Towards optimized utility of proteasome inhibitors with peptide epoxyketones

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The ubiquitin/proteasome pathway is the primary means by which intracellular protein degradation occurs. The 26S proteasome, a multicatalytic proteolytic machine, plays a central role in regulating most facets of cell physiology and has been the target of drug discovery programs in cancer and inflammatory diseases. Proteasome inhibition is a validated therapeutic strategy for the treatment of B-cell neoplasms. Originating from the natural product epoxomicin, we have generated several peptide epoxyketones, with distinct pharmaceutic and pharmacologic profiles as proteasome inhibitors. One of these compounds, carfilzomib, has recently received FDA approval for the treatment of relapsed and refractory myeloma. A second compound, oprozomib, which is an orally bioavailable analog of carfilzomib, has entered clinical trials with encouraging initial results in the treatment of multiple myeloma. Another focus of our research is subunit selective inhibitors of the proteasome. Our discovery of subunit-selective peptide epoxyketones has helped elucidate distinct roles for both the immunoproteasome and constitutive proteasome in immune cell biology. Immunoproteasome selective inhibitors are highly efficacious in mouse models of autoimmunity and represent a new class of therapeutics for the treatment of inflammatory diseases.