Poster Presentation

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Structural studies of proteins involved in the activity of novel antibiotics

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The emergence of multidrug-resistant Gram-negative bacteria such as P. aeruginosa has become a growing challenge for developing new drugs. One of the strategies recently used to improve the efficacy of the antibiotics is to increase their uptake by exploiting bacterial transport systems such as the siderophore-mediated iron acquisition system. BAL30072, a new monosulfactam conjugated to a siderophore moiety has been shown to have potent activity against many Gram-negative bacteria [1]. Several proteins affecting susceptibility to this antibiotic have been identified in Pseudomonas aeruginosa [2]. As part of the Translocation project (Innovative Medicines Initiative), we have undertaken structural studies of these proteins and have solved the three dimensional structures of two of these targets. The structure of PiuA, a TonB-dependent siderophore transporter involved in the uptake of siderophore antibiotics across the outer membrane [2,3] has been solved to a resolution of 1.9 Å. The structure of PiuC, an Fe(II)/α-ketoglutarate-dependent dioxygenase, has been solved to a resolution of 2.6 Å. The structural and biochemical studies of these proteins will help us to understand the mode of action of these novel antibiotics and subsequently help to design new drugs acting against multidrug-resistant bacteria.

[1] *Page et al., Antimicrob. Agents Chemother. 2010, 54, 2291-2302.,* ***[2]*** *van Delden et al., Antimicrob. Agents Chemother. 2013, 57, 2095-2102.,* ***[3]*** *McPherson et al., Antimicrob. Agents Chemother. 2012, 56, 6334-6342.*

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