

Boron and Its Application to Cancer

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ABSTRACT: Recently, boron compounds have attracted increasing attention both in academic laboratories and in the pharmaceutical industry. Boron, in particular the ^{10}B isotope, has the unique capability of absorbing a slow neutron to initiate a nuclear reaction with release of energetic particles such as α - and Li-particles, which is not observed in its carbon analogues. The nuclear capture reaction concept has been adopted in radiation therapy and used in boron neutron capture therapy (BNCT). BNCT is a potentially promising treatment for malignant brain tumors as well as other cancers, despite the limitation of a scarcity of neutron sources. There is the need in advanced research centers to construct high boron-containing composites as BNCT agents and develop more efficient drug carriers. Recent works have been done on the development of boron-based therapeutic nanomaterials as BNCT agents. Boron Neutron Capture Therapy (BNCT) is a radiation science which is emerging as a hopeful tool in treating cancer, by selectively concentrating boron compounds in tumour cells and then subjecting the tumour cells to epithermal neutron beam radiation. BNCT bestows upon the nuclear reaction that occurs when Boron-10, a stable isotope, is irradiated with low-energy thermal neutrons to yield α particles (Helium-4) and recoiling lithium-7 nuclei. A large number of 10 Boron (^{10}B) atoms have to be localized on or within neoplastic cells for BNCT to be effective, and an adequate number of thermal neutrons have to be absorbed by the ^{10}B atoms to maintain a lethal $^{10}\text{B}(n, \alpha)$ lithium-7 reaction. The most exclusive property of BNCT is that it can deposit an immense dose gradient between the tumour cells and normal cells. BNCT integrates the fundamental focusing perception of chemotherapy and the gross anatomical localization proposition of traditional radiotherapy.

The boron neutron capture therapy (BNCT) has been utilized for cancer treatment from last decade, where chemotherapy and radiation have their own shortcomings. However, the improvement in the already existing (BPA and/or BSH) localized delivery agents or new tumor-targeted compounds are required before realizing the full clinical potential of BNCT. Patients undergoing BNCT are given a boron-based reagent, often injected intravenously, which accumulates in cancer cells. When a stable boron isotope (boron-10) of the reagent is hit by a beam of neutrons in the cancer cells, it captures neutrons, which causes a nuclear reaction and creation of energetic helium (alpha particle) and lithium nuclei. The nuclei deposit their energy within the tumour cell, causing damage and cell death. The tumour is targeted by selectively introducing the boron reagent into tumour cells, and not by aiming the beam at the cells, as in other radiation therapies, in which healthy tissue still may get damaged as a result. The high biological effectiveness of this procedure and the precisely targeted cell damage are major advantages of BNCT in clinical therapy.

KEYWORDS : Boron, cancer, therapy, applications, neutron, nanomaterials

I. INTRODUCTION

Recently, boron neutron capture therapy (BNCT) has attracted attention because it is a strategy for binary targeting and noninvasive treatment of cancer. BNCT is a possible treatment methodology for cutaneous melanomas, extramammary Paget's diseases of genital regions, vulvar melanoma, neck and head cancers, and high-grade gliomas. An appropriate number of ^{10}B atoms must be introduced to the neoplastic cells that could be irradiated with adequate number of neutrons to obtain a successful BNCT reaction. It is reported that a cell required an average of 3–7 alpha-particles (from ^7Li nuclei) and $^{10}\text{B}/\text{g}$ to destroy a tumor tissue of ca. $15\ \mu\text{g}$. Therefore, the production of clusters having high boron content play an important role if BNCT is clinically accepted to evolve the treatment for cancer. In the early days of formulating boron carriers for BNCT, mostly mixture of ^{10}B (19.9%) and ^{11}B (80.1%) isotopes of natural boron were used. In clinical applications, the ^{10}B enriched boron carriers are used due to its higher neutron capture cross-section 3837 barns as compared to 0.005 barns of ^{11}B . Alpha particles are more valuable than X-ray for radiotherapy, due to their following properties (a) no need of oxygen for alpha particles to increase their biological effectiveness; (b) much higher relative biological effect (RBE) of alpha particles and (c) Both dividing and nondividing tumor cells can

