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Validation of HAV6 peptide in the transient modulation of Blood Brain Barrier in the treatment of Brain tumors

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Background:

The blood-brain barrier (BBB) poses a major obstacle by preventing potential therapeutic agents from reaching the desired target at sufficient concentrations. While transient disruption of the BBB has been used to enhance chemotherapeutic efficacy in treating brain tumors, limitations in terms of magnitude and duration of BBB disruption exist.

Objective:

HAV6 is a novel peptide that binds to cadherin and transiently opens the BBB. In this study, the safety and efficacy profile of HAV6 peptide was evaluated in a murine brain tumor model.

Methods:

Transient opening of the BBB in response to HAV6 peptide administration was quantitatively characterized using magnetic resonance imaging (MRI) and gadolinium contrast. We characterized the effects of HAV6 peptide on BBB integrity using a mouse model. The efficacy of concurrent administration of HAV6 peptide and a small molecule inhibitor, Adenanthin, in the treatment of medulloblastoma was tested by bioluminescence imaging of tumor bearing mice.

Results:

Systemic administration of HAV6 caused transient, reversible disruption of BBB in mice. HAV6 caused a rapid onset of increased BBB permeability in all regions of the brain. Quantitative assessment of Gd-DTPA contrast indicated ~2–4-fold increase in Gd-DTPA intensity and was most apparent within 6-9 minutes. Mass spectroscopy determined that Adenanthin would not cross the BBB. However, concurrent administration of HAV6 peptide and Adenanthin facilitated the delivery of this inhibitor across the BBB to the brain and caused reduced tumor growth and increased survival in tumor bearing mice. Mice receiving HAV6 peptide and Adenanthin showed significant improvement in tumor response with median survival of 30 days post-tumor cell injection, compared to controls; median survival 20 days.

Conclusion:

The rapid onset and transient nature of the BBB modulation produced with the HAV6 peptide along with its uniform disruption and excellent safety profile is well-suited for CNS drug delivery applications, especially in the treatment of brain tumors.

Conclusion:

Preliminary results suggest that communities with COHI do not have significantly lower rates of dental surgery to treat S-ECC. However, including other known risk factors of S-ECC in further statistical analyses will help to determine whether COHI leads to lower rates of surgery under general anesthesia.