cell line RPMI 8226; (iv) crystal structures in complex with yeast 20S proteasomes.
Results: Synthetic methodology was established for analogs with a variety of LG potentials and identities. Analogs bearing good LGs generally exhibited enhanced potency in bioassays. LG analogs gave rise to prolonged duration proteasome inhibition compared to non-LG analogs. Intermediate results were observed for fluorosalinosporamide, with poor LG potential. A model for the mechanism of irreversible inhibition by LG analogs versus slow substrate, non-LG analogs was developed. Crystal structures of inhibitor-20S proteasome complexes offered insights into inhibitor-active site interactions. A subset of LG analogs showed enhanced inhibition of C-L activity while maintaining good potency against CT-L and T-L sites.
Conclusions: Proteasome inhibition is enhanced by the presence of a good LG. Analogs that bear a substituent with good LG potential give rise to a common, highly stable cyclic ether product that cannot be deacylated and thus induces prolonged duration of proteasome inhibition. This "irreversible binding" holds true for all three proteolytic subunits. Specific LG identities resulted in enhanced potency against the C-L site.

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The selective proteasome inhibitor carfilzomib in combination with chemotherapeutic agents improves anti-tumor response in solid tumor xenograft models

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Background: Since treatment options for previously treated solid tumors are limited, novel combination therapies are warranted. Carfilzomib is a first in class selective epoxyketone proteasome inhibitor that is currently being evaluated in Phase 2 trials in solid tumors and multiple myeloma. Because the proteasome plays a central role in the regulation of a broad spectrum of cell signaling and protein homeostatic pathways, combining proteasome inhibition with standard chemotherapies represents a promising avenue for increasing anti-tumor responses and overcoming drug resistance in solid tumor cells. **Aim:** To determine the tolerance and efficacy of treatment regimens combining carfilzomib and approved chemotherapeutic agents for solid tumors in mouse tumor models.
Methods: Maximum tolerated doses (MTDs) of cisplatin (CDDP), carboplatin, irinotecan, docetaxel or Doxil on clinically relevant dose schedules in combination with carfilzomib were determined in immunocompromised (BNX) mice. Toxicity was assessed by body weight changes and clinical observations. BNX mice bearing established subcutaneous tumors of lung (A549) and colorectal (HT-29) human tumor cells were treated with carfilzomib, docetaxel, Doxil or combinations of carfilzomib and docetaxel or Doxil.
Results: Carfilzomib treatment was well tolerated in combination with a DNA-cross linking agent (carboplatin), a topoisomerase inhibitor (irinotecan), a microtubule disrupting agent (docetaxel) and an anthracycline (Doxil) at the MTD for each individual agent. A carfilzomib and CDDP combination resulted in increased toxicity if dosing commenced on the same day, but was well tolerated with a staggered dose schedule. The combination of carfilzomib and docetaxel resulted in a significant reduction in A549 tumor growth compared to vehicle controls or treatment with either single agent ($p < 0.001$ vs. control; $p < 0.01$ vs. carfilzomib or docetaxel alone). Similar observations were noted in the HT-29 xenograft model where a carfilzomib and Doxil combination significantly reduced tumor burden ($p < 0.001$ vs. control or carfilzomib alone; $p < 0.01$ vs. Doxil alone).
Conclusions: These results demonstrate that carfilzomib can be combined with chemotherapeutic agents of multiple classes. More importantly, the combination of carfilzomib with either docetaxel or Doxil improved anti-tumor responses in multiple solid tumor models. Clinical investigation of combining carfilzomib to standard of care in solid tumors is merited.