論文 / 著書情報
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Title(English)	Application and Functional Modification of Drug Delivery Systems based on Poly(vinyl alcohol) and Boronophenylalanine
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（博士課程）
Doctoral Program

論 文 要 旨

THESIS SUMMARY

系・コース： Department of, Graduate major in	生命理工学 ライフエンジニアリング	系 コース	申請学位（専攻分野）： Academic Degree Requested	博士 (工学) Doctor of (engineering)
学生氏名： Student's Name	小成田 翔		審査員主査： Chief Examiner	西山伸宏

要旨（英文 800 語程度）
Thesis Summary（approx.800 English Words ）

1. Introduction

Boron neutron capture therapy (BNCT) is emerging cancer treatment technique, utilizing the nuclear fusion reaction between boron isotope ^{10}B and thermal neutrons. L-4-Boronophenylalanine (L-BPA) is only approved BNCT agent and commonly used clinically. L-BPA selectively accumulates in cancer cells via the amino acid transporter LAT1, which is reported to be up-regulated in many cancer cells. L-BPA has achieved high therapeutic efficacy in clinical practice of locally recurrent head and neck cancer, and it is expected to be expand the application to other cancers. However, BPA has poor tumor retention and cannot maintain sufficient boron concentration in tumors during thermal neutron irradiation, which takes 30-60 minutes after the end of administration. This is because of the antiport mechanism of LAT1. When extracellular L-BPA concentration is high, L-BPA is taken up with the exchange of intracellular amino acids, such as glutamine through LAT1, but when the concentration of extracellular L-BPA decrease, intracellular L-BPA is efflux with the exchange of extracellular amino acid, such as tyrosine. Thus, in order to maintain the intratumoral boron concentration sufficiently high during the irradiation time of 30-60 minutes, continuous administration of BPA during irradiation as described above is essential. In addition, with the development of neutron irradiation technology, the types of cancers to which BNCT can be applied will become more diverse, including cancers that require longer irradiation times than conventional BNCT (described in introduction of chapter 2). However, as the more irradiation time, it needs more administration of boron compound, meaning the risk of adverse events derives from overdose. Further, during neutron beam irradiation, only the patient is allowed to enter the treatment room, so there remain issues such as being unable to respond immediately to accidents such as an IV needle falling out, or sudden changes in the patient's physical condition. Hence, there has been a need to maintain high intratumoral boron concentrations without continuous administration. In this regard, the therapeutic effect of L-BPA can be greatly improved by binding the polymer PVA to L-BPA with boronate ester (PVA-BPA) to change its intracellular uptake pathway from LAT1 antiport mechanism to LAT1-mediated endocytosis, thereby improving its intracellular retention and tumor accumulation amount. This PVA-BPA complex showed high therapeutic potential, surpassing that of L-BPA only. In addition to the high therapeutic capacity, PVA-BPA is very simply prepared by mixing of PVA and BPA in aqueous solution. Further, PVA could be simple manufacturing and has long history as a biocompatible material. Hence, PVA-BPA is expected to be used in clinical translation in the future. Also, PVA-BPA has excellent property as drug delivery system (DDS) for tumor targeting. Here, I investigated the feasibility of PVA-BPA for the clinical translation and the functional modification of PVA-BPA as new DDS.

2. Research Content

1) Firstly, I described the basic studies on the preliminary step toward the ultimate goal of clinical application of this PVA-BPA complex. PVA is obtained by polymerization of vinyl acetate and saponification of polyvinyl acetate. And the molecular weight (degree of polymerization) and the saponification ratio of PVA may affect the tumor accumulation property of PVA-BPA. Hence, firstly the relationships between the structural property of PVA and tumor accumulation was evaluated in CT26 tumor bearing balb/c mice. In addition, when considering the clinical application of PVA-BPA, it is essential to arrange the composition of PVA-BPA solution because the conventional method of preparation of PVA-BPA used a weakly basic solution, which may cause alkalosis and other adverse events due to the very high dosage. In this regard, I prepared a new PVA-BPA solution, under near physiological pH conditions by adding sorbitol, a solubilizer of BPA currently used in clinical BNCT, and this new PVA-BPA solution was termed PVA-sorbitol-BPA, evaluating the toxicity. Then, the tumor targetability and therapeutic effect of PVA-sorbitol-BPA solution were evaluated, using clinically relevant tumor model in which human lung cancer-derived A549-luc cells were seeded into the pleura of Athymic mice. And it was found that PVA-sorbitol-BPA reduced the adverse events caused by PVA-BPA, while retaining the drug delivery capacity and therapeutic efficacy of PVA-BPA.

2) Secondly, I investigated the effect of structural changes of BPA as a component of PVA-BPA on the pharmacokinetics: BPA is an amino acid derivative that has two mirror-image isomers, L-4-boronophenylalanine (L-BPA) and D-4-boronophenylalanine (D-BPA). The one used clinically is L-BPA, which is the mirror-image isomeric form of the amino acid found predominantly in nature. On the other hand, D-BPA shares structure with the non-natural form of the D-amino acid and D-BPA has been considered an inactive molecule with poor tumor accumulation in previous studies of BPA. However, some studies have shown that D-BPA may have high LAT1 and tumor selectivity. Hence, there was possibility that this selectivity could develop a new PVA-BPA complex with enhanced tumor selectivity. Thus, we evaluated this new drug delivery system, PVA-D-BPA, in terms of cellular uptake, drug delivery capacity in a mouse model, and therapeutic efficacy in BNCT, and found that it showed similar or better tumor selectivity and therapeutic efficacy than PVA-L-BPA. Importantly, this is a result that could not be achieved with single-agent D-BPA. This is significant as the world's first research result showing that the use of PVA increases the usefulness of D-amino acid derivatives as pharmaceuticals.

3. Conclusion

In this research, I demonstrated the high potentiality for clinical translation of PVA-BPA, and discover the unprecedent function of PVA-BPA complex by the use of optical isomers of BPA, adding new insights into drug delivery concepts.

備考 ： 論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note : Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1copy of 800 Words (English).

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