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研究課題名（和文）Development of novel tumor-targeting nanoparticles for malignant brain tumor neutron capture therapy and diagnosis

研究課題名（英文）Development of novel tumor-targeting nanoparticles for malignant brain tumor neutron capture therapy and diagnosis

研究代表者

ザボロノク　アレクサンドル（Zaboronok, Alexander）

筑波大学・医学医療系・助教

研究者番号：２０７２３１１７

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研究成果の概要（和文）：ホウ素中性子捕捉療法（BNCT）用の新規複合ホウ素ナノ粒子（BNP）を開発しました。BNPsは、現在使用されているボロノフェニルアラニン（BPA）よりも毒性が低く、腫瘍細胞への蓄積時間が長く、より顕著な照射効果を示しました。腫瘍を標的とするリガンドも合成されました。新しい計算方法を用いて、中性子照射後の金の活性化に基づく吸収線量評価を行いました。ホウ素と金の共有結合が困難なため、リポソームベースの構造で両重要元素を結合させました。実際の臨床に近いBNCTの技術的側面を研究するために、自然発生した腫瘍を持つ大型動物（猫や犬）への照射も行われました。

研究成果の学術的意義や社会的意義
With the development of accelerators for BNCT, there is a need for new, more effective boron compounds with absorbed dose estimation to improve cancer therapy. Our complex nanoparticles providing therapy and diagnosis will help further BNCT development and clinical application worldwide.

研究成果の概要（英文）：Novel complex boron nanoparticles (BNPs) for boron neutron capture therapy (BNCT) have been developed. BNPs showed low toxicity, more prolonged accumulation in the tumor cells, and a more prominent irradiation effect than currently used boronophenylalanine (BPA). Tumor-targeting ligand has also been synthesized. Using new calculation methods, the absorbed dose evaluation based on gold activation after neutron irradiation was done. Due to difficulties in the covalent binding of boron and gold, a liposome-based structure was used to couple both critical elements. Irradiation of larger animals (cats and dogs) with spontaneous tumors was also done to study the technical aspects of BNCT close to actual clinical conditions.

研究分野：radiation oncology

キーワード：BNCT　glioma　nanoparticles　boron　gold　dosimetry　tumor targeting　liposomes

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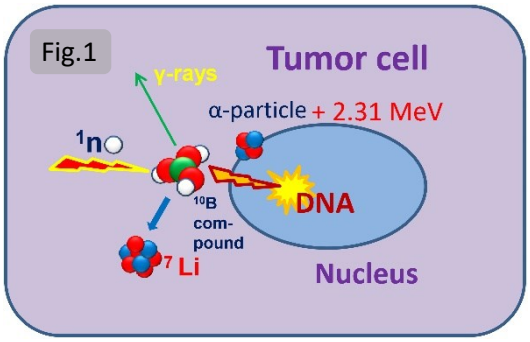
様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９（共通）

１．研究開始当初の背景

Invasive malignant tumors, such as glioma, head and neck cancer, and malignant melanoma, are challenging to treat and, in most cases, are fatal with a short average life expectancy (about 14 months in the case of glioblastoma) despite the use of modern treatments. Boron Neutron Capture Therapy (BNCT) is a more effective method to treat such invasive tumors. It is based on the accumulation of boron-10 isotope in tumor cells and subsequent tumor irradiation with epithermal and thermal neutrons, resulting in neutron capture by boron and its decay into alpha-particles and lithium nuclei with high energy release (2.31 MeV) damaging tumor cell DNA (Fig.1). The particle pathway is about ~10 µm, i.e. it is limited by the size of the tumor cell, while healthy cells without boron can remain intact.



BNCT at nuclear reactors was effective in treating gliomas, extending the life of patients to an average of 25.7 months. Neutron-producing proton accelerators that can be placed in hospitals have been developed in Japan and other countries. However, clinically used boron compounds, boronophenylalanine (BPA) and sodium borocaptate (BSH), couldn't cure all patients with malignant gliomas. BPA and BSH carry only 1 or 12 boron atoms per molecule and are washed from tumor tissue after injection. With the development of more accessible accelerator-based neutron sources, there is a need for the development of new boron compounds that can deliver larger amounts of boron atoms and keep them in tumor cells during BNCT, increasing therapeutic efficacy. Also, as neutron capture and boron decay with energy release take place inside tumor cells, estimating the absorbed dose received during BNCT remains challenging.

