Development of novel boron cluster conjugated PEG derivative for BNCT

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INTRODUCTION:

There has been a growing interest in Boron Neutron Capture Therapy (BNCT) because they are expected to be next generation therapy in minimally invasive cancer treatment. And the clinical trial was started using boronophenylalanine (BPA) as boron drugs in Japan, 2017. However it is difficult that all patients fully remit from cancer by BNCT using BPA. Because, BPA is difficult to maintain sufficient ^{10}B concentration in tumor during neutron irradiation. Therefore, the purpose of this study is to development novel boron drug which become efficient in accumulation and retention in tumor.

MATERIALS AND METHODS:

1. Synthesis of boron cluster conjugated PEG derivative

Novel boron compound (named BAMP [1]) was synthesized by reacting polyethylene glycol (PEG) and mercaptododecaborate (BSH) using cross-linker. This reaction was carried out at room temperature and in phosphate-buffered saline. After that, the synthetic product was identified by MALDI-TOFMS and HPLC.

2. Biodistribution of BAMP in tumor-bearing mice

The tumor-bearing mice were prepared by grafting 5×10^6 of mouse colon carcinoma cells (CT26) to the right thigh of female BALB/cA mice (4 weeks old, weighing 16-20 g) to have a tumor diameter of 6-8 mm. About 12 days after, BAMP was administered by tail vein injection. At selected time intervals after administration, mice were anesthetized, bled via the retro-orbital sinus, killed by cervical dislocation and dissected. Each Organ was excised and their ^{10}B content was measured by ICP-AES [2].

3. Therapeutic effect of BNCT using BAMP in tumor-bearing mice

The tumor-bearing mice were prepared similarly to the experiment of biodistribution and each sample was administered by tail vein injection before irradiation. And the irradiation was performed

with thermal neutrons with a flux of 1.8-4.0 x 10^{12} neutrons/cm^2 over 1 hour. The tumor size was measured over time after the irradiation until Day 24 and calculated using the general formula [3].

RESULTS AND CONCLUSION:

We succeeded in synthesis of novel boron cluster conjugated PEG derivative (BAMP). The yield was 66.0% and purity was 99.8%. In addition, the compound was provided without error of molecular weight. When BAMP was administered, it was rapidly eliminated from normal tissue including liver and kidney but remained in the tumor, as observed in 48 hour after injection. In the experiment of thermal neutron irradiation using tumor-bearing mice, BAMP significantly suppressed the tumor growth as compared to other control groups, indicated its excellent candidate drug potential for BNCT.

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