2026 ACG-IRG Pilot Grant

IgG subclass switch to arm macrophages against neuroblastoma

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Abstract:

Background: Neuroblastoma is the most common solid tumor in infants, accounting for 700-800 new cases annually in the U.S. Despite aggressive multimodal therapy, survival for high-risk disease remains below 50%. The current FDA-approved immunotherapy, dinutuximab—an anti-GD2 antibody—kills tumor cells via antibody-dependent cellular cytotoxicity (ADCC) but requires co-administration of cytokines such as IL-2 and GM-CSF to enhance immune cell activation. Unfortunately, these cytokines cause severe, sometimes life-threatening toxicities, highlighting an urgent need for safer and more effective immunotherapies.

Objective and Hypothesis: This project aims to develop an improved anti-GD2 antibody that eliminates neuroblastoma cells without cytokine co-administration. Based on preliminary data, ***we hypothesize that anti-GD2 G4 induces pro-inflammatory phenotype in TAMs, resulting in T cell activation*.**

Specific Aim: Identify the impact of IgG4-S228P anti-GD2 (anti-GD2 G4)-mediated macrophage phenotype change on T cells. This aim will determine whether anti-GD2 G4-mediated pro-inflammatory macrophage activity and antigen presentation enhances T cell responses, establishing its potential as a cytokine-free immunotherapy and a foundation for combination therapy with immune checkpoint inhibitors.

Study Design: Human Fcγ receptor expressing mouse macrophages will be co-cultured with GD2-positive neuroblastoma cells and treated with IgG1 or IgG4-S22iP anti-GD2 antibodies, with or without CD64 blockade. Cytokine profiles (e.g., TNF-α, IL-6, IL-1β, TGF-β, IL-10) will be measured by ELISA arrays to evaluate macrophage polarization. Antigen presentation capacity will be assessed using OT-II T cell proliferation assays following macrophage co-culture. To connect in vitro findings with in vivo mechanisms, transcriptional signatures from single-cell RNA sequencing of xenograft tumors (from Year 1 Aim 2) will be compared with cytokine and T cell activation data to identify macrophage phenotypes associated with anti-GD2 G4 activity.

Expected Outcomes: We expect anti-GD2 G4 to increase pro-inflammatory cytokine secretion and enhance macrophage antigen-presenting capacity in a CD64-dependent manner, leading to greater T cell activation. These findings will define a new mechanism of macrophage-mediated tumor control and inform future studies testing anti-GD2 G4 in combination with PD-1/PD-L1 inhibitors in neuroblastoma.

Cancer Relevance: This study could lead to a new, less toxic immunotherapy for children with neuroblastoma and may also open the door to combining this antibody with existing immune checkpoint drugs for even stronger anti-cancer effects.