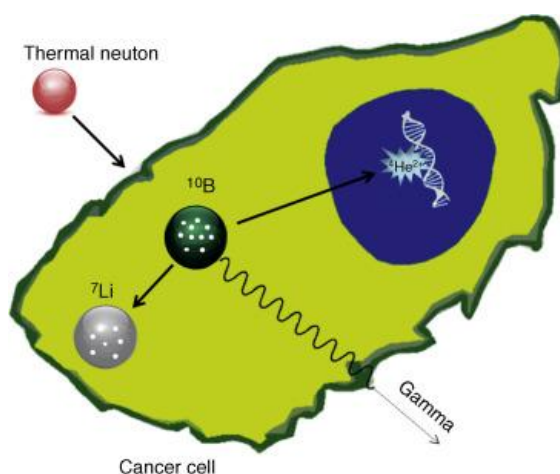
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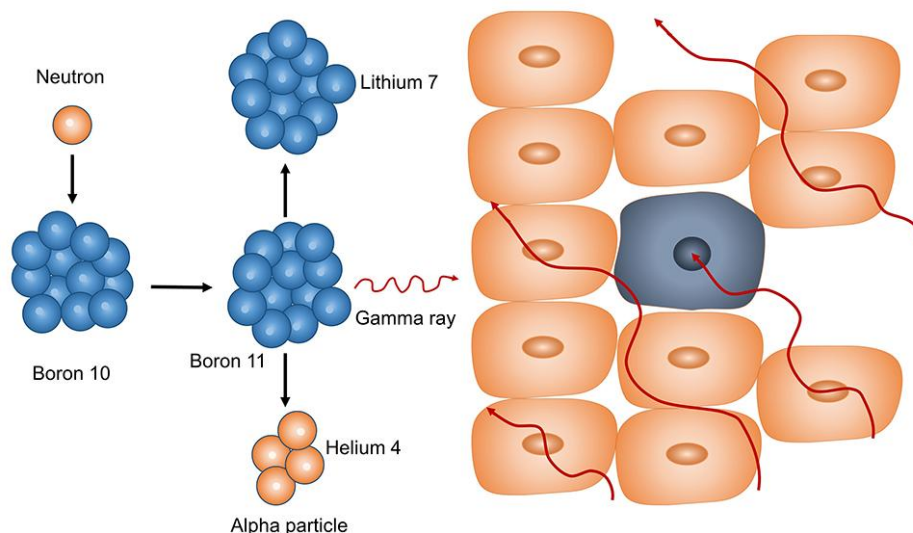
be killed by alpha particles . These properties enable alpha particles tagged with B-10 to selectively kill various types of cancer cells without damaging the normal cells, that helps to prevent the side effects for patients.[1]

The ideal boron-containing agent should fulfill the following requirements: (i) low systemic toxicity; (ii) approximately 30 μg ^{10}B /g tumor concentrations; (iii) high tumor uptake and low normal tissue uptake; and (iv) rapid normal tissue clearance but persistence in tumor tissue during BNCT.[2]



Process of BNCT

For BNCT to be successful, a sufficient number of ^{10}B atoms (approximately 10^9 atoms/cell) should be selectively delivered to the tumor, and enough thermal neutrons must be absorbed by them to sustain a lethal $^{10}\text{B}(n,\alpha)^7\text{Li}$ -capture reaction. [3] The destructive effects of these high-energy particles are limited to boron-containing cells, and having both particles a range comparable to the diameter of a cell, they can cause selective tumor cell death without significant damages to the surrounding normal tissues, provided that the boron-carrier compound accumulates preferentially in tumor cells [10]. In this context, BNCT is a potentially promising treatment for malignant brain tumors as well as for other cancers, despite the limitation due to a scarcity of neutron sources. It is worth mentioning that unlike other elements used in radiotherapy, the ^{10}B employed in BNCT treatment is nonradioactive. Nanostructured boron compounds have emerged as one of the promising frontiers in boron chemistry. These species possess unique physical and chemical properties in comparison with classical small boron compounds. The nanostructured boron composites generally have large amounts of boron contents and thus have the potential to deliver significant amount of boron to the tumor cells, that is crucial for boron neutron capture therapy (BNCT).[4] In theory, BNCT is based on a nuclear capture reaction with the ^{10}B isotope absorbing a slow neutron to initiate a nuclear fission reaction with the release of energetic particles, such as lithium and helium (α particles), which travel the distance of around nine microns within the cell DNA or RNA to destroy it. The recent studies have demonstrated that the nanostructured boron composites can be combined with the advanced targeted drug delivery system and drug detection technology. The successful combination of these three areas should significantly improve the BNCT in cancer treatment.[5]



