Development of *S*-Alkyl-*closo*-Dodecaborate-Containing Amino Acids as Boron Carrier for BNCT

Yoshihide Hattori[1], Miki Ishimura[1], Joe Kuan-Hsuan Chen[1], Yoichiro Ohta[1], Kouki Uehara[2], Tomoyuki Asano[2], Mitsunori Kirihata[1]

[1] *Research Center of Boron Neutron Capture Therapy, Osaka Prefecture University, Sakai, Japan*

[2] *Stella Pharma Co., Osaka, Japan*

E-mail: kirihata@biochem.osakafu-u.ac.jp

Introduction

In the development of useful boron carriers for BNCT, unusual boron amino acids represented by L-*p*-boronophenylalanine (BPA) have long being recognized as tumor seeking compounds due to structural analogy to usual L-amino acid, because L-amino acid transport system is enhanced compared with normal tissues to sustain the proliferation of tumor cells. On the other hand, dodecaborate ($[B_{12}H_{12}]^{2-}$), the mother nucleus of mercapto-*closo*-dodecaborate (BSH) is a versatile and available boron cluster bearing high boron occupancy.

In the course of our developing studies on new boron carrier for BNCT, we have designed and synthesized thiododecaborate ($[B_{12}H_{11}S]^{2-}$) unit-containing L-amino acids, a new class of tumor seeking and water soluble amino acid. Recently, S-octyl sulfoniododecaborate ($[B_{12}H_{11}S^{+}octyl]^{-}$) unit containing amino acids (AS-DBA) showed high cell membrane permeability, low cytotoxicity and high water-solubility, and these compounds could deliver large amount of boron to several kinds of tumor cells.

To develop a new boron carrier for BNCT, we designed and synthesized novel L-type neutral amino acid based boron carrier (AP-ADBs), in which the medium-chain alkyl sulfoniododecaborate is linked to *C* terminal of L-BPA. Here, we present the biological evaluation of novel boron compounds as boron carriers for BNCT.

Results and Discussion

To evaluate the AP-ADBs, we examined the cytotoxicity and cellular uptake of AP-ADB, and compared them with that of BPA and AS-DBA.

The cytotoxicities of AP-ADBs were slightly low (IC_{50} value against tumor cells >0.1mM). However, the toxicity of AP-ADBs higher than that of AS-DBA and clinical used boron compounds.

In the next step, we measured the boron concentrations in tumor cells by ICP-OES. The intracellular boron concentration of AP-ADBs in MCF-7 (human breast cancer) cells and SAS (human carcinoma) cells was greater than that of L-BPA, with fewer doses of the compound (dose of BPA: 1.2mM, dose of AP-ADBs: 0.1mM). Our results show that AP-ADBs is useful candidate as ^{10}B carriers.