

**G3139 (BCL-2 antisense oligonucleotide) Therapy in Waldenstrom's
Macroglobulinemia (WM):**

Laboratory evaluation of potential clinical efficacy

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Bcl-2 is an attractive target for anti-cancer therapy in a number of malignancies, as its expression is associated with inhibition of the apoptotic program and resistance to traditional therapeutic agents. Bcl-2 anti-sense therapy with G3139 (oblimersen sodium, Genasense™, Genta Inc., Berkeley Heights, NJ) is in clinical trials for a number of malignancies including myeloma, non-Hodgkin's lymphoma and chronic lymphocytic leukemia. In these B-cell malignancies, blocks to apoptosis may play a role in disease progression and chemotherapeutic resistance. *In vitro* G3139 has been shown to downregulate bcl-2 in myeloma cells, sensitizing them to chemotherapeutic agents. With the support of the Research Fund for Waldenstrom's, we have undertaken a project to evaluate anti-sense inhibition strategies in WM, and whether, similar to other B-cell malignancies, the bcl-2 pathway may provide a therapeutic target in this disease. We will present data showing that bcl-2 is expressed in WM cells *in vitro* and that downregulation of bcl-2 and other anti-apoptotic signal transduction proteins may be achieved by treatment with G3139 anti-sense oligonucleotide. Treatment of WM cells with G3139 as a single agent is associated with increased cell death and shows potential synergy with chemotherapeutic agents active in WM. This preliminary data suggests that Bcl-2 downregulation via G3139 anti-sense treatment may have potential anti-cancer efficacy in WM *in vitro*, and further studies to address its effects on clinical specimens is warranted, in anticipation of using this agent in WM clinical trials.