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Non-competitive regulation of the human proteasome by natural products and natural product inspired scaffolds

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Abstract

Multiple myeloma (MM) is an incurable 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. The underlining mechanism of resistance to bortezomib has been attributed, in part, to the formation of clusters of mutations in the proteasomes β5 subunit, which prevent drug binding. Unfortunately, since all clinically and second generation proteasome inhibitors proceed via the same mechanism of binding, all of them exhibit high cross-resistance. Thus, proteasome inhibitors that proceed via a different mechanism of action are desperately needed.

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. These non-competitive modulators acts 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.

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.