Abstract

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Studies on the selected methods potentially improving the therapeutic effectiveness of 4-borono-L-phenylalanine in boron neutron capture therapy

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Treatment of cancerous diseases still remains one of the biggest challenges of modern medicine. A promising alternative to conventional therapeutic modalities is boron neutron capture therapy (BNCT), a method currently experiencing a renaissance, due to the latest advances in the development of accelerators. The principle of BNCT is the use of a nuclear reaction occurring between ^{10}B isotope, specifically delivered to the tumour site, and thermal neutrons from the external beam, provided by accelerators or nuclear reactors. The products of this reaction are heavy ions that destroy cancerous cells. A significant limitation, however, is the lack of appropriately effective boron carrier. The modification of a boron compound already implemented in clinical practice with e.g. the use of modern drug delivery systems, may be a promising solution to obtaining an appropriate boron carrier for BNCT.

In this study, I focused on the methods potentially improving the therapeutic effectiveness of 4-borono-L-phenylalanine (BPA), a boron compound already used in clinical practice in BNCT, by investigating two aspects. The first one concentrated on the design and characterization of molecularly imprinted polymers (MIPs), modern polymeric materials, as BPA delivery systems. The second, cellular-assay-based, concerned using the L-amino-acidic analogues of BPA in order to increase the BPA uptake in cells. L-amino acids are transported through an antiport mechanism coupled with a substrate, which causes the preloading with the chosen analogue to enhance BPA uptake. In order to assess this uptake, I developed a new method for the determination of boron concentration in cells using single cell inductively coupled plasma mass spectrometry (SC-ICP-MS).

I successfully synthesized MIPs of honeycomb-like structure using radical polymerization method, which were specific towards BPA and have shown no cytotoxicity towards tested cancerous and normal cell lines. Preloading with L-tyrosine has shown statistically significant effect on the BPA uptake in both non-small cell lung carcinoma cells and normal lung fibroblasts. The use of SC-ICP-MS in boron determination provided new

information on its distribution in cells and highlighted the heterogeneity in boron content in the case of cancerous cells.

The research proved that the designed MIPs have the potential for further *in vivo* applications as BPA carriers in BNCT, and that preloading with L-tyrosine seems a promising additional tool in BNCT treatment using BPA. Moreover, the newly developed method of boron analysis using SC-ICP-MS may become a significant technique in further research on boron-based therapies.