

MCC-C3 Padres Pedal the Cause Spring 2021

Identifying inhibitors of the feedback suppression of immune regulator signaling as novel cancer therapeutics



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Scientific Abstract:

Cancer is a devastating disease. New therapies are still needed to effectively combat cancer. Type I interferons (IFN-I) mediate immune responses via activation of the JAK-STAT signaling pathway and expression of IFN stimulated genes (ISGs). IFN-I elicit anti-proliferative effects on cancer cells and have been clinically used to treat more than 10 different types of cancers. In addition to being used directly in anticancer therapy, intrinsically produced IFN-I are critical in chemotherapy, radiation therapy and immunotherapy. However, due to the negative feedback regulation of IFN signal transduction, most ISGs are only transiently expressed limiting the efficacy of IFN therapy and IFN dependent therapies. Therefore, development and application of small molecule drugs to counteract the feedback suppression of IFN's anticancer effect directly or in combination treatments will greatly benefit cancer patients.

We cloned the USP18 gene and discovered that USP18 is a potent inhibitor of IFN-I signaling. IFN-activated JAK-STAT signaling and ISG expression are strongly enhanced and substantially prolonged in the absence of USP18. Therefore, USP18 mediates a major negative feedback regulation of IFN-I. Importantly, inhibition of USP18 greatly enhances immune responses in anticancer treatment. We propose to develop a toolbox of assays for identification of small molecule immunomodulators that target USP18 for cancer therapy, in collaboration among investigators in MCC and SBP using a C3 shared Chemical Library Screening (CLS) core facility. The results from this proposed work wilays the foundation for further bench-to-bedside translational studies and for a grant proposal in response to a recent NIH/NCI funding opportunity Announcement.

Lay Abstract:

Cancer is the most devastating human disease in the world. It affects almost everyone directly or indirectly. The immune cells of the human body secrete a group of proteins called "cytokines" that have specific effects on the interactions and communication between cells. A subset of these, Type I interferons (IFN-I) "interfere" with growth and promote the death of tumors. Indeed manufactured IFN-Is have been used to treat more than ten types of cancer. However, "feedback" mechanisms suppress their anticancer effectiveness over the long term. Therefore we propose to develop methods to identify and verify compounds that potently and selectively block this feedback suppression that could become the basis for novel cancer therapeutics. The proposed studies will be conducted in collaboration among scientists in Moores Cancer Center (MCC) and Sanford Burnham Preby's Medical Discovery Institute (SBP) using the SBP C3 Chemical Library Screening shared resource facility. resource facility. The results from this proposed work will also provide critical preliminary data in support of a future funding application from the National Cancer Institute and lays the foundation for further bench-to-bedside translational studies in our cancer center.