Inhibitors of the pilus-associated protease, Mpg

Yin S.[1], Luan C.H.[2], Schiltz G.E.[3], Chateau A.[1], Stohl E.A.[1], Seifert H.S.[1]

Department of Microbiology-Immunology, Northwestern University Feinberg School of Medicine, Chicago, USA[1]; CLP-High Throughout Analysis Lab, Northwestern University, Evanston, USA[2]; Department of Pharmacology, Northwestern University, Evanston, USA[3]

Abstract

N. gonorrhoeae FA1090 locus NGO1686, encodes a M23B-class, zinc-metalloprotease (Mpg) that possesses both endopeptidase and DD-carboxypeptidase activities. Mpg localizes to the Neisseria gonorrhoeae periplasm and cleaves the crosslinks of the cell wall peptidoglycan (PG). Deletion or mutation of Mpg active site residues prevents full piliation and reduced resistance to hydrogen peroxide- and neutrophil-mediated killing. We are isolating compounds that inhibit Mpg enzymatic activity to interfere with pilus-mediated adherence and resistance to neutrophil killing during infection.

We used a fluorescence-based, thermal shift (FTS) assay to screen a > 100,000 small molecule library of compounds, and conducted an in-silico screen for compounds that could bind to Mpg active site. The screen identified 85 candidates, many of which inhibit Mgp's enzymatic activity. We have also modeled the interaction of Mpg with PG and are mutating Mpg residues predicted to bind the lead compounds and PG.

References

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