II. OBSERVATIONS

BNCT represents a promising treatment modality, with data suggesting the safety and efficacy of treatment in patients with advanced tumors. Caution should be taken when interpreting the data from BNCT. The studies exhibit a high degree of heterogeneity in inclusion criteria, boronated compounds used, times for infusion, and neutron dose given, which creates difficulty in comparing studies even within the same disease site. Additionally, there are no current studies investigating the outcomes of BNCT compared to other standards of care, which limit interpretation of the results. Well-designed phase II/III studies are needed to define the efficacy and safety of BNCT in a variety of tumor types.[6]

Although initial results with BNCT are promising, toxicity rates remains relatively high. Further research into developing more selective boronated compounds is needed to improve the therapeutic ratio of treatment and decrease potential toxicity. In the era of immunotherapy and targeted agents, ^{10}B can conceivably be conjugated to these agents to increase selectivity, an area of needed research. Alternatively, BNCT may be coupled with immunotherapy to achieve optimum synergy between immune activation by the high LET attributes of BNCT and immunotherapy that maintains lymphocytes in an activated state.[7]

Another barrier to adoption of BNCT is the high cost of developing and maintaining a BNCT treatment center. Currently, there are no centers in the United States treating with BNCT. Nakagawa et al. estimated that a BNCT facility in Japan costs approximately 1200 million Yen (approximately \$11.4 million) to construct with an annual personnel cost of 113 million Yen (approximately \$1 million). The substantial initial startup costs are a barrier to developing a BNCT center in the United States, especially with a lack of studies investigating the cost effectiveness of BNCT compared to other modalities.[8]

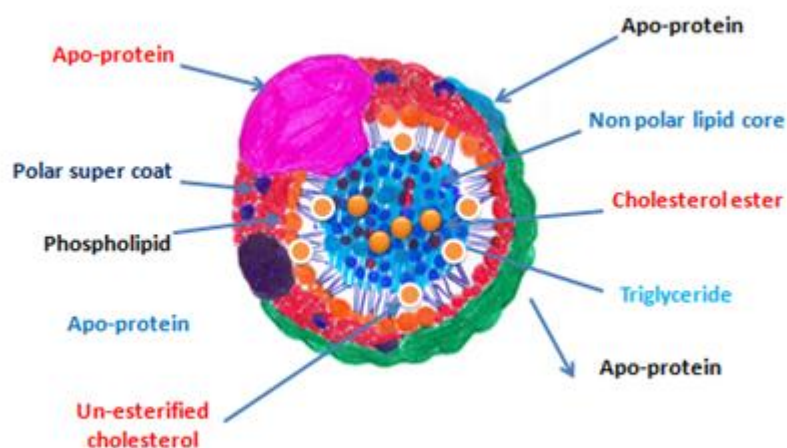
Another potential area of research is using non-boronated compounds, which, while offering similar mechanisms as BNCT, may have improved treatment effects or mitigation of BNCT limitations. ^{157}Gd in particular has generated considerable interest, in no small part due to its role as a contrast agent in MRI and notable high uptake in (brain) tumor cells, where the large magnetic moment of the Gd^{3+} ion may be detected. Unlike ^{10}B , which releases both high LET He and Li ions, the $^{157}\text{Gd}(n,\gamma)^{158}\text{Gd}$ capture reaction generates gamma rays, x-rays, and internal conversion, Auger, and Coster-Kronig electrons. These electrons are similarly high-LET with limited range, concentrating damage within a diameter of approximately one cell and effectively generating double strand breaks. This offers unique potential if a highly localizing gadolinium-based agent can be achieved. However, the presence of gamma and x-rays broadens the dose delivery region, and may somewhat limit selectivity. In comparison with

