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# Design of mechanistically distinct proteasome inhibitors for the treatment of multiple myeloma

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Multiple myeloma (MM) is anincurable and fatal type of cancer that affects plasma cells, which will accumulate in the bone marrow leading to bone destruction. Although the leading MM drug, bortezomib, is undoubtedly one of the biggest breakthroughs in this field, nearly all patients become intolerant or resistant within a few years, after which the average survival time is less than one year. We will present the total synthesis and biological activity of several natural products and natural product-inspired scaffolds as mechanistically distinct proteasome inhibitors. The heterocyclic, small molecule proteasome inhibitors regulate proteasome activity via a non-competitive mechanism, by binding in a site not previously targeted by any drugs. Considering that these agents interact with the proteasome via a non-competitive mechanism they act additively with and overcome resistance to classic MM drugs such as bortezomib. The cellular activity of these orally available small molecules translates well *in vivo* and delayed tumor growth in an MM xenograft model to a similar extent as bortezomib. This presentation will discuss thesynthesis and biological properties in cell culture and *in vivo* of this alternative way of regulating the human proteasome.

## Biography

Jetze J Tepe received his PhD from the University of Virginia in 1998 with Prof. Timothy L. Macdonald and continued his post-doctoral studies with Prof. Robert M. Williams at Colorado State University. In 2000, he joined the faculty at Michigan State University where his lab is focused on the synthesis and biological evaluation of heterocyclic natural products. In 2003, he received the American Cancer Research Scholar award and he was the recipient of the Multiple Myeloma Research Foundation Senior Award in 2008 and 2010 and the International Myeloma Senior Award in 2013.

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