Canterbury Medical Research Foundation

Final report for Project Grant 01

Grant recipient

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Grant details

GRANT TYPE	Project Grant	FUNDING ROUND	2018 Major Project Grant
GRANT REFERENCE	01	GRANT AMOUNT	$99,250

Final report

1. Report for the Scientific Assessing Committee

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700.5 KiB

2. Brief summary

The bacterium *Staphylococcus aureus* is an opportunistic human pathogen causing a range of serious health issues, from common skin infections to infections associated with surgical implants like hip replacements, to heart, bone and blood infections, toxic shock syndrome and pneumonia. One major challenge in treating *S. aureus* infections is the bacterium's ability to establish long-term persistent and naturally resistant infections, they have a remarkable range of strategies that help them persist on and in the body as well as an ability to regulate when they live singly or communally in bacterial biofilms. Worryingly, there is also an increasing number of strains (for example MRSA) that are resistant to most currently used antibiotics. This study focused on understanding the role of menaquinone biosynthesis in survival and biofilm formation of the pathogen *Staphylococcus aureus (Sau)*. Menaquinone (vitamin K2) is a small molecule vitally important in electron transport and energy generation in a range of pathogenic bacteria. While menaquinone is made by bacteria humans cannot make it themselves, making the bacterial biosynthesis pathway enzymes interesting targets for drug discovery. Aims of this work included 1) testing inhibitors of the *Mycobacterium tuberculosis* (*TB*) MenD, a menaquinone biosynthesis enzyme, for inhibitory effects against the *Sau* MenD and for effects on growth and biofilm formation of *Sau*, and 2) identifying additional enzymes within the menaquinone biosynthesis pathway that could be drug target candidates.Results of this work show that the natural inhibitor of the *TB* MenD, 1,4 dihydroxy-2-naphthoic acid, binds to and inhibits *Sau* MenD. Treatment of *Sau* strains with this compound inhibited their growth and increased their biofilm formation. Several synthetic inhibitor compounds were also identified that negatively affect *Sau* growth. Furthermore, successful x-ray crystallography experiments have led to a collection of *Sau* MenD structures that will be useful for structure-based drug design.Additional menaquinone biosynthesis enzymes were identified in the *Sau* genome and one of these candidates has been successfully produced facilitating future work to determine its suitability as a drug target candidate for *Sau*.

3. Photographs

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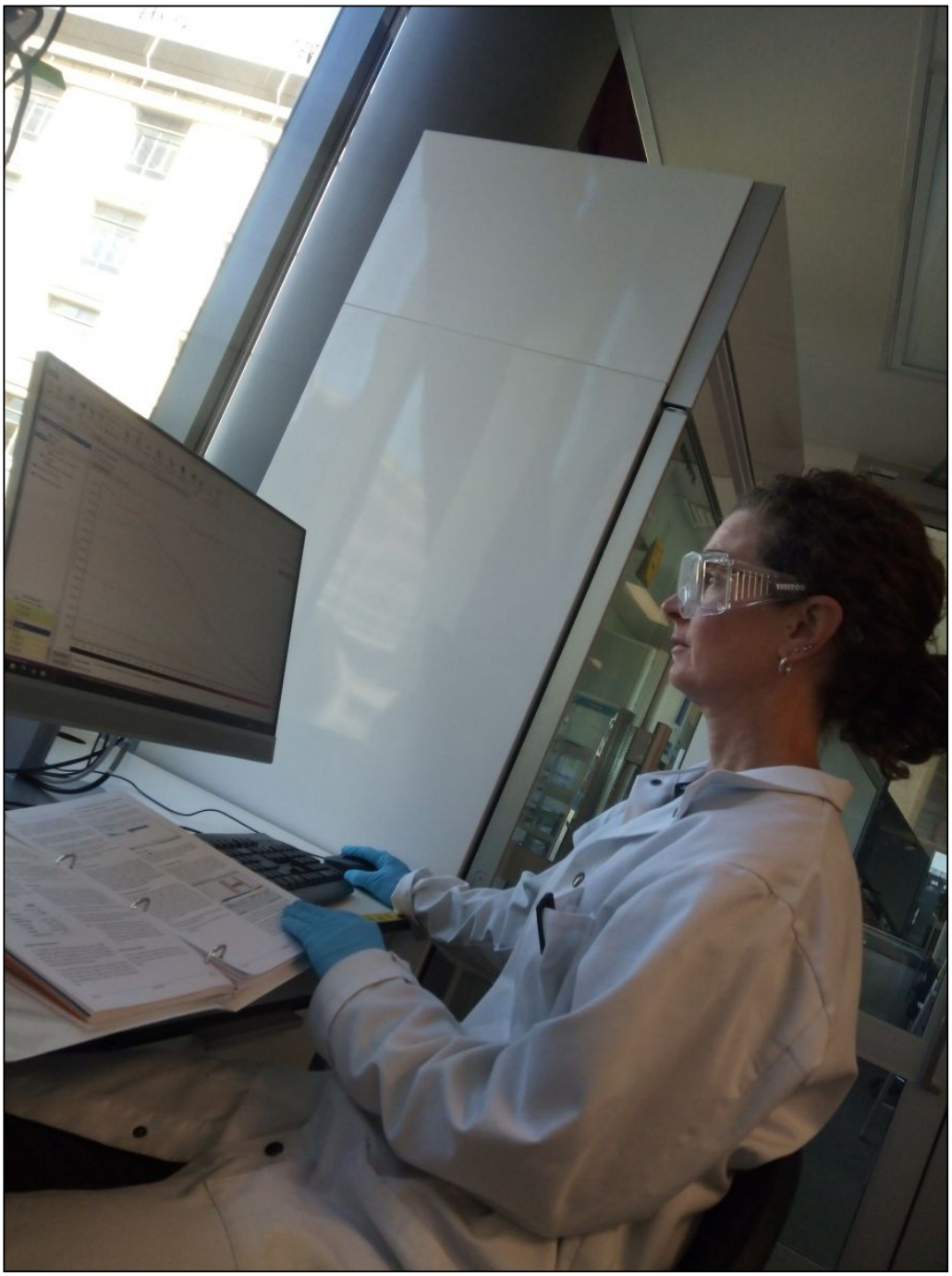

5. Feedback

Dr Stanborough and I have greatly appreciated the support from the CMRF in this project. As a new lecturer who came back to my home town of Canterbury in 2018 to take up a role at the University it has been amazing support to my research to have support from the CMRF to develop my research and establish my research laboratory at UC. Infectious diseases is of increasing concern and it has been incredibly valuable to have this support to research in this area. In addition having Dr Stanborough join my laboratory funded by the CMRF has enabled us to train a number of new research students in areas of her expertise thus contributing to the development of Canterbury's next generation of medical researchers. Thank-you.

Publication

Date

03/12/2021