Waldenstrom macroglobulinemia (WM) is characterized by bone marrow infiltration by malignant B-cells with lymphoplasmacytic morphology and hypersecretion of monoclonal immunoglobulin M (IgM) protein. While therapies are available to treat the symptoms associated with WM, this malignancy remains incurable and more effective therapies to inhibit the malignant cells and suppress IgM production are needed. It is therefore critical to understand the mechanisms that result in the increased serum levels of IgM and to determine the factors in the bone marrow microenvironment that support malignant cell growth.

In initial work, we identified BAFF (B-cell Activating Factor/TNFSF13B), a member of the TNF family, as increased in the serum and bone marrow of WM patients and as a significant contributor to the increased serum IgM levels. We found that BAFF signaling is constitutively activated by a mutation in the BAFF receptor, BAFF-R, and that cytokines such as IL-6 and IL-21 promote BAFF-mediated IgM production. We showed that IL-6 signaling through the JAK/STAT pathway increased the secretion of IgM, and that IL-6 secretion is regulated in part by CCL5. Similarly, IL-21 is present in the bone marrow of WM patients and significantly increases IgM secretion by WM cells. Similar to IL-6, IL-21 induces phosphorylation of the JAK/STAT pathway, particularly STAT3, and treatment with a STAT3 inhibitor abolished the IL-21-mediated increase in IgM secretion. IL-21 also increased the expression of known STAT3 targets involved in B cell differentiation including BLIMP-1, XBP-1, IL-6 and IL-10.

These findings highlight the importance of cytokine-mediated JAK/STAT signaling in regulating IgM production in WM and suggest that targeting cytokine signaling may be clinically beneficial in this disease.