2025 ACG-IRG Pilot Grant

IgG subclass switch to arm macrophages against neuroblastoma

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Abstract:

Neuroblastoma is the most common solid tumor in infants, with only a 50% cure rate for high-risk cases. The FDA-approved treatment, dinutuximab, targets GD2, a molecule found on neuroblastoma cells, helping the immune system eliminate tumors through antibody-dependent cellular cytotoxicity (ADCC). To enhance this effect, dinutuximab is given with cytokines, which activate immune cells. However, this approach has severe side effects, with over 50% of high-grade toxicities linked to cytokines, including life-threatening complications. Safer alternatives that activate ADCC without cytokines are needed to improve treatment effectiveness while reducing side effects. The goal of this study is to bring an improved antibody therapy for neuroblastoma, which has enhanced efficacy with less adverse effects. We previously found that tumor-associated macrophages (TAMs) can be activated to kill cancer cells without cytokines by modifying antibody subclasses. Switching an antibody targeting integrin αvβ3 from IgG1 to IgG4 enhanced its binding to CD64, a receptor found only on macrophages. This approach effectively reduced αvβ3+ lung and pancreatic tumors in mice and patient- derived tissues. Since neuroblastoma tumors are rich in TAMs but have few other ADCC-related immune cells, this strategy could be particularly effective for neuroblastoma, offering a potential new therapy with fewer side effects.

While the IgG4 anti-αvβ3 antibody improves tumor cell killing through ADCC, it does not trigger phagocytosis (ADCP) due to high CD47 levels, which signal macrophages not to attack. We found that adding SIRPα, a CD47 blocker, to the antibody restores ADCP activity. We have developed a series of IgG4 anti-GD2 antibodies, with SIRPα conjugations. Aim 1 (Identify which anti-GD2 antibody presents the best efficacy with least side effects.) will test the hypothesis that this series of anti-GD antibodies achieves greater neuroblastoma growth inhibition via macrophage-mediated ADCC and/or ADCP compared to dinutuximab, using neuroblastoma xenograft models readily available in PI's laboratory.

While monoclonal antibody therapy is a key treatment approach for patients with advanced-stage cancers, its efficacy, particularly in solid tumors, remains limited compared to small molecule inhibitors targeting same pathways. Our preliminary data show that macrophages are the main immune cells driving ADCC in these cancers. Switching of antibody subclass from IgG1 to IgG4 enhances macrophage-mediated ADCC, promotes anti-tumor activity, and increases TAM proliferation. Similarly, IgG4 anti-GD2 antibodies selectively activate macrophages, offering a promising approach to improve antibody therapy effectiveness for solid tumors, including neuroblastoma, while reducing the limitations of current treatments. Aim 2 (Determine how anti-GD2 G4 activates anti-tumor phenotype of TAMs.) will test the hypothesis that engagement of IgG4 with CD64 on TAMs promotes macrophage proliferation and ADCC, by comparing signaling pathways in TAMs from xenograft tissues from mice treated with vehicle or the IgG4 anti-GD2 antibody.

If successful, this study will lead to better antibody treatments for neuroblastoma, helping to save the lives of babies and toddlers while reducing the severe side effects of current therapies. It will also lay the groundwork for future research to develop more effective antibody treatments for other types of cancer.