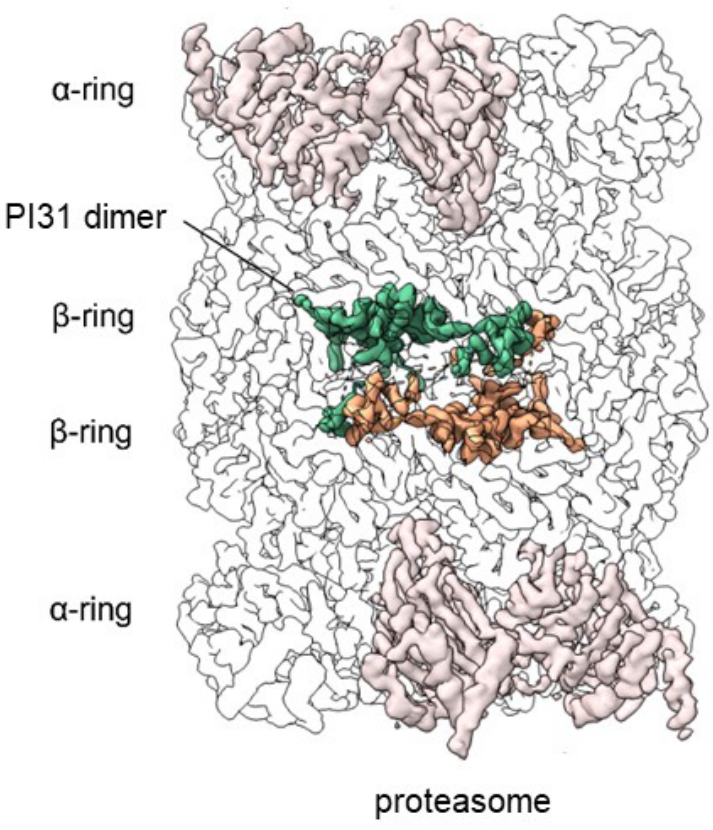
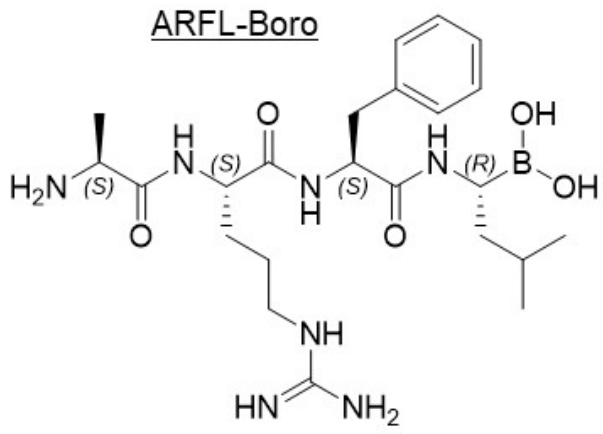
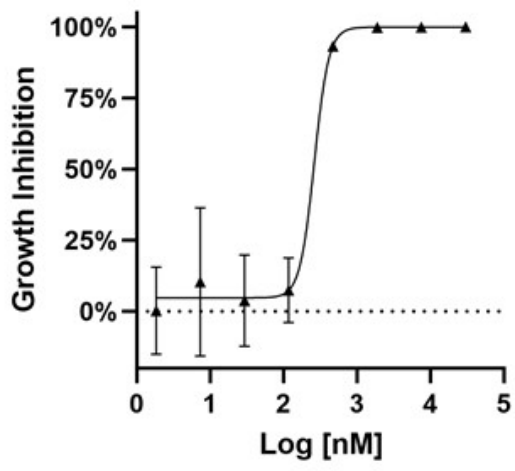
First Look

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







Clinical Need

Proteasome inhibitors are a multi-billion-dollar class of drugs approved for multiple myeloma. However, these drugs have significant limitations including therapeutic resistance and severe side effects. Furthermore, although the proteasome has three different active sites (β1, β2, β5), all three approved drugs target the same site (β5).

Our Innovative Approach

PI31 is an endogenous protein inhibitor of the proteasome. We discovered the inhibitory mechanism by which PI31 enters the proteasome and simultaneously inhibits all three active sites through direct interactions. This finding led to a new rational approach to develop proteasome inhibitors based on PI31's evolutionarily optimized mechanism.

Results

We developed a series of potent and specific β2 inhibitors. The lead molecule, ARFL-boronic acid, is highly effective *in vitro* (IC_{50}=45 nM) and in multiple myeloma cell lines (IC_{50}=105 nM). ARFL-boro shows strong synergistic activity with existing β5 inhibitors like Velcade. We hypothesize that such combination therapies could be useful in reducing rates of resistance and severe side effects. We tested ARFL-boro against 160 cancer cell lines and identified 3 other tumor types showing strong sensitivity.

Commercial Potential

This first-in-class approach has the potential to supplant current drugs—either as standalone agents or as synergistic combination therapies—and to expand the reach of this important drug class into new clinical indications.

MGB Innovation Contact
Alexia Filipputti
afilipputti@mgb.org

John Hanna, MD PhD
Pathologist and Principal Investigator, BWH;
Associate Professor of Pathology, HMS
jwhanna@bwh.harvard.edu