

# What compound should be used for Boron Neutron Capture Therapy?

-A comparison between BPA,BSH and the third generation agents

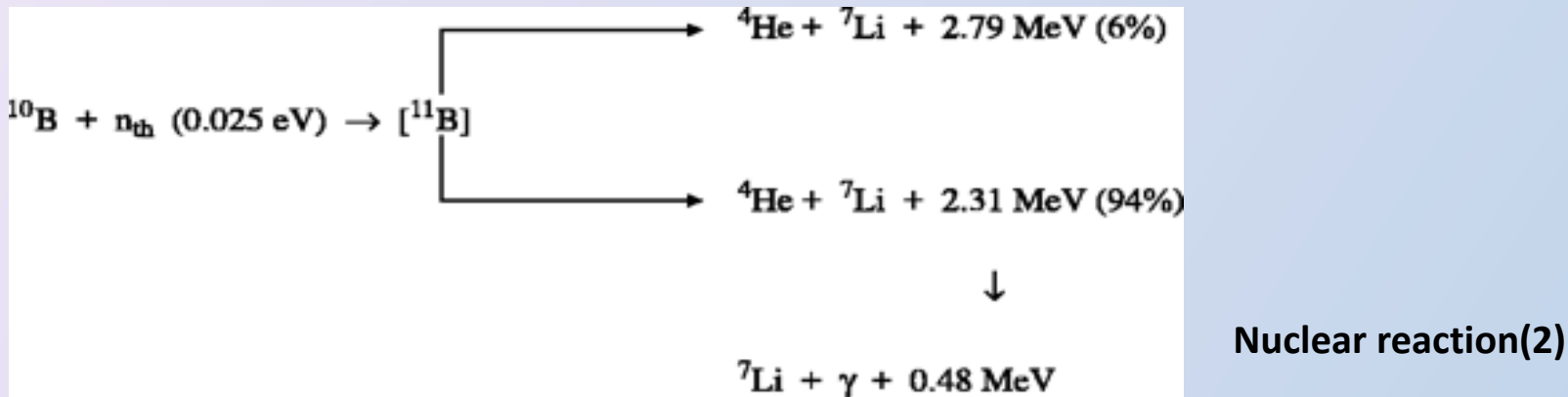
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## Introduction

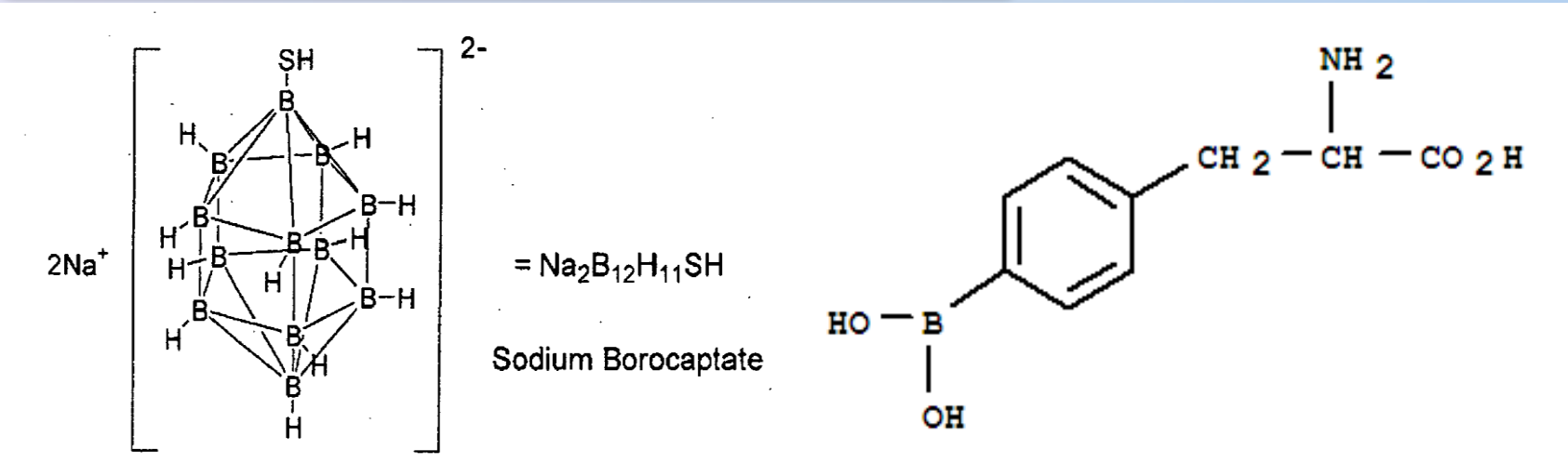
BNCT (boron neutron capture therapy) is a cutting-edge cancer treatment, especially for treating high-grade gliomas. BNCT is theoretically possible due to its binomial system. Firstly, it is based on the nuclear capture and fission reactions. In this reaction,  $^{10}\text{B}$  is irradiated with neutrons produced by accelerator to create  $\alpha$  particles and Li with high energy, both of them ionise nearby tissues within a short range of about one cell. During this process, only these tissues containing  $^{10}\text{B}$  are affected and killed theoretically because of the short range of about 5-9 $\mu\text{m}$ .<sup>(1)</sup> BSH and BPA in the second generation of agents are two clinically used compounds, however, there are many potential candidates for agents.



