Folate-modified cyclodextrin improved the active tumor accumulation of BSH and showed a strong therapeutic effect of BNCT.

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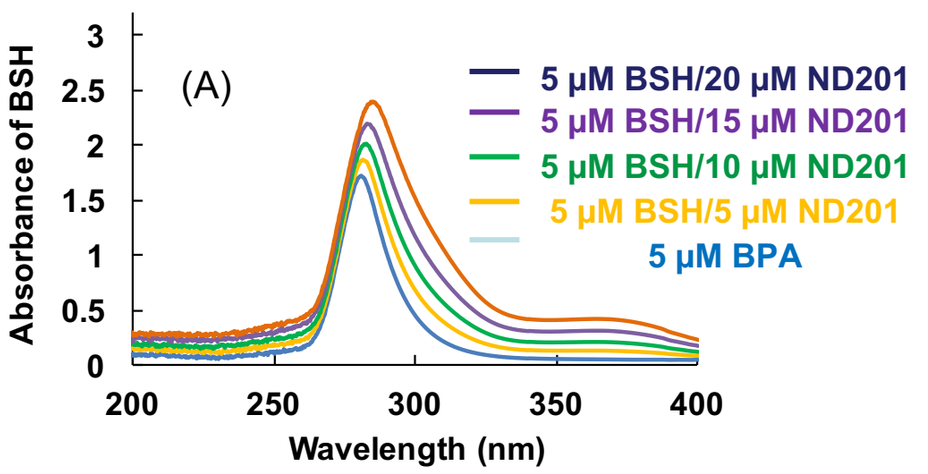
[Abstract] The therapeutic effect of boron neutron capture therapy (BNCT) greatly depends on the boron accumulation into the tumor, but the accumulation of existing compounds is limited. In this study, folic acid-modified cyclodextrin (ND201) purified with folate receptor (FR) was used to examine the improvement of specific and active accumulation of boron compounds on tumors. Colon-26 (FR+) and A549 (FR-) cells were inoculated to the behind of right legs of mice. The BSH mixed with ND201 was subcutaneously injected to the back of the neck of the mice. Boron concentration in the tumor cells was measured with ICPS-8100 (Shimadzu Corporation). The stability constant (Kc) and the stoichiometric ratio of BSH/ND201 complex (ND-BSH) were 1.4×10^4 (/M) and 0.5, respectively. It was found that ND- BSH stably binds in the blood, and the mixing ratio of 1: 1 is most efficient. ND-BSH showed high boron concentration (38.5 ppm) compared with BSH alone (11.25 ppm) for Colon-26 (FR+) tumors. The maximum tumor/blood ratio (T/B ratio) by ND-BSH was too high (6.58) compared with BSH alone (1.04) for Colon-26 (FR+) tumors. On the other hands, T/B ratio was similar between ND-BSH and BSH for A549 (FR-) tumors. After neutron irradiation, ND-BSH showed significant tumor suppressing effect compared with BSH alone (only for Colon-26 tumor). It was suggested that the usefulness of BSH-ND201 depends on the expression of folate receptor and chemical modification targeting folate receptor to existing boron compounds may contribute to improvement of therapeutic effect of BNCT.



System	K_c (M^{-1})
BSH/ND201 complex	$1.4x10^4 \pm 0.2x10^4$

- ✓ BSH form a complex with ND201 with a stability constant of 10^4/M
- ✓ BSH forms a complex with ND 201 at a ratio of 1:1 (or 1:2)

Fig.1 Stability constant (K_c) and stoichiometric ratio between CD201 and existing boron compounds, BSH