２．研究の目的

We aimed at the synthesis, physical and chemical analysis, and preclinical evaluation of elemental boron nanoparticles as high molecular weight agents and the main components of complex nanoparticles, including gold as a diagnostic component for determining the absorbed dose, combining therapeutic and diagnostic purposes. Particle surface functionalization with tumor-targeting molecules was aimed at increasing the efficiency of drug accumulation in tumor cells.

３．研究の方法

The synthesis of boron nanoparticles was performed and tested at the initial experimental stage and was represented by cavitation dispersion of amorphous boron microparticles (0.5-4 µm) in an aqueous dispersion medium at 80 °C followed by a two-step cascade fractionation.

Stabilization of nanoparticles at this stage was performed by forming a polymer shell in an aqueous solution using hydroxyethyl cellulose (HEC) solutions of various concentrations.

Transmission electron microscopy (TEM) was used to visualize nanoparticles, studying their form, structure, and size distribution using a JEM-1400 transmission electron microscope (JEOL Ltd., Tokyo, Japan) operating at an accelerating voltage of 120 kV.

The cytotoxicity of boron and gold nanoparticles and BPA was studied using the MTS assay (Cell Titer 96® Aqueous One Solution, Promega Corporation, Madison, WI, USA). Long-term cytotoxicity two weeks after irradiation was assessed using the colony-forming assay (CF-assay).

The accumulation of boron and gold in the samples was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES and ICP-MS).

The main experimental cell lines in this study were human gliomas T98G, U251, and U87.

In *irradiation experiments*, cell cultures were irradiated with epithermal and thermal neutrons using a tandem-type neutron-producing proton accelerator. The accelerator was operated at a

proton current of 1.725-1.812 mA and an energy of 2.032 MeV. Cell samples were placed in plastic tubes inside a Plexiglas phantom to maximize neutron deceleration to thermal energies.

The effectiveness of tumor growth suppression was assessed using a colony-forming assay (CF assay). Cell survival curves as a function of neutron fluence or boron concentration were fitted to the linear-quadratic (LQ) model using the equation $SF=e^{-(\alpha C+\beta C2)}$, where SF is the survival fraction. The difference in survival fractions of cells between eBNPs, BPA, and irradiation without boron was calculated using areas under the fitted curves (AUCs) comparison by adopting LQ function definite integrals with the neutron fluence (F) as a function of x.

Dosimetry was performed by measuring gold activation in the samples using a germanium spectrometer immediately after neutron irradiation.

Liposomal synthesis was done in additional experiments using phase reversion followed by extrusion to address the issue of intracellular boron delivery and further boron and gold coupling techniques, as well as a surface modification with a tumor-targeting molecule.

Irradiation conditions close to clinical BNCT were tested using gadolinium-containing dimeglumine gadopentetate (Gd-DTPA, 0.6 mL/kg b.w.) in animals with incurable spontaneous tumors.

Animal irradiation was performed at the neutron-producing tandem proton accelerator with the tumor area placed under the beam-shaping assembly and with lithium-containing plastic shielding the unaffected animal body parts to absorb unnecessary neutron irradiation.

Statistical analysis: the data were presented as means± SDs. The difference between the results was determined by one-way analysis of variance (ANOVA), where p-values ≤ 0.05 indicated statistical significance.

4．研究成果

Two fractions of 2–5 and 11-15 nm of synthesized core boron nanoparticles (eBNPs) were visualized by TEM with slightly elongated spherical shapes (Fig.2). The particles appeared in two fractions, which was confirmed by dynamic light scattering (Fig.3). Using the X-ray diffraction analysis, we could see the peaks characterizing amorphous boron before and after ultrasonic processing, which indicated that the obtained nanoparticles had the amorphous composition. eBNPs differed in size and formed larger clusters in water over time; therefore, a stabilizing agent, HEC, was used. The formation of complexes with HEC could realize in the creation of more homogeneous nanoparticles of a larger size, and the stability of the solution was improved. The cytotoxicity eBNPs was relatively low and didn't affect cellular tumor cell proliferation at the minimally clinically relevant therapeutic concentration of 20 μg/mL. A further increase in boron concentration led to a slightly more prominent suppression of cell proliferation at concentrations over the minimum therapeutic range (50–250 μg/mL). A higher sensitivity in terms of cytotoxicity was observed in U251 cells that more prominently reacted to the increased concentration of boron nanoparticles compared to the other cell lines. The proliferation ability of all cells was significantly reduced by eBNPs within the whole neutron fluence range

