Metalloprotease Inhibitors as Lead Candidate Drugs to Treat Lymphatic Filariasis and Other Roundworm Infections

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Lymphatic filariasis (elephantiasis) is a Neglected Tropical Disease caused by the parasitic nematodes Wuchereria and Brugia. Over 120 million people worldwide are infected and more than 1.4 billion people are at risk of infection. Adult worms live inside lymphatic tissue for several years and chronic infections lead to tissue swelling, pain, and enlarged limbs. Only the adult stage causes the disease and currently, there are no optimal drugs that eliminate the adult worms. The focus of this study was to identify a compound or drug that could inhibit the adult worm's proteolytic enzymes which are important to the worms' survival. Previous results showed that the metalloprotease inhibitor, 1,10-Phenanthroline (1,10P) was highly effective in killing adult Brugia pahangi within 48 hours. In this study, FDA-approved drugs and a preclinical drug that are all metalloprotease inhibitors were assayed with adult B. pahangi in vitro for 5 days at 100 micromolar (m): Lisinopril, Luteolin, Captopril, Alendronate, Verapamil, Doxycycline, Tetracycline, and 4,7-Dimethyl-1,10-Phenanthroline (4,7-D). Of these drugs, Luteolin, 1,10P, and 4,7-D were the most effective drugs with IC50s of 32 µm, 15 µm, and 7 µm, respectively. To determine if metalloproteases are also critical to the survival of other parasitic nematodes, Anisakis, was assayed with the metalloprotease inhibitors. Luteolin and 1,10P inhibited the motility of the infectious stage of Anisakis in vitro by 85% and 90%, respectively. Biochemical assays showed that Luteolin and 4,7-D inhibited the metalloproteases in Anisakis worm lysates by 100% compared to the control. These results suggest that metalloprotease inhibitors may be useful as lead candidates to treat lymphatic filariasis and other roundworm infections.

Awards Won:
Third Award of $1,000