had recurrent tumors of the head and neck region. Two of us (Barth and Yang) have convincingly demonstrated that transient disruption of the BBB by intracarotid

infusion of a hyperosmotic solution of mannitol, combined with administration of either BSH or BPA, resulted in a threefold increase in tumor boron concentrations in F98 glioma bearing rats [49–52]. This enhanced tumor uptake of BSH and BPA resulted in a three- to four-fold increase in MST following BNCT. Although this procedure has been used clinically to administer cytoreductive chemotherapeutic agents to patients with high grade gliomas, it requires a very specialized team, which may make it difficult to carry out in patients who will be receiving BNCT [132–134]. An alternative approach [135–137] could be the use of pulsed ultrasound [109, 138] initially to enhance tumor uptake of ^{18}F -BPA for PET imaging. ^{18}F -BPA PET imaging [121–124] is now a well-established technique used as part of the treatment planning protocols both in Japan and Finland, the two countries where the largest number of patients have been treated by BNCT. Although some of the clinical results that have been obtained in these two countries have been impressive [44], especially in the treatment of genital cancers [18]. It remains to be determined if the results would be sufficient to convince a broader group of physicians, who are taking care of cancer patients on a day-to-day basis, that BNCT would be worth pursuing. The challenge to those of us who have been working in this field is to come up with truly convincing data!

Abbreviations

BBB: blood brain barrier; BNCT: boron neutron capture therapy; BPA: boronophenylalanine; BPA-F: boronophenylalanine-fructose complex; BSH: sodium borocaptate; CEA: carcinoembryonic antigen; CED: convection enhanced delivery; EGFR: epidermal growth factor receptor; EGFR_{iii}: EGFR variant; LET: linear energy transfer; MoAb: monoclonal antibody; MST: mean survival time; PEG: polyethylene glycol; PET: positron emission tomography; ROS: reactive oxygen species; SIMS: secondary ion mass spectrometry; TK1: thymidine kinase 1; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

Authors' contributions

RFB wrote 70% of the manuscript and PM wrote the remaining 30%. WY carried out the studies relating to the boron delivery agents shown in Fig. 2, which subsequently were reported in a number of peer-reviewed publications, many of which he was the first author and are cited in this review. He also reviewed the final version of the manuscript. Accordingly, all three of the authors give their consent for the publication of this Review and none of them have any competing interests. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data presented in this manuscript all have been published and can be retrieved by going to the references indicated. There are no materials relating to this review.

Consent for publication

All three of the authors have given their approval for publication of this manuscript.

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