Abstracts

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DIPG-92. IMMUNE ACTIVATION STUDIES WITH THE NEOANTIGEN-BASED PEPTIDE VACCINE RHSC-DIPGVAX DEMONSTRATE ANTIBODY-MEDIATED RESPONSES AND EPITOPE SPREADING IN PEDIATRIC PATIENTS WITH DIFFUSE INTRINSIC PONTINE GLIOMAS (DIPG)

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BACKGROUND: Approximately 80% of DIPGs carry gain-of-function lysine-to-methionine (K27M) mutations in histone H3 proteins that frequently co-occur with other protein aberrations, including p53, ACVR1, and PDGFRα. Because the DIPG microenvironment has few infiltrating immune cells, resolution of negative regulatory mechanisms through checkpoint blockade may be necessary to promote vaccine-induced anti-tumor responses. Accordingly, rHSC-DIPGVax is a neoantigen-based peptide vaccine combined with checkpoint inhibitors currently under investigation in a clinical trial, NCT04943348. The vaccine contains 16 neoantigen peptides, QS-21 adjuvant, and recombinant heat shock protein, Hsc70. In this study, we investigate vaccine-induced antibody-mediated immunity and the phenomenon of epitope spreading, an extension of the immune response to secondary epitopes not directly targeted by the therapy, thus promoting distinct, individualized responses. METHODS: rHSC-DIPGVax is administered every two weeks to patients with DIPG and blood is collected pre-treatment and prior to each dose. To investigate vaccine-induced immunoreactivity to neoantigens targeted by rHSC-DIPGVax, DIPG lysates resolved by two-dimensional gel electrophoresis are immunoblotted with pre- and post-vaccine patient plasma containing antibodies against vaccine antigens. Proteins are immunoprecipitated (IP) from DIPG lysates, followed by mass spectrometry (MS) identification and validation. RESULTS: In eight subjects to date, vaccination with rHSC-DIPGVax consistently induces IgM and IgG antibodies against proteins directly targeted by the vaccine, including strong immunoreactivity to ACVR1. Furthermore, antibodies against several secondary proteins are also detected in post-vaccination plasma. Immunoblotting and IP-MS analysis identified several distinct candidates of epitope spreading, including the tumor antigens CEP290, DNAH3, HRNR, KDM6B, LAMA5, and TRPA1. CONCLUSIONS: rHSC-DIPGVax induces antibody-mediated tumor-specific responses to DIPG neoantigens, including direct vaccine targets and secondary targets via intra- and inter-molecular epitope spreading. We also present an experimental protocol to investigate vaccine-induced immune activation. Our ongoing studies aim to validate epitope spreading candidates and determine the important biological correlates between antibody responses and clinical outcomes.