Peds-ONC Immunotherapy Center:
Enhancing Antigen and Cytokine Expression to Break Immune Tolerance

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Abstract

Gliomas, like other solid tumors, restrict immune recognition of aberrant cancer cells. Further complicating this, pediatric cancers also have lower mutation rates than adult tumors making them more difficult to generate an immunotherapeutic response. This proposal addresses three mechanisms contributing to immune resistance in pediatric tumors: 1) low mutational loads, 2) myeloid immunosuppressive environment, and 3) MHC downregulation (immuno-editing). We have developed a multimodal virus-based vaccine platform that uses the virus's natural ability to recruit immune cells and break immune tolerance to improve immune activity against the tumor. By encoding tumor associated self-antigens within the viral genome so that they are expressed during infection our results show that we can convert the antiviral response into an anti-tumor response. The studies described in our proposal seek to improve our virus-based multi-modal vaccine approach to overcome immune restriction in one of the most difficult to treat solid tumors, malignant glioma.

Hypothesis

Engineered viral modifications that enhance native and adoptive immune cell activity will improve durable anti-tumor activity in treatment-resistant pediatric gliomas

Background

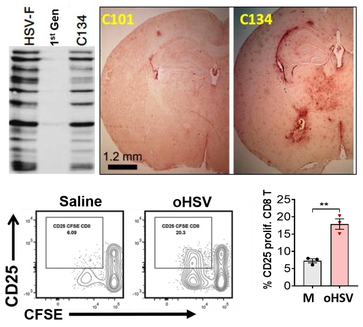

Fig 1 C134 is a next generation virus that evades translational arrest and stimulates early IFN and chemokine signaling (Cassady 2017). In some tumor models, oHSV treatment stimulates tumor specific T cells that recognize and suppress tumor growth after virus infection has resolved (Ghonime and Cassady, CIR, 2018). Other tumors however are less responsive and OV therapy induces an antiviral rather than tumor specific response. Pediatric Tumors have low mutational loads and are less immune reponsive. Our project focuses on improving virotherapeutic response in cold tumors

Pediatric tumors are less immunoresponsive

- High Mutational load Adult Cancers
- Lower mutational rate and expression of embryonic self antigens.
- Increased myeloid-associated cells immunosuppressive environment
- MHC I and II immuno-edited tumors impair T cell antigen responses

"Hot Tumors"

"Cold Tumors"

Aims

Aim I OVERVIEW

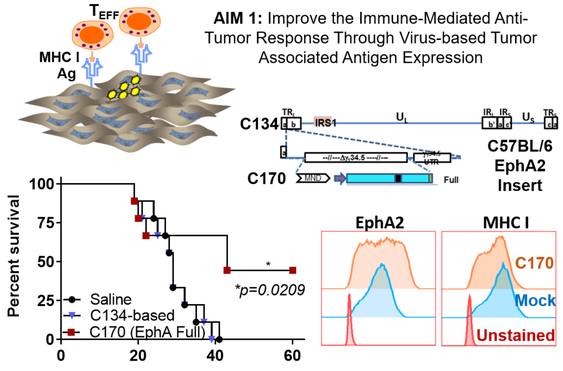

Fig 2 OV-based tumor associated antigen (TAA) expression improves anti-tumor activity and overall survival in an immunotherapy resistant EphA2(+) C57BL/6 based glioma

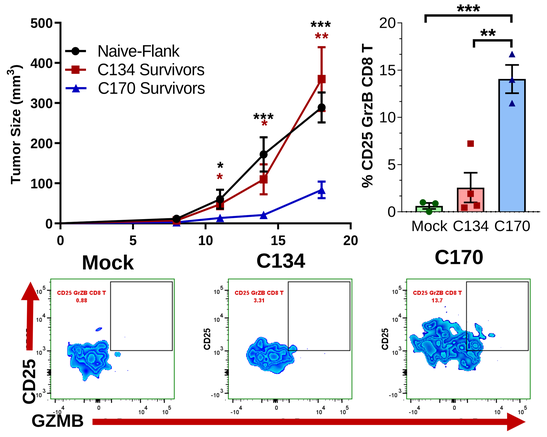

Fig 3 C170-treated mice suppress tumor growth on re-challenge and possess circulating CTLs with EphA2 functional response (Granzyme B production and CD25 upregulation shown after peptide pulsing)

