Development of peptide vaccine for diffuse intrinsic pontine glioma

Executive Summary

Hypothesis-
Our hypothesis is that a peptide vaccination targeting H3.3\textsuperscript{K27M} will be an effective tumor-specific therapy for patients with gliomas expressing this mutation, without antigen escape or toxicity.

Goals-
To identify an effective therapy that will prolong the survival of children with DIPG.
We will pursue the following two specific aims:

1. To design an H3.3\textsuperscript{K27M} peptide vaccine and determine if it is immunogenic.
2. To determine if H3.3\textsuperscript{K27M} peptide vaccine can significantly prolong the survival of H3.3\textsuperscript{K27M} mutant DIPG-bearing mice.

Background-
Diffuse intrinsic pontine glioma is a type of brain cancer that arises in children and is incurable. Recently K27M mutations were described in H3.1 and H3.3 in up to 80% of human DIPGs.

Clinical Significance
DIPG is an incurable tumor. We are proposing to explore a new therapeutic strategy by developing a peptide vaccine against the mutant histone, a tumor specific antigen. Successful completion of this project will provide the scientific rationale for a clinical trial of a peptide vaccine for children with DIPG whose tumors harbor the H3.3K27M mutation (60% of children with DIPG).

Design and Methods of the proposed study-
This proposal brings together two labs: the Becher lab and the Sampson lab. The Becher lab has expertise in genetically engineered mouse models of DIPG and the Sampson lab has expertise with the development of peptide vaccines for gliomas. Aim 1 will be performed in the Sampson lab and Aim 2 will be performed in the Becher lab.

Aim 1- To design an H3.3\textsuperscript{K27M} peptide vaccine and determine if it is immunogenic.
We propose to develop and test a vaccine consisting of a peptide encompassing the mutant amino acid methionine substituting for a lysine. Our peptide design will be a 25-mer and will be called PEP-H3.3\textsuperscript{K27M}. The mutant amino acid is highlighted \textcolor{red}{15APRQLATKAARMSAPSTGGVKKPH}\textsuperscript{39}. The control 25-mer peptide will be called PEP-H3.3\textsuperscript{WT}: \textcolor{red}{15APRQLATKAARKSAPSTGGVKKPH}\textsuperscript{39}. We will vaccine mice at day 1, 7, 14 and on day 21 and assess the immune response by IFN\textgamma ELISpot to wild type and mutant peptides.

Aim 2- To determine if H3.3\textsuperscript{K27M} peptide vaccine can significantly prolong the survival of H3.3\textsuperscript{K27M} mutant DIPG-bearing mice.
we propose to test the efficacy of the PEP-H3.3\textsuperscript{K27M} peptide vaccine in mice bearing H3.3K27M mutant DIPGs. Cohorts will receive intradermal PEP-H3.3\textsuperscript{K27M} vaccination or intradermal PEP-H3.3\textsuperscript{WT} vaccination at the tail base once weekly for three weeks starting at 3 weeks post injection of virus-producing cells (postnatal D3-4). If we do not observe significant efficacy, we will then attempt strategies designed to overcome these barriers such as T-cell immunomodulatory agents (lymphodepletion with temozolomide) and/or adjuvants (KLH).