## Main criteria for agents

- Agents must have low toxicity in order not to be lethal to healthy tissues.
- Agents must have a high concentration of  $^{10}\text{B}$ (about 20 $\mu\text{g } ^{10}\text{B /g tumour}$ ) in order to achieve sufficient concentration of  $^{10}\text{B}$  in the tumour cells.
- Tumour cells should be able to uptake significantly higher amounts of  $^{10}\text{B}$  than healthy tissues, so a high ratio (>3-4:1) is required.
- Agents should have a rapid clearance time so that they will not have a significant influence on the human body.
- Agents should remain stable during treatment , otherwise the treatment will not be effective at targeting.

## Properties of BSH and BPA



Structure of BSH(Sodium borocaptate)(3)

Structure of BPA(boronophenylalanine)(4)

- BSH: 1.Toxicity: severe side effects on animals were reported.
2. Concentration of  $^{10}\text{B}$  : average boron concentration was  $19.9 \pm 9.1$  ppm and  $9.8 \pm 3.3$ ppm in the EORTC phase I trial (11961).
- 3.Uptake ratio: 2.0( $\pm 1.1$ )(Bremen) 1.3( $\pm 0.3$ )(Graz) 1.9( $\pm 4.4$ )(Lausanne) 1.6( $\pm 1.8$ )(Lund).
- 4.Clearance : 19.8ml/min and the terminal half life was between 44.0 and 92.8 hours.
- 18.3 $\pm 4.5$ ml/min and the terminal half life was 79.6 $\pm 32.8$  hours.<sup>(5)</sup>
- 5.stability: questions still remain for BSH under physiological conditions, as the SH group can be converted to BSSB (B24H22S2)-4 dimer

- BPA:1.Toxicity: no significant side effects
- 2.Concentration of  $^{10}\text{B}$  : range between 15 to 40 ppm <sup>(6)</sup>
- 3.Uptake ratio : between 2.5 and 3.7(varies greatly between patients and between samples)
- 4.Clearance : renal clearance of the BPA (  $T_{1/2}$  ) = 3 h
- 5.Stability: stable within in 12 days with proper protection

## Development of the third generation

Currently, BPA and BSH has not met our expectations. Thus, scientists are developing the third generation of compounds. In this section, we will mainly discuss the nanomaterial-based agents and boronated porphyrins as they show promising results and capture the most interest from scientists.

### 1.Nanomaterial-based agents-Boron peptides and antibodies

EGFR, which is known as epidermal growth factor receptor and its mutant form EGFRVIII are always over expressed in the brain tumours, as a result, many agents are designed to target them. Boronated EGF or anti-EGFR monoclonal antibodies are always selected as targets.

### 2.Nanomaterial-based agents-Liposomes

Liposomes contain membranes of phospholipids. Liposomes are thought to be able to carry large quantities of  $^{10}\text{B}$  to localized tumours. However, the usage of liposome has the problem of rapid clearance by the reticuloendothelial system and it has been shown that if the diameters of liposomes are above 50nm, it will be difficult to pass through the blood brain barrier.

### 3.Nanomaterial-based agents-Magnetic nanoparticles

Magnetic nanoparticles are tumour specific which can decrease the required dose and the undesirable side effects. People are developing a new generation of magnetic liposomes which contain both drugs and ferromagnetic material. In theory, when an external magnetic field is present, liposomes can function as a drug carrier and the dose of drug is only 20% of the regular dose.

### 4.Nanomaterial-based agents-Carbon and Boron nanotubes

Carbon nanotubes (CNTs) are allotropes of carbon with a cylindrical nanostructure to achieve high boron content, Nido-carborane units were attached to sidewalls of SWCNTs. Boron nanotubes(BNT)are aimed to deal with the limitations of the carbon nanotubes and the first single-wall BNT was synthesised successfully in 2004. Boron nitride nanotubes(BNNTs)have many similar properties as CNTs, and have a high boron content of above 40% and have been proved to be nontoxic, but more in vivo studies are needed to prove them as an efficient candidate for BNCT.

### 5.Boronated porphyrin

Porphyrin was found to be both selective and can remain for a long time in the tumours, as a result, many boronated porphyrins were made and expected to be an efficient vehicle. It was considered possible to improve the efficiency and develop the dual application of BNCT and PDT (photodynamic therapy) as boronated porphyrins can act as photosensitisers.

## Future work

- 1.Comparison between the properties and compare their advantages and disadvantages.
- 2.Select the most important of the five main criteria to determine which compound is the most suitable.
- 3.Explore the future potential of those compounds such as cost and the development of technology and make the conclusion of what compound is the most suitable to be used, the second generations(BPA and BSH) or one of the developing agents in the third generation.
- 4.Indication of the lack of clinical trials for the ongoing development of agents in the third generation and problems this may cause.

### Key reference:

1. Boron neutron capture therapy-Wikipedia
2. Boron Neutron Capture Therapy of Cancer: Current Status and Future Prospects
- 3.Avaialbe from <http://www.pharmainfo.net/reviews/boron-neutron-capture-therapy-overview>
4. Available from <http://www.lookchem.com/cas-905/90580-64-6.html>
5. Drugs for BNCT:BSH and BPA
6. BPA uptake in rat tissues after partial hepatectomy