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boronated compounds, the wider irradiation range may offer improved treatment of nearby cells undergoing limited deposition, forming a spectrum of utility amongst boronated and gadolinium-based agents. As such, treatment efforts hinge on the development of gadolinium-based compounds, of which many have been developed and assayed, though deployment within *in vivo* models has been limited. Early results were promising, such as Tokumitsu and colleagues' deployment of chitosan nanoparticles in 1999, finding significant suppression in a B16F10 murine melanoma model. Uniquely, combination agents have been introduced: a gadolinium/boron agent, bound to low-density lipoproteins (LDL), has demonstrated preliminary success in MRI-monitorable detection and treatment success both *in-vitro* and in a murine model. [9,10]



Lipoproteins as drug delivery vehicles

III. DISCUSSION

The successful treatment of cancer by boron neutron-capture therapy (BNCT) requires the selective concentration of boron-10 within malignant tumors. The potential of liposomes to deliver boron-rich compounds to tumors has been assessed by the examination of the biodistribution of boron delivered by liposomes in tumor-bearing mice. Small unilamellar vesicles with mean diameters of 70 nm or less, composed of a pure synthetic phospholipid (distearoyl phosphatidylcholine) and cholesterol, have been found to stably encapsulate high concentrations of water-soluble ionic boron compounds. The hydrolytically stable borane anions B10H10(2-), B12H11SH2-, B20H17OH4-, B20H19(3-), and the normal form and photoisomer of B20H18(2-) were encapsulated in liposomes as their soluble sodium salts. The tissue concentration of boron in tumor-bearing mice was measured at several time points over 48 h after *i.v.* injection of emulsions of liposomes containing the borane anions. Although the boron compounds used do not exhibit an affinity for tumors and are normally rapidly cleared from the body, liposomes were observed to selectively deliver the borane anions to tumors. The highest tumor concentrations achieved reached the therapeutic range (greater than 15 micrograms of boron per g of tumor) while maintaining high tumor-boron/blood-boron ratios (greater than 3). The most favorable results were obtained with the two isomers of B20H18(2-). These boron compounds have the capability to react with intracellular components after they have been deposited within tumor cells by the liposome, thereby preventing the borane ion from being released into blood. [11]

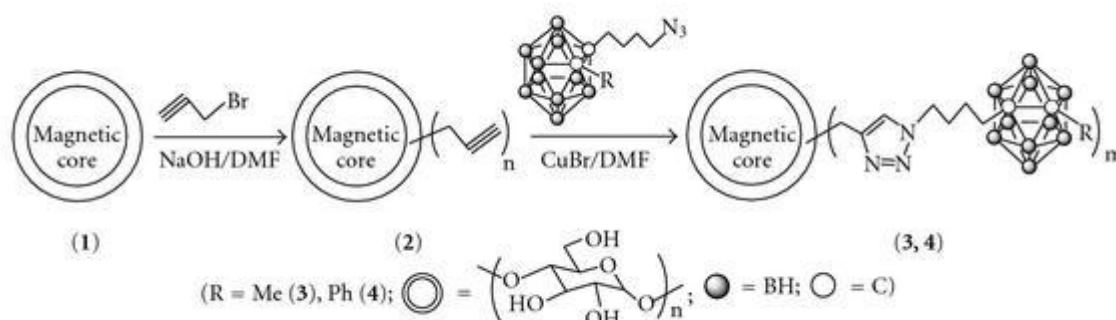
Commercially available magnetic nanoparticles of iron oxides matrixed with starch have been enriched with the carborane cages, 1-R-2-butyl-*ortho*-C₂B₁₀H₁₀ (R = Me, 3; Ph, 4), by catalytic azide-alkyne cycloaddition reactions. This reaction has been extensively developed and widely used in chemical transformations in biological applications

