Development of Halogenated Phenazine Prodrugs and Antibiotic Conjugates as Antibacterial Therapeutics

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Introduction

Bacterial biofilms are surface-attached communities of antibiotic-tolerant bacteria that pose a significant threat to human health as they are innately tolerant to every class of antibiotic currently used in the clinic.[1] Each year in the United States, there are 17 million new biofilm-associated bacterial infections and 550,000 deaths resulting from biofilms. Biofilms house metabolically dormant, non-dividing persister cells encased within a protective extracellular polymeric matrix of biomolecules and display tolerance to antibiotic as a result of their non-replicative phenotype. Despite the urgent need for clinical agents to effectively kill persistent biofilms, no biofilm-eradicating therapeutic exists. *Advancing the first biofilm-eradicating therapeutic agent to the clinic would be one of the most critical biomedical breakthroughs of the twenty-first century.*

Experimental

Solid stock of halogenated phenazine (HP) prodrug-antibiotic conjugate that we chemically synthesize will be dissolved into ~ 500 µL of deuterated chloroform or DMSO containing 0.03% trimethylsilane. NMR experiments will be conducted on 600 MHz NMRs at AMRIS to provide critical information of multiple stereochemically complex compounds. Note: We have also performed analogous experiments with other HP small molecules, including alternative prodrug moieties, which will serve as diverse molecular triggers for future HP-antibiotic conjugates.

Results and Discussion

Over the past year, we have utilized synthetic chemistry to investigate several prodrug strategies to translate our halogenated phenazine biofilm eradicating agents. To do this, we have utilized our extensive structure-activity relationship findings with our halogenated phenazines to identify positions on this scaffold to append prodrug moieties. We recently reported our progress to develop novel prodrugs in *J. Med. Chem* (which acknowledged this award).[2] We are continuing to work to optimize our halogenated phenazine-antibiotic conjugate with various halogenated phenazine-erythromycin conjugates; however, we have not published these findings to date, but aim to do so in 2019.

We are finalizing another study that we plan to submit to *J. Med. Chem.* in the coming months that show HPs are active in animal models of wound infection. We will continue to pursue this line of work in 2019 as developing biofilm-eradicating small molecules is a top priority in our in the clinic and our research lab.

Conclusions

We conclude that our progress, in part supported by this award, has enabled the identification of new small molecules that could play a role in bringing new and effective biofilm-eradicating agents to the clinic. Without this award and the NMRs at the National High Magnetic Field Laboratory, this work would not be possible.

Acknowledgements

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References

[1] Garrison, A. T., *et. al., Curr. Top. Med. Chem.*, **17**, 1954-1964 (2017).
[2] Garrison, A. T., *et. al., J. Med. Chem.*, **61**, 3962-3983 (2018).