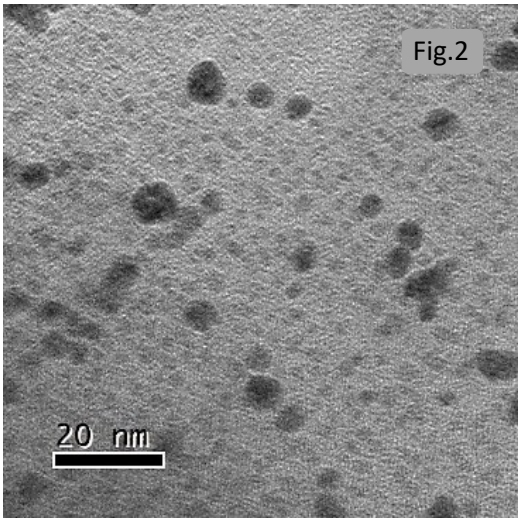


Fig.2

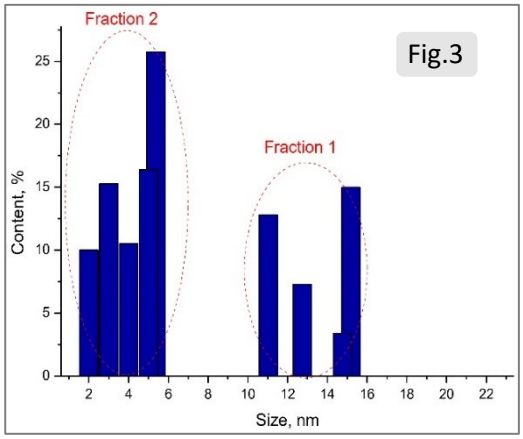
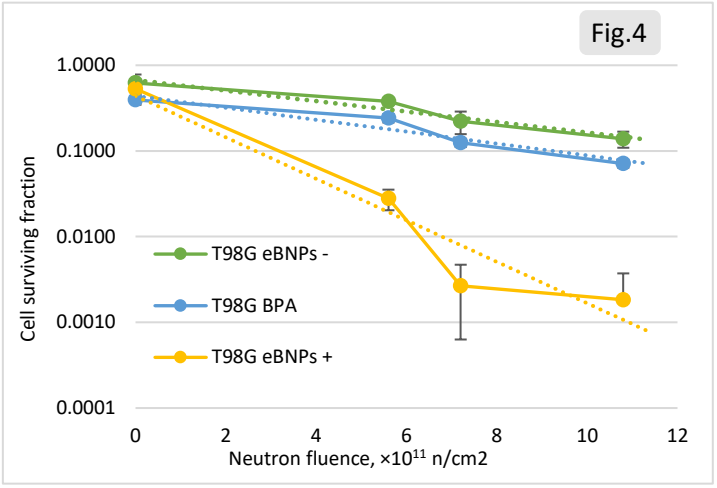


Fig.3

compared to unirradiated cells or cells irradiated without boron. The cell-killing effect was more significant in T98G cells, which could be related to a higher accumulation of nanoparticles and a lower accumulation or wash-out of BPA, where little or no effect was observed (Fig.4).



eBNPs and BPA both induced a significant exponential decrease in U251 cell survival after neutron irradiation compared to tumor cells irradiated without boron. In U251 cells, the effect of BPA and eBNPs didn't differ significantly after irradiation with the fluence of 5.370×10^{12} n/cm^2 irradiation. In U87 cells, all irradiation groups were different in response except for BPA and irradiated control when irradiated with 2.685×10^{12} n/cm^2 irradiation. Thus, eBNPs didn't significantly influence cell proliferation without neutron irradiation but showed a prominent therapeutic effect reducing the number of colonies in all cell lines after neutron irradiation. The effect of eBNPs and BPA varied in different cell lines. Compared to BPA, eBNPs remained in cells after placement in a blank medium before irradiation.

