

# IFN $\gamma$ Susceptibility in Chordoma

Sadagopan, Ananthan (School: Westborough High School)

**Purpose:** Chordomas are rare spinal neoplasms uniquely characterized by their high expression of the transcription factor brachyury. Recently, defects in endogenous antigen presentation, a well-known tumor immune evasion mechanism undermining the efficacy of immune checkpoint inhibition, has been reported in solid tumors. The purpose of this study is to utilize the tumor suppressive cytokine gamma interferon (IFN $\gamma$ ) to upregulate these components rendering cells susceptible to checkpoint blockade. **Procedure:** The expression of human leukocyte antigens (HLA) and HLA class I antigen processing machinery (APM) components, proteins critical to endogenous antigen presentation, were monitored via intracellular flow cytometry in IFN $\gamma$  treated cells. Resistance mechanisms were delineated through genomics analysis and Western blotting. **Results:** Upregulation of HLA class I APM components follows high-dose IFN $\gamma$  treatment in chordoma cell lines CH22, MUG-CC1, MUG-Chor1, and U-CH1. However, both CH22 and MUG-CC1 possess IFN $\gamma$  resistance at lower doses. Further investigation reveals that defects in the IFN $\gamma$  signal transducer Janus kinase 1 (JAK1) confers this resistance. Genomics analysis and in-vitro work corroborate that these defects arise from the brachyury-mediated downregulation of this component. **Conclusion:** Several factors contribute to chordoma pathogenesis and limit the efficacy of immune checkpoint blockade. This exploratory investigation established that brachyury-mediated JAK1 downregulation conferring low-dose IFN $\gamma$  resistance plays a role.

## Awards Won:

Fourth Award of \$500