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Okayama University research: Nanotechnology for making cancer drugs more accessible to the brain

(Okayama, 22 February) **In a study reported in the *Journal of Controlled Release*, researchers from Okayama University describe the use of nanocarriers in selectively transporting anticancer drugs to brain tumors.**

Glioblastoma is an aggressive form of brain cancer that is best treated with boron neutron capture therapy (BNCT). BNCT involves the use of an agent that delivers boron into tumor tissues. When subsequently hit with radiation, boron (typically the 10B isotope is used) emits particles that kill neighboring cells. However, current methods do not cargo boron into cancer cells homogenously. Now, Associate professor MICHIUE Hiroyuki and Okayama university Neutron Therapy Research Center (NTRC) team have successfully used a nanocarrier that selectively delivers boron into brain tumors.

The carrier, known as the A6K peptide, is a nano-scale structure that spontaneously clusters to form hollow tubes when immersed in water. The peptide has a positively charged core, which attracts any negatively charged molecules in the vicinity and traps them inside it. Another bonus feature is that the assembled tubes easily pass through cell membranes. The researchers first combined varying concentrations of the A6K peptide and BSH (disodium undecahydro-mercapto-closo-dodecacarborate), a negatively charged boron-containing chemical. The ensuing complexes formed were observed under the electron microscope.

At high ratios of A6K: BSH a chaotic mess of branched complexes were produced, whereas at concentrations of 1:5 and lower, ordered spherical complexes were created. Seemingly, the BSH particles had been engulfed. These low concentration complexes were then introduced into glioma cells to find that they effectively penetrated the cancerous cells. However, the localization of only BSH into glioma cells was almost ten times less. A6K was thus highly competent in ushering BSH particles into the cells. Additionally, A6K-BSH did not induce any toxicity in the cells by itself.

To then investigate how the complexes were transported in the body, A6K-BSH was injected into the tails of mice with glioblastoma. Within 2 hours the levels of A6K-BSH peaked within the brain tumors of these mice. What's more, no drug complex was found in healthy tissues. Finally, the tumor-killing properties of A6K-BSH were assessed by treating cells with the complex and then bombarding the cells with radiation for 30 minutes. Within 24 hours, cells irradiated for 15 minutes or more stopped proliferating. The BSH-containing nanotubes were successful in targeting and preventing the growth of cancer cells.

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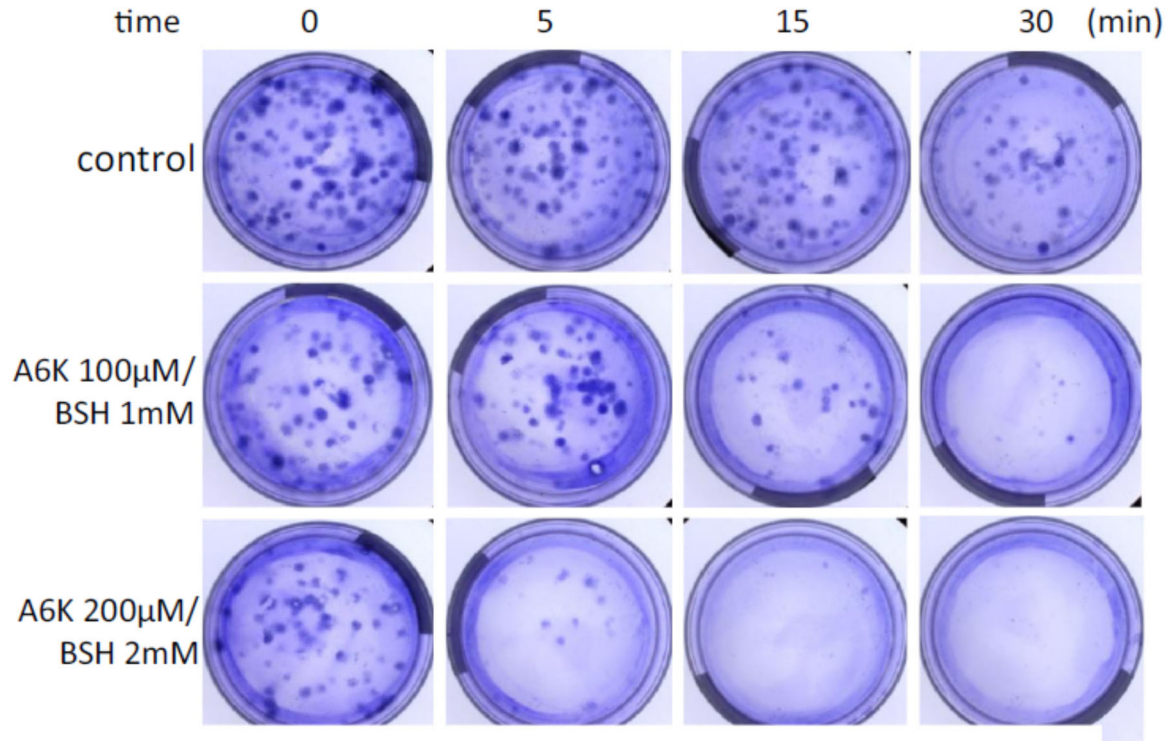
"We aimed to demonstrate a new boron delivery system based on A6K peptide and BSH, and open up a novel direction for boron agents in the next generation of BNCT," claim the researchers. They also point out the convenience of using this system which simply involves one mixing step before use. While the system remains to be fully tested in animals, it paves the way for directed killing of hard-to-reach tumors.