In *dosimetry experiments*, the activation of gold-containing samples was measured, and the absorbed doses were calculated. The detailed dose calculation is shown in *Table 1*.

Cells	Initial B conc., ppm	Number of cells, x10^6	Boron concentration, ppm				Mass of gold					k=	7.4E-13	D=(k*N*n)/m	
			In 10^6 cells	In all cells	In 1mL MEM	In cells + MEM	In 10^6 cells, µg	In 1mL MEM, µg	In all cells, µg	In cells+ MEM, µg	Convert to g	Count rate in gold line	Decays per second	N – number of activated gold atoms	Boron dose in samples, GyE
B-Au+	0	2.75	0	0	0	0	47.57	6.39	130.82	137.21	1.37E-04	10	212.77	71421246	0
B10Au+	10	3	0.049	0.148	9.95	10.10	46.94	3.06	140.83	143.89	1.44E-04	12.9	274.47	92133408	4.80
B20Au+	20	2.15	0.069	0.148	19.95	20.10	43.22	19.03	92.91	111.94	1.12E-04	13.3	282.98	94990257	12.65
B40Au+	40	2.9	0.189	0.549	39.82	40.37	48.54	3.07	140.78	143.85	1.44E-04	12.9	274.47	92133408	19.18
B-Au+	0	1.25	0	0	0	0	47.57	30.18	59.46	89.64	8.96E-05	12.9	274.47	92133408	0
B10Au+	10	1.7	0.049	0.084	9.97	10.06	46.94	23.40	79.80	103.20	1.03E-04	10.3	219.15	73563884	5.32
B20Au+	20	2.1	0.069	0.145	19.95	20.10	43.22	19.75	90.75	110.50	1.11E-04	10.3	219.15	73563884	9.93
B40Au+	40	2	0.189	0.379	39.87	40.25	48.54	17.64	97.09	114.73	1.15E-04	8.8	187.23	62850697	16.36
B-Au+	0	1.6	0	0	0	0	47.57	24.63	76.11	100.74	1.01E-04	11.9	253.19	84991283	0
B10Au+	10	1.4	0.049	0.069	9.98	10.05	46.94	28.09	65.72	93.81	9.38E-05	11	234.04	78563371	6.24
B20Au+	20	1.75	0.069	0.120	19.96	20.08	43.22	24.79	75.63	100.42	1.00E-04	6.9	146.81	49280660	7.31
B40Au+	40	1.1	0.189	0.208	39.93	40.14	48.54	32.20	53.40	85.60	8.56E-05	8.1	172.34	57851209	20.13

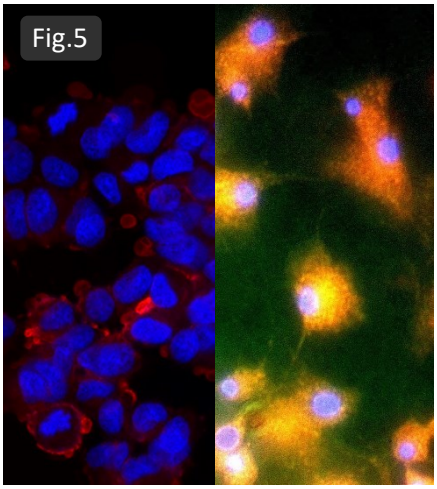
Table 1. Absorbed dose calculations for each boron and gold concentration based on gold activation by neutrons and ^{198}Au isotope decay in three independent experiments. Conc.- concentration, MEM—medium, GyE- gray equivalent. Spectrometer reading values were absolute numbers, sensitivity in gold line (411 KeV) = 0.047, number of decays per second = reading values/sensitivity, Au^{198} half-life = 232,675.2 s, number of activated gold atoms = number of decays per second/$(1-2^{(-1/Au198\ half\text{-}life)})$. Boron dose calculation formula: D = (k × N × n)/m, where D - the absorbed dose (GyE), k - depth-related irradiation coefficient, N - number of activated gold atoms, n - boron concentration (ppm), m - the mass of gold (g).

Boron-related absorbed doses calculated based on gold activation are shown in *Table 2*. The evaluated results are presented as average values with standard deviations. BNCT efficacy was confirmed by the CF-assay and the comparison of the areas under curves (AUCs) of the exponential cell survival decrease after neutron irradiation.

