Ph-like B cell acute lymphoblastic leukemia with over expression of CRLF2 (CRLF2 B-ALL) is associated with high relapse rates and poor outcomes. CRLF2 is part of a receptor complex that is activated by the cytokine, TSLP. Our in vitro studies show that high physiological doses of TSLP induce upregulation of the Suppressor of Cytokine Signaling (SOCS) genes and shutdown of CRLF2 pathway signaling. In vivo, high physiological doses of human TSLP exert anti-leukemia effects, essentially eliminating CRLF2 B-ALL cells in patient-derived xenografts. These studies identify the human TSLP cytokine as a potential biologic for the treatment of CRLF2 B-ALL.