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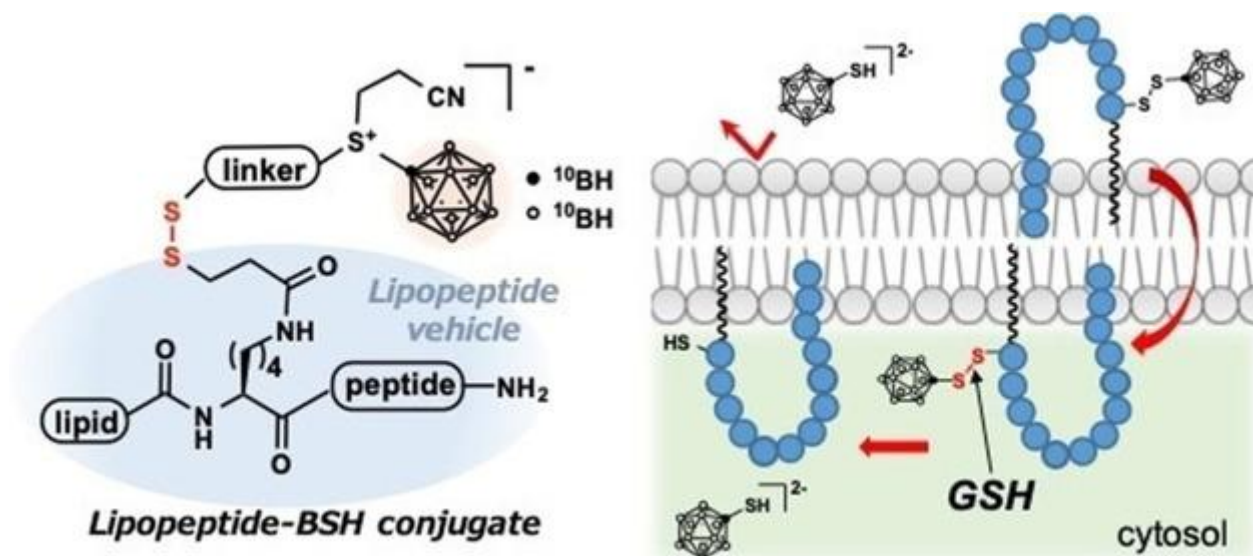
and materials chemistry [9], such as cell surface labelling [3], biopolymers-viruses conjugation [1], and block copolymer synthesis [2]. In our case, starch modified magnetic nanoparticles were enriched with allyl-groups by reactions of free hydroxyl groups in starch with propargyl bromides in DMF in the presence of sodium hydroxides. There were no significant changes in the IR spectra before and after immobilization of propargyl groups. However, after immobilizing the carborane cages, a new peak appeared at $\nu = 2575\text{ cm}^{-1}$, assigned to the B-H bond stretching. Compared with the starting compound 1-Me-2-(CH₂)₄N₃-1,2-C₂B₁₀H₁₀, the absorption of $\nu_{\text{N}=\text{N}}$ at 2097 cm⁻¹ disappeared in IR spectra of 3. These results confirm the successful immobilization of propargyl and carborane groups. The successive attachments are consistent with the thermal gravimetric analysis (TGA) of compounds 1, 2, and 3, the curves indicate a weight% loss of 27.7 and 33.2 for 1 and 2, respectively, while compound 3 has a much smaller loss of 15.7%. For the propargyl group, a loading amount of 1.40 mmol per gram of starch-matrixed magnetic nanoparticles has been reached based on TGA and elemental analyses. Unfortunately, a lack of knowledge of the final TGA product of 3 prevented our determination of the loading amounts of carborane [13]. However, the ICP-OES analysis was decisive in obtaining a loading amount of 9.83 mmol boron atom/g starch-matrixed magnetic nanoparticles. [12]



Boron drug delivery by encapsulated magnetic nanocomposites

IV. RESULTS

Boron neutron capture therapy (BNCT) is a radiation therapeutic technique in which cancer cells are selectively targeted by intense beams of particles (α -particles and ⁷Li particles) arising from the nuclear reaction caused by ¹⁰B atoms selectively pre-embedded in cancer cells with relatively low-energy thermal neutrons¹. In contrast to other forms of radiation such as X-rays or gamma rays, the α -particles and ⁷Li particles produced in this process travel extremely short distances—just approximately 5 to 9 μm —in soft tissues; such distances are limited to the diameter of a single cell, and thus the selective uptake of ¹⁰B atoms by tumor cells could kill the tumor cells in a pinpoint manner. BNCT is the pioneering radiation therapy used for cancer treatment in Japan in 1968 for the first time in the world. Establishing this useful application of nuclear-reaction in Japan, which is the only country in history to have suffered nuclear bombs attack, would be profound significance. In the past, large experimental nuclear reactors have been used as neutron sources, but compact accelerators (or *cyclotrons*) for BNCT have recently been developed in Japan that is small enough to be installed in laboratories or hospitals. Since 2012, the nationwide rollout of preclinical trials using them has increased the momentum toward practical application of this technology². [13,14]



