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Proteasome inhibition enhances HLA-class-II antibody-dependent polymorphonuclear cell mediated cytotoxicity against B-cell lymphoma

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Monoclonal antibodies (mAb) complemented the therapy of malignant lymphomas. Currently, mAb against CD20 or CD52 are approved and CD22 or HLA-class-II mAb are in clinical trials for the treatment for malignant B-cell lymphomas. Mechanism of action *in vivo* is not yet completely understood, but direct induction of apoptosis, activation of complement, and Fc-receptor dependent mechanisms including antibody-dependent-cellular-cytotoxicity (ADCC) seem to contribute to their clinical efficacy. At the same time proteasome inhibitors (PI) were developed as a novel class of anti-neoplastic agents. Their proposed mechanism of action include inhibition of the NFκB pathway by blocking the degradation of IκB in the proteasome, overriding of Bcl-2 mediated resistance in lymphoma cells and induction of apoptosis. MG262 (Z-Leu-Leu-Leu- $B(OH)_2$) is a PI belonging to the peptide boronate class of PIs including the clinically successfull PI Bortezomib (Velcade), which is approved as third line treatment of multiple myeloma.

We have previously demonstrated that polymorphonuclear granulocytes (PMN) are potent effector cells mediating ADCC against a wide range of malignant B-cell opsonized with HLA-class-II mAb. In the presence of suboptimal concentrations of HLA-class-II directed mAb F3.3 isolated PMN mediated modest amounts of cytotoxicity in Cr-release assays, which were significantly enhanced in the presence of the PI MG262 (31 ± 12%, 15 ± 3%, 68 ± 8% specific lysis for F3.3, MG262 and F3.3+MG262). In the absence of PMN as effector cells mAb F3.3 at the suboptimal concentration of 0.01 μg/mL elicited no significant cytotoxicity, whereas MG262 mediated concentration dependent target cell death up to 15 ± 3% specific lysis at 2.5 μM.

However, whereas PMN mediated significant lysis with HLA-class-II mAb, no significant lysis was observed with CD20, CD22 or CD52 directed antibodies. The promising results with the combination of HLA-class-II mAb and PI encourage us to extend our experiments to the combination of PIs, including bortezomib, with Rituximab (CD20), Epratzumab (CD22) or Alemtuzumab (CD52) mAb mediated cytotoxicity using PMN as effector cells.