AIM 1 studies will

- Determine how tumor associated EphA2 antigen and MHCI expression impacts C170 efficacy
- Evaluate whether C170 treatment induces epitope spread
- Delineate predictive immune markers of C170 anti-tumor response using CyTOF

Aim 2 OVERVIEW

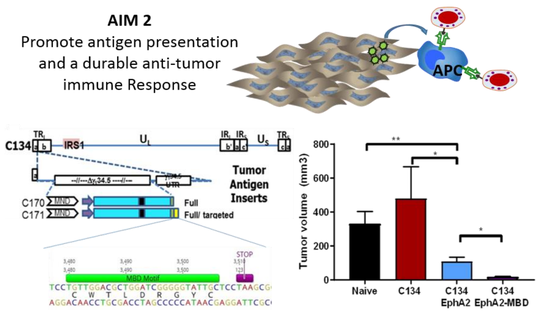

Fig 4 Myeloid targeting domains incorporated in the virus expressed antigen improve anti-tumor immune activity and suppresses tumor growth on re-challenge.

AIM 2 Studies will:

- Delineate how myeloid targeted TAAs enhance the anti-tumor immune response
- Improve anti-tumor T cell response by incorporating antigen presenting cell targeting domains in the TAAs for myeloid rich tumors
- Suppress tumor associated myeloid populations to improve the immune mediated T cell anti-tumor activity (In collaboration with **Dr. Cripe**)

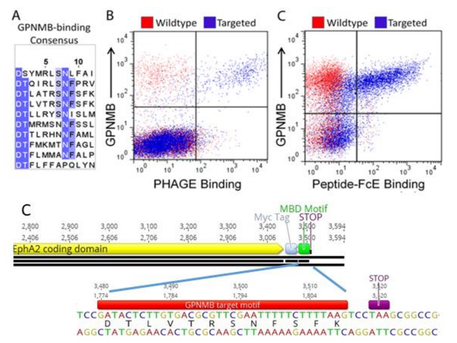

Fig 5 Phage binding studies identified a consensus 12mer peptide domain that binds GPNMB (a surface protein involved in macrophage polarization and T cell activation). By incorporating this 12 AA sequence into the expressed antigen, we postulate that this will both improve EphA2 uptake by antigen presenting cells and improve T cell immunity against the viral expressed TAA

Aim 3 OVERVIEW

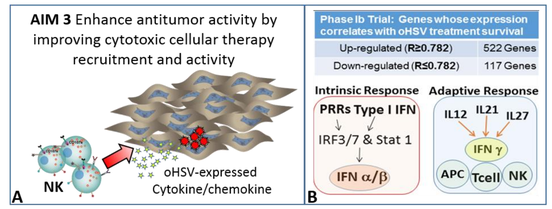

Fig 6 Phase I clinical studies show that antiviral Type I IFN and adaptive immune cell responses correlate with OV-mediated survival. Immunoedited tumors (e.g. MHC I downregulated) may suppress virus-TAA therapy. We postulate that oHSV cytokine & chemokine expression in combination with adoptive cellular therapy will overcome these restrictions.

Aim 3 Studies will:

- Evaluate OV-based cytokine and chemokine effect with native immune cell activity
- Improve adoptive cellular therapy (NK and CAR-NK) recruitment and anti-tumor activity using oHSV-based chemokine and cytokine expression (in collaboration with **Dr. Lee** and **Dr. Cairo**)

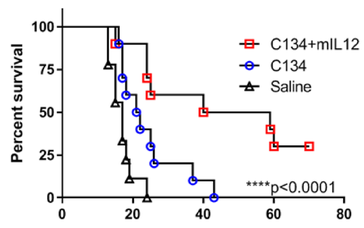

Fig 7 Treatment with a C134 based IL12 expressing virus improves survival in Balb/c mice with DBT malignant glioma brain tumors.

Impact

If successful, this flexible multimodal viral vaccine platform will harness and direct both native and adoptive cellular therapeutics against low mutational load immunotherapy-resistant tumors

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