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Targeting tumor-associated macrophages to improve immunotherapy in neuroblastoma

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Scientific Abstract:

Neuroblastoma is the most common extracranial pediatric cancer. Despite aggressive treatments, including anti- GD2 immunotherapy, high-risk patients show poor prognosis. The immunosuppressive tumor microenvironment (TME) generated partly by tumor-associated macrophages (TAMs) dampens effective anti-tumor immune responses and promotes resistance to immunotherapy in neuroblastoma. Independent studies from the Joshi lab and the Varner lab have identified two targets expressed in TAMs, Syk, and PI3Kγ, that promote immunosuppression in the TME. Preliminary and published data from the Joshi lab have shown that genetic deletion of myeloid Syk or use of Syk inhibitor, R788, destabilizes hypoxia-inducible factor (HIF1/2α) to promote T-cell mediated anti-tumor responses in various tumors, including neuroblastoma. Published studies from the Varner lab have shown that genetic or pharmacological inhibition of PI3Kγ promotes NF-kB-dependent immune-stimulatory macrophage polarization, CD8+ T cell activation, and reduced tumor growth in various cancer models. These results led to several clinical trials of PI3Kγ inhibitor (eganelisib) either alone or with checkpoint inhibitors and chemotherapy in adult solid tumors. Hence, we propose to test the central hypothesis that inhibition of Syk or PI3Kγ will skew the immunosuppressive TME towards immunostimulation and, together with anti-GD2 mAb, activate anti-tumor immunity in high-risk neuroblastoma. Furthermore, we propose that combined inhibition of Syk and/or PI3Kγ will maximally reduce macrophage-mediated immunosuppression and enhance responses to anti-GD2 mAb in mouse models of high-risk neuroblastoma. This collaborative proposal by Dr. Joshi and Dr. Varner aims to develop new therapeutic options targeting Syk and/or PI3Kγ to improve outcomes for children with neuroblastoma.

Lay Abstract:

Neuroblastoma is a cancer that accounts for more than 15% of all childhood cancer deaths. Despite multimodal therapy, the 5-year survival rate of children with high-risk disease is very low. Hence, novel and safe therapies are needed to combat this childhood cancer. Here, we propose a targeted strategy to improve the effectiveness of anti-cancer therapy for this childhood cancer. In studies performed in the laboratory, we found that two enzymes, Syk and PI3K gamma, each controls the tumor-promoting properties of immune cells called macrophages. When cancer cells start to develop in the body, macrophages are quickly recruited into the tumor to kill and destroy cancer cells. However, these macrophages are very quickly re-educated by cancer cells to promote tumor growth and suppress the activity of other immune cells, especially tumor-killing T cells. This change in macrophages prevents killer T cell entry into tumors and suppresses the efficacy of current therapy. Our studies have shown that inhibiting the action of Syk or PI3K gamma causes macrophages and T cells to mount a continued response against various experimental solid tumors. Indeed, early clinical studies of the inhibitor eganelisib in adult cancer patients demonstrated improved clinical responses to the standard of care therapy. Hence, we propose that Syk inhibitors or/and PI3K gamma inhibitors together with
anti-GD2 immunotherapy have the potential to improve the survival of pediatric cancer patients with neuroblastoma. The results of our proposed preclinical studies may be rapidly translated into therapy against neuroblastoma to improve the survival of children with high-risk disease.