Hot Topics in Pharmacognosy: An "Ancient" Antibiotic with a New Use

By Dr. David Newman

For those of you who, like me, were playing with microbial natural products in the early 1960's, the news that the depsipeptide thiostrepton and its very close chemical cousin, siomycin A are now being considered as potential antitumor agents, comes as quite a pleasant surprise. (In my lexicon, microbes would definitely fall under a broad definition of pharmacognosy). These agents were both reported towards the beginning of the period now often referred to as the "Golden Age of Antibiotics," but they had problems being useful due to a predilection for solvents such as dimethylformamide (DMF), glacial acetic acid and others not considered to be "useful diluents for pharmaceutical usage!"

They were both potent inhibitors of protein synthesis in bacteria. Thiostrepton was shown in the early 1970s to bind to the 50S bacterial ribosome and inhibit enzymatic and non-enzymatic translocation in *Bacillus megaterium*.[1] This was followed the next year by the demonstration that in *B. megaterium*, thiostrepton's primary function was the inhibition of the functional binding of amino-acyl-tRNA to the ribosomal A site, a different conclusion from the work by Pestka1 and probably due to the lack of co-factors in the *in vitro* studies.[2]

Much work was performed on this compound in the next 30 years, including a total synthesis by the Nicolaou group in 2004,[3] along with further definition of the binding site(s) in the excellent review by Wilson (2009) that also included all reported bacterial translocation inhibitors.[4] In 2008, the "game changed" with the publication by Kwok et al., demonstrating that thiostrepton selectively inhibited breast cancer cells by inhibiting the expression of the Forkhead Box M1 (known as the "FOXM1" in later papers).[5] This paper was rapidly followed by others demonstrating similar activities in different human tumor cell lines and identifying thiostrepton as a proteasome inhibitor.[6] Later work by Wang and Gartel from the University of Illinois at Chicago, Illinois, demonstrated that in *in vivo* xenograft models, a nanoparticle composed of encapsulated thiostrepton suppressed FOXM1 and tumor growth in MDA-MB-231 and HepG2 xenografts.[7] To enable readers to appreciate the explosion of interest in targeting FOXM1, the very recent review by Halasi and Gartel should be consulted,[8] as well as the one by Sengupta et al., both in 2013, showing preliminary activity against Ewing's sarcoma in in vivo xenograft studies.[9]

A more than 50-year old structure is now a possible route to novel antitumor agents, and just to show how researchers are thinking ahead, Zhang and Kelly have recently published a review of the methodologies for production of variants on the thiopeptides, including thiostrepton.[10] ■

The bottom line in all of this work is "never throw out a natural product structure, irrespective of how many times it infringes Lipinski's rules. And remember, natural product structures are not expected to obey these rules."

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