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“Elucidating the role of Syk kinase and Syk inhibitors combined with Radiation Therapy in Neuroblastoma”

Shweta Joshi, PhD (MCC)
Andrew Sharabi, MD, PhD (MCC)



SAN DIEGO'S NATIONAL CANCER INSTITUTE – DESIGNATED CANCER CENTERS



SCIENTIFIC ABSTRACT

Neuroblastoma (NB) is the most common extracranial pediatric cancer and even after aggressive multimodal treatments including high dose chemotherapy, radiotherapy, and immunotherapy, high risk patients succumb to progressive disease. One of the reasons underlying failure of these therapies in NB is the highly immunosuppressive tumor microenvironment generated by M2 polarized macrophages (M Φ) that inhibit both innate and adaptive immune responses. Recently Joshi lab has discovered that Syk kinase is abundantly present in M Φ s from NB and that increased expression of Syk kinase promotes immunosuppressive macrophage polarization and tumor progression in a MYCN-driven mouse model of NB. Furthermore, in a collaborative study, Sharabi lab and Joshi lab have preliminary data suggesting Syk inhibitors may enhance the efficacy of radiotherapy and checkpoint blockade. **Our central hypothesis is that Syk kinase programs M Φ s to an immunosuppressive phenotype and Syk inhibition combined with radiotherapy or checkpoint inhibitors will reverse M Φ s mediated immunosuppression and activate anti-tumor immune responses.** In Aim 1 we will dissect the role of macrophage Syk Kinase in neuroblastoma tumor progression and identify downstream factors of Syk kinase that are important in mediating immunosuppression. In Aim 2 we will determine whether inhibition of Syk kinase enhances responses to radiotherapy in combination with checkpoint blockade immunotherapy in neuroblastoma. Ultimately the goal of this collaborative proposal by Dr. Joshi and Dr. Sharabi is to develop new therapeutic options targeting Syk kinase to improve outcomes for children with NB.

LAY ABSTRACT

Neuroblastoma is a cancer that develops in certain types of nerve tissues and is responsible for more than 15% of all childhood cancer deaths. Despite aggressive treatments including chemotherapy, radiation, and immunotherapy the 5 year survival of children with high risk neuroblastoma is only 40-50%. We are proposing a targeted strategy to make immunotherapy and radiotherapy more powerful in this cancer. In a study performed in mice, we found that Syk kinase controls the response of immune cells called macrophages. When cancer cells start growing in body, macrophages get recruited into the tumor and try to kill and destroy cancer cells, but very soon these macrophages get educated by cancer cells to promote tumor growth and to suppress the activity of other immune cells, especially T cells. This change

in phenotype of macrophages does not allow the T cells to enter in to the tumor and it also interferes with the success of immunotherapy. Similarly, after radiotherapy, macrophages hinder the activity of T cells which leads to tumor relapse. Our studies have shown that inhibiting the action of Syk kinase caused macrophages and T cells to mount a continued response against pediatric tumors grafted onto mice. Moreover, we found that combination of Syk inhibitors with checkpoint inhibitors improved survival of mice grafted with pediatric tumors. Since macrophage response is suppressed in pediatric cancer patients, these results might be translated into therapy against neuroblastoma and can be combined with conventional radiotherapy and checkpoint inhibitors to improve survival of these children.