Colon-26

FR+,
Mouse,
Colorectal cancer

A549

FR-,
Human,
Lung cancer

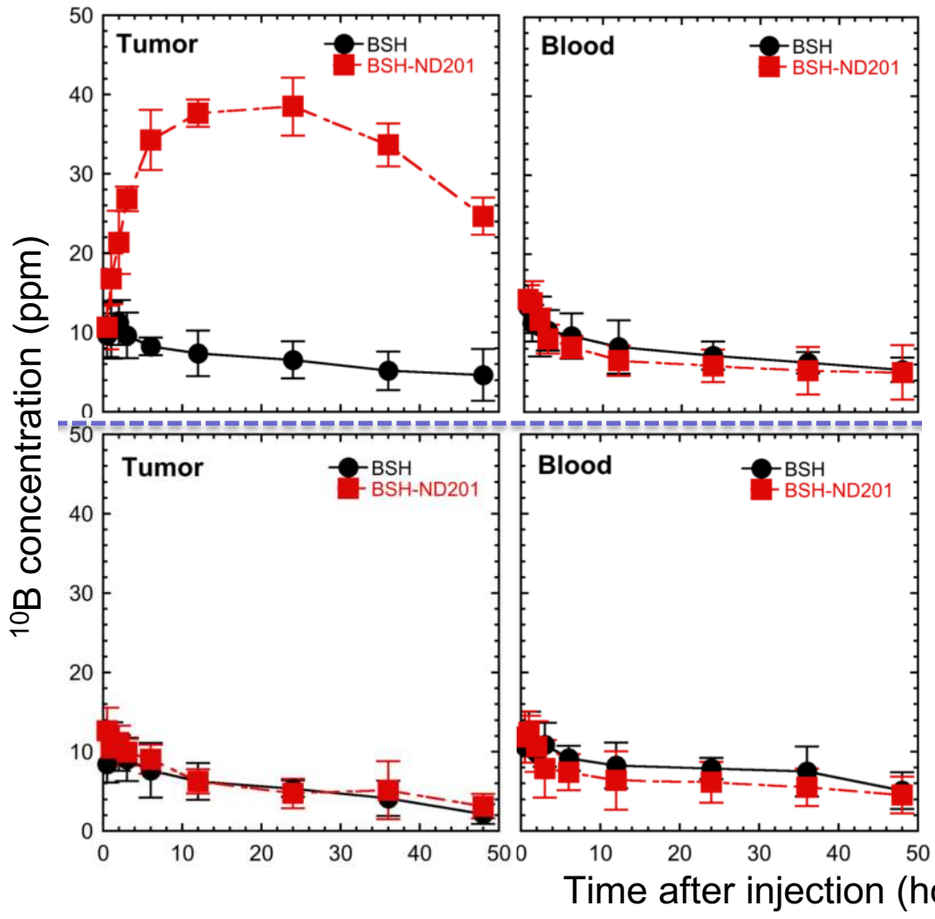


Fig. 2 Pharmocokinetics of boron compounds in tumor and blood, and tumor/blood (T/B) ratio at each time point after boron compounds injection

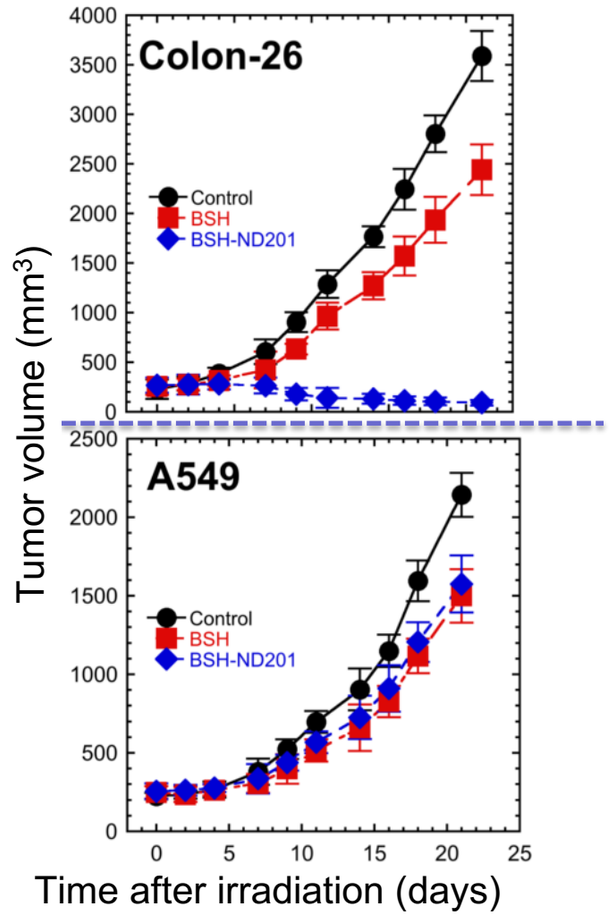
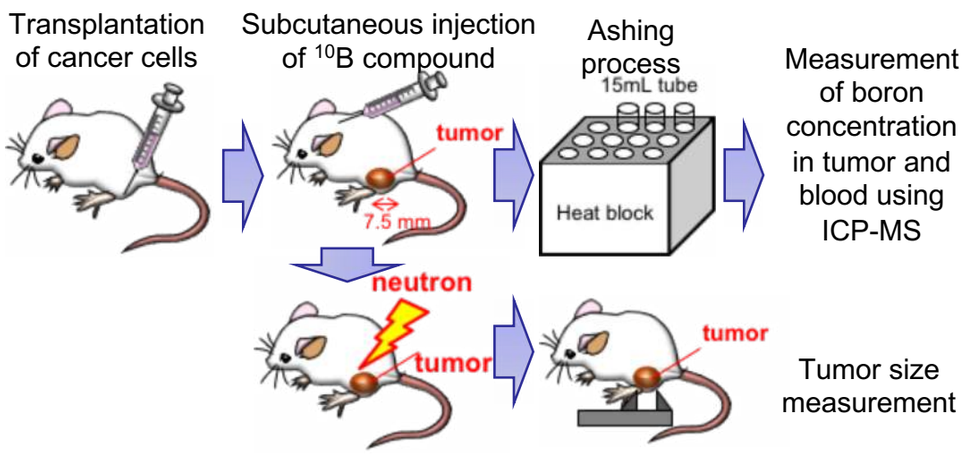


Fig. 3 Antitumor effects of BNCT using BSH-ND201 after Accelerator type BNCT system

[Experimental procedure]



[Irradiation condition]
Beam current=1 (mA), irradiation time=60 (min),
total fluence of thermal neutron≒$1.92x10^{12}$ (n/cm^2)

[Conclusion]

1) Binding stability and stoichiometric ratio

- ND201 stably bind with BSH, and efficiently bound at a concentration ratio of 1:1 or 1:2

2) Pharmacokinetics of BSH and BSH-ND201

- BSH-ND201 showed higher tumor accumulation (Max=38.5 ppm), high T/B ratio (Max.=6.58) and high tumor retention (6 - 36 h).

3) Antitumor effect of BNCT using BSH-ND201

- BSH-ND201 showed significant antitumor effect compared with BSH at 24 hours after inoculation.

[Future plan]

- Evaluation of normal tissue damage (hematologic and skin toxicity) of BSH-ND201 in vivo
- Evaluation of intracellular boron distribution using FITC-labeled BSH-ND201

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