Table 2	Experiment	B- Au+	B10 Au+	B20 Au+	B40 Au+
Dose in samples, GyE	1	0	4.80	12.65	19.18
	2	0	5.32	9.93	16.36
	3	0	6.24	7.31	20.13
AVERAGE		**0**	**5.45**	**9.96**	**18.56**
SD		0	0.73	2.67	1.96

The cell survival decreased correlated with boron concentration, and the effect was the most prominent at the concentration maximum of 40 µg/mL. The results of the combined boron and gold irradiation were in line with the results of the irradiated cells with elemental boron nanoparticles; the presence of gold in the samples didn't influence cell survival significantly. Thus, our proposed dosimetry method, based on gold activation by neutrons and measurement of gamma rays, emitted by gold atoms, doesn't influence the effects of radiotherapy significantly but allows for dose calculation after irradiation. This method allows for tumor drug distribution analysis and the adoption of isotope scanning methods for in-treatment diagnosis during BNCT.

In *liposomal delivery* experiments, fluorescence microscopy was confirmed to be an effective, rapid method for determining the intracellular localization of boron-containing liposomes with fluorescent markers. Simultaneous fluorescence was seen in U87 cells after 24 h of incubation with BSH-containing Cy3- (Fig.5 left) and Nile Red- and FITC- (Fig.5 right) labeled liposomes.



Lipophilic and water-soluble markers delivered by liposomes were both uniformly distributed in U87 cells. Higher accumulation in tumors compared to normal tissues in SCID mice was observed when using pegylated liposomes. After intravenous injection in the retro-orbital sinus at 5 µl/g of body weight containing 3000 ppm of boron, liposomes delivered several-fold higher amounts of boron to tumors with the maximum at 6 h after injection in U87 brain tumor-bearing mice. Thus, fluorescence microscopy can track boron delivery by liposomes in tumors and normal tissues, acting as an effective screening method in new boron compound development.

In a *large animal irradiation* study, after Gd-DTPA injection and neutron irradiation, mild and reversible treatment toxicity was observed. Though clinical improvement and tumor regression after neutron capture therapy were temporary, we made every effort to approximate the therapeutic conditions to those of the actual clinical environment and perfected our therapy techniques utilizing the accelerator-based neutron source. Animals with spontaneous tumors of different origins and locations *(Table 3*) received a median of 30 Gy-Eq in the tumors with the tumor/normal tissue ratio of 3/1 and skin and mucosa limits of 18 and 12 Gy-Eq, respectively.

№	**Type**	**Age, years**	**Pathological diagnosis**	**Tumor location** *Table 3*
1	**cats**	11	highly differentiated adenocarcinoma	nasopharynx
2		6	squamous cell carcinoma	nose with bone destruction,
3		11	highly differentiated squamous cell carcinoma	gum and jaw lymphadenopathy
4		10	squamous cell carcinoma	oral cavity, jaw
5		7	sarcoma	femur and ilium
6	**dogs**	14	chondrosarcoma	nose
7		13	–	lung cancer, lung metastases

This study clarified the *technical aspects* of neutron capture therapy using different compounds and showed that further experiments on the development and preclinical evaluation of new, more advanced compounds are necessary for the progress of this unique cancer treatment method. The combination of such diagnostic elements as gadolinium or gold with a ^{10}B isotope allows for the advancement of the method not only in clinical but also in veterinary applications, where neutron capture therapy remains the only modality to improve the patient's condition.

Further development of *more selective tumor-targeting* is warranted to improve the efficacy of neutron capture therapy, and the *combination of diagnostic and therapeutic compounds* can be alternatively and effectively achieved by employing such complex nanostructures as liposomes.

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掲載論文のDOI（デジタルオブジェクト識別子） 10.1007/s10895-020-02637-5	査読の有無 有
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４．発表年
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〔図書〕　計0件

〔産業財産権〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考
研究分担者	中井　啓 (Nakai Kei) (50436284)	筑波大学・医学医療系・准教授 (12102)	

６．研究組織（つづき）

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考
研究分担者	鶴淵　隆夫 (Tsurubuchi Takao) (70778901)	筑波大学・医学医療系・講師 (12102)	
研究分担者	ＭＡＴＨＩＳ　ＢＲＹＡＮ (Mathis Bryan) (80794635)	筑波大学・附属病院・病院講師 (12102)	

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

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