Design, Synthesis, and Evaluation of Lipopeptide Conjugates of Mercaptoundecahydrododecaborate for Boron Neutron Capture Therapy

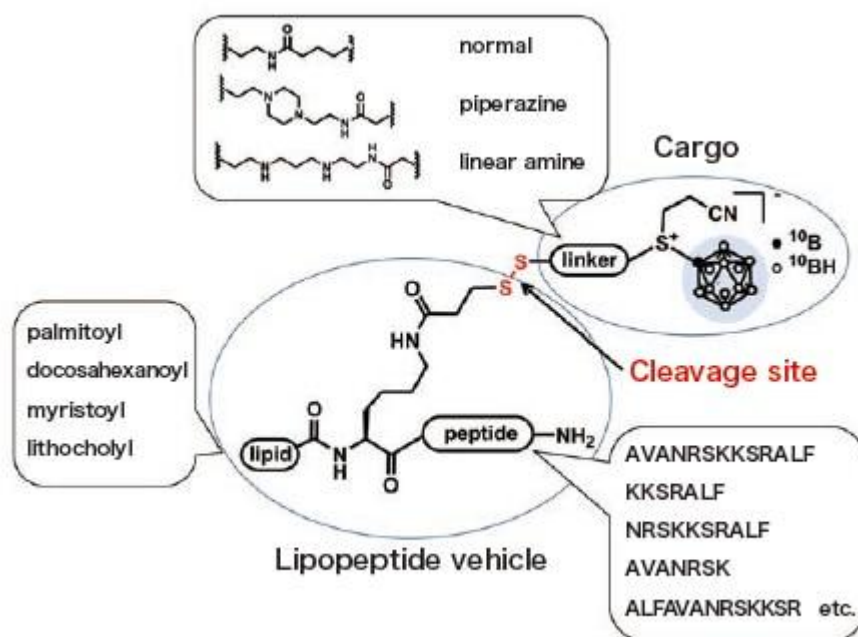
For all of these reasons, BNCT offers promising potential to develop into a near-ideal cancer therapy with few side effects if a boron carrier is developed that can selectively delivers and accumulates ¹⁰B atoms in tumors. At present, the only boron carriers to be applied for clinical use are sodium borocaptate (BSH) and L-p-boronophenylalanine (BPA), and neither of these accumulates sufficiently in tumor cells. Thus there is an urgent need to develop new boron carriers capable of accumulating high concentrations of ¹⁰B atoms selectively in cancer tissue. With this as a motivation, we have initiated a research program to develop tumor-selective boron carriers based on peptide chemistry^{3, 4}. In recent work, we have developed boron carriers based on the chemical delivery system using membrane-permeable lipopeptides (1)⁵. In the molecular design of the boron carriers, an anionic boron cluster BSH was loaded on membrane-permeable lipopeptide vehicles via a suitable linker (2). Because ionic boron clusters are not membrane-permeable, we attempted to accumulate BSH sufficiently in cells by a structural optimization of the lipopeptide moiety.

For the structural modifications of the lipopeptide units, we designed a wide variety of vehicle molecules by combining peptides with various amino-acid sequences and multiple kinds of lipids. Since the lipopeptides synthesized by solid phase method had a relatively large molecular weight of 1,000 or more and were also highly hydrophilic, it was difficult to follow the reaction by TLC as in the case of general organic synthesis. Instead, a reaction-tracking protocol based on LC-DAD-MSD was utilized to effectively promote diversity-oriented synthesis of middle-size molecules. [15]

