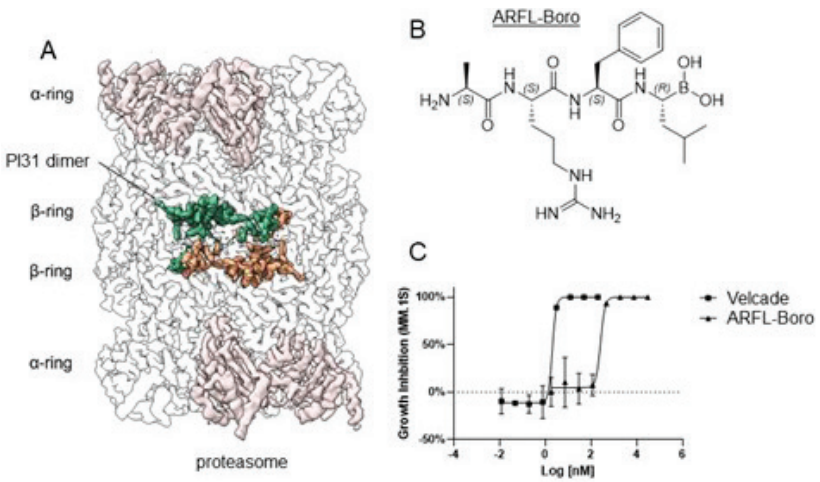

A) Cryo-EM structure of PI31 bound to the proteasome. B) Chemical structure of ARFL-boronic acid, a potent and specific inhibitor of human β2 designed using PI31's natural mechanism. C) Effective killing of multiple myeloma cells (MM.1S) by ARFL-boro.

First-in-Class Proteasome Inhibitors for Multiple Myeloma and Other Cancers

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Proteasome inhibitors are a multi-billion-dollar class of drugs approved for multiple myeloma. Despite their success, current inhibitors have major limitations including therapeutic resistance and severe side effects. The field is concentrated, with only three drugs supplied by two companies, and the market leader, bortezomib (Velcade), lost exclusivity in 2022. Furthermore, although the proteasome has three separate active sites (β1, β2, β5), all three drugs target the same site (β5).

We identified an endogenous proteasome inhibitor, PI31, that simultaneously targets all three active sites (Fig. 1A). A high-resolution structure of this protein bound to proteasome facilitated a new rational approach to proteasome inhibitor design and the development of a series of potent and specific β2 inhibitors derived from PI31. The lead molecule, ARFL-boronic acid (Fig. 1B), shows an in vitro half-maximal inhibitory concentration (IC50) of 45 nM against β2 with little activity against β5 or β1 (IC50>4000 nM). ARFL-boro strongly inhibited growth of multiple myeloma cells in culture (IC50=105 nM), suggesting favorable cell permeability and establishing β2 as a promising therapeutic target in myeloma for the first time (Fig. 1C). Combining ARFL-boro with an approved β5 inhibitor, Velcade, showed strongly synergistic activity against myeloma cells. We hypothesize that such β2/β5-targeting combination therapies might reduce therapeutic resistance and severe side effects.

We examined the efficacy of ARFL-boro against 160 cancer cell lines representing a broad spectrum of human malignancy, and identified three other tumor types showing strong sensitivity to ARFL-boro: acute lymphoblastic leukemia, acute myelogenous leukemia, and renal cell carcinoma.

Leveraging a fundamental breakthrough to develop a rational structure-guided approach to proteasome inhibitor discovery, we have identified a new therapeutic target in multiple myeloma (β2) and a series of potent and specific cell-permeable β2 inhibitors. These first-in-class compounds could potentially supplant current drugs, either as standalone agents or as a synergistic β2/β5 combination therapy. In addition, β2 inhibition could broaden the therapeutic applications of proteasome inhibitors to other oncologic indications.