An inhibitor of proteasome β2 sites sensitizes myeloma cells to immunoproteasome inhibitors

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Proteasome inhibitors bortezomib, carfilzomib and ixazomib (approved by the US Food and Drug Administration [FDA]) induce remissions in patients with multiple myeloma (MM), but most patients eventually become resistant. MM and other hematologic malignancies express ubiquitous constitutive proteasomes and lymphoid tissue-specific immunoproteasomes; immunoproteasome expression is increased in resistant patients. Immunoproteasomes contain 3 distinct pairs of active sites, β5i, β1i, and β2i, which are different from their constitutive β5c, β1c, and β2c counterparts. Bortezomib and carfilzomib block β5c and β5i sites. We report here that pharmacologically relevant concentrations of β5i-specific inhibitor ONX-0914 show cytotoxicity in MM cell lines similar to that of carfilzomib and bortezomib. In addition, increasing immunoproteasome expression by interferon-γ increases sensitivity to ONX-0914 but not to carfilzomib. LU-102, an inhibitor of β2 sites, dramatically sensitizes MM cell lines and primary cells to ONX-0914. ONX-0914 synergizes with all FDA-approved proteasome inhibitors in MM in vitro and in vivo. Thus, immunoproteasome inhibitors, currently in clinical trials for the treatment of autoimmune diseases, should also be considered for the treatment of MM.