

Structural studies of the AcrB transporter and inhibitor development

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Inaccurate and over prescription of antibacterial drugs has accelerated the development of antibiotic resistance amongst bacteria, hereby increasing susceptibility to bacterial diseases. AcrAB-ToIC is a major and constitutively expressed membrane multidrug efflux system in Gram-negative bacteria. It plays an essential role in intracellular metabolite detoxification and is involved in both intrinsic and acquired resistance to antibiotics. An inner membrane component of the system, AcrB, is responsible for energy transduction, substrate recognition and selection, making it an important target for drug discovery.

Over the years, various compounds have been screened and subsequently modified as AcrB inhibitors. However, progress has been hindered by their low efficacy, toxicity and the narrow spectrum of targets available. To date, only one inhibitor, D13-9001, has been co-crystallized with the full-length AcrB trimer. Therefore, a better understanding of the molecular and conformational events that underpin substrate efflux are urgently needed.

In this work, various potential inhibitors have been identified by in silico drug screening. In addition, compounds that demonstrated an ability to enhance the effects of known antibiotics have been selected by high throughput drug screening. Efflux assays indicate these compounds have high efficacy in preventing *E. coli* cells from transporting doxorubicin, a fluorescent substrate of AcrB. Furthermore, AcrB crystals diffracting to 3 Å have been obtained with different space groups. Co-crystallization of AcrB with potential inhibitors is ongoing.

[1] Murakami, S. et al. (2002). *Nature*, 419, 587-593.

[2] Nakashima, R. et al. (2013). *Nature*, 500, 102-106.

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