Background

Boron neutron capture therapy (BNCT): BNCT is a commonly used combination of drug and radiation therapy for cancers that are hard to target with traditional chemotherapy. BNCT involves transferring boron-containing compounds into cancer cells, and subsequently irradiating the cells with neutron beams. However, there are several challenges associated with traditional BNCT, such as ensuring that boron is escorted into tissues uniformly.

Pharmaceutical scientists are now designing novel delivery systems for these boron-containing compounds. A vast array of synthetic polymers has been investigated for this purpose, but these pose additional issues such as toxicity and degradation of the boron agents. The A6K nanotube is a small peptide molecule that has been used to deliver gene therapy in the past. This study demonstrates that the peptide can usher many more substances.



Caption

Colonies of cells treated with the A6K-BSH complex reduced greatly when exposed to radiation for 15 minutes or more suggesting that the growth of cancer cells was halted.

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Reference
Hiroyuki Michiue, Mizuki Kitamatsu, Asami Fukunaga, Nobushige Tsuboi, Atsushi Fujimura, Hiroaki Matsushita, Kazuyo Igawa, Tomonari Kasai, Natsuko Kondo, Hideki Matsui, Shuichi Furuya. Self-assembling A6K peptide nanotubes as a mercaptoundecahydrododecaborate (BSH) delivery system for boron neutron capture therapy (BNCT). *Journal of Controlled Release*, 2020 Nov 11;330:788-796.
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Reference (Okayama Univ. e-Bulletin): Professor MICHIUE's team
OU-MRU Vol.14 : Simplified boron compound may treat brain tumours

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Okayama University is one of the largest comprehensive universities in Japan with roots going back to the Medical Training Place sponsored by the Lord of Okayama and established in 1870. Now with 1,300 faculty and 13,000 students, the University offers courses in specialties ranging from medicine and pharmacy to humanities and physical sciences.

Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

Website: http://www.okayama-u.ac.jp/index_e.html

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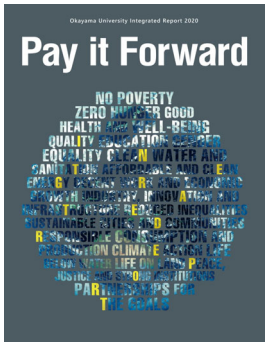

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An integrated report is intended to explain how an organization creates value over time through an organic integration of the vision and the combination of financial information and other information. Through this report we hope to promote greater interest in Okayama University among readers everywhere. In order to help us make improvements in future editions, we encourage you to contact us with any comments and suggestions you may have.

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