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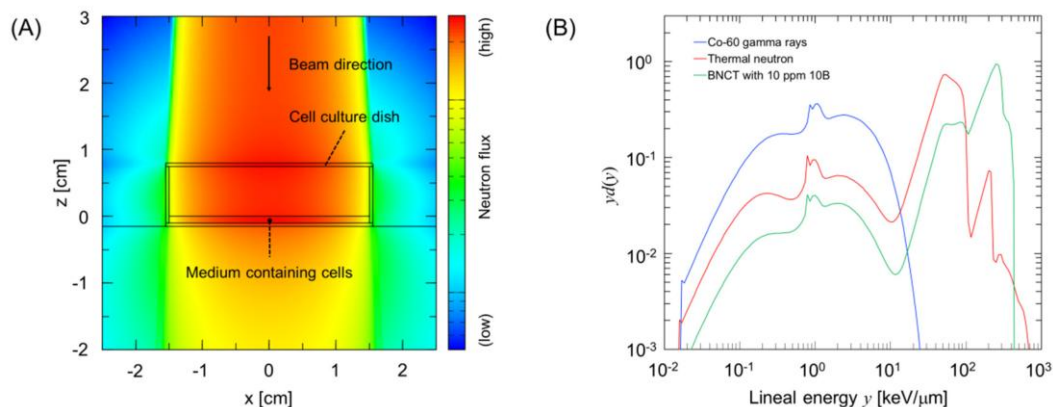
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In the development of boron carriers for BNCT

Analysis of the correlation between the peptide sequence and intracellular boron uptake revealed that compound 3 with an original sequence of 13-amino acid peptide derived from P1pal-13 and a palmitoyl group permeated into the cells in the largest amount. The boron carriers with peptide of the C-terminal 7 or 10 residues excluding the N-terminal from the original sequence hardly entered the cells. On the other hand, boron carrier with a peptide of the N-terminal 7 and 10 residues penetrated into the cells moderately. These results suggested that the N-terminal sequence of P1pal-13 is important for cellular penetration. The derivative with the peptide in which three hydrophobic residues at the C-terminal were moved to the N-terminal showed moderate intracellular uptake. Compounds with randomly arranged peptide sequences or peptides with an reverse sequence were hardly incorporated into cells. Next, intracellular uptake of boron carriers having the original 13 amino acid peptide with modified lipid structure were also examined. Boron carrier with acetyl group instead of palmitoyl group or with lithocholic acid did not enter the cells. Compounds with docosahexanoic acid, a linear unsaturated fatty acid, and myristoyl group, a linear saturated fatty acid, showed moderate uptake. As a result, it was found that palmitoyl group is necessary for intracellular penetration. For further improving cellular uptake of boron carrier, we evaluated the introduction of a polyamine linker and a piperazine linker which are expected to be cationic under physiological conditions, but no significant increase in the cellular uptake was observed. From the above results, we examined the radiosensitizing effect of compounds 2 and 3, which showed good penetration into cells, with thermal neutron beams in T98G glioblastoma. Since the D_{10} value and the colony formation rate in the BSH treatment were almost equal to those of the control, under the experimental conditions of this study, BSH was found to hardly enter cells and had no radiosensitizing effect.[20] On the other hand, the enhancement effect (D_{10} of control / D_{10} with boron carrier) of the newly developed compounds 2 and 3 were 5.79 and 7.69, respectively, indicating that they have strong sensitizing effect.[16]



Estimating dose rate effect on cell killing of human melanoma after BNCT

V. CONCLUSION

Boron neutron capture therapy (BNCT), a technique that deposits highly targeted radiation into tumour cells, was first investigated as a cancer treatment back in the 1950s. But the field remains small, with only 1700 to 1800 patients treated to date worldwide. This may be about to change.[19] “The field of BNCT seems to be progressing rapidly at the moment,” said Stuart Green, director of medical physics at University Hospital Birmingham. “The big difference compared with five or ten years ago is that the commercial interest from a variety of companies is strong now and this is driving the field.”BNCT is a two-stage treatment. First, a ^{10}B -containing drug (most commonly boronophenylalanine) is infused into the patient’s bloodstream. After a couple of hours, the drug accumulates preferentially in tumour cells and starts to wash out of healthy tissues. At this point, the tumour target is irradiated with low-energy neutrons, which split the ^{10}B atoms into alpha particles and ^7Li ions – highly ionizing particles that are delivered directly into the cancer cells.“BNCT is high-LET [linear energy transfer] radiotherapy targeted at the cellular level,” Green explained. As neither the neutron beam nor the drug are toxic by themselves, damage to healthy tissue is minimized. “BNCT is relatively safe compared with administering radioactive drugs or chemotherapy, where toxicity may be experienced all around the body.[17,18]

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