UK Health Security Agency

Case Study
Antimicrobial Resistance

Tuberculosis

UK Health Security Agency's Vaccination Development and Evaluation Centre (VDEC) has developed a standardised assay as a tool to screen compound libraries against *Mycobacterium tuberculosis* in conjunction with a commonly used chemotherapy drug, to both reduce the development of antimicrobial resistance and hopefully improve patient treatment.

TB

! Tuberculosis caused by *Mycobacterium tuberculosis* leads to 1.6 million deaths a year.

Target

Elevated levels of resistance to drugs makes treatment of tuberculosis particularly difficult and contributes to the growing threat of antimicrobial resistance (AMR). To meet the World Health Organisation (WHO) goal of ending Tuberculosis by 2035 we urgently need novel therapies that shorten treatment time and include strategies which target AMR *Mycobacterium tuberculosis*.

Aims

An important aim for improving tuberculosis treatment is to shorten the period of antibiotic therapy without increasing relapse rates or encouraging the development of antibiotic-resistant strains. Pyrazinamide (PZA) is a key component of front-line chemotherapy against *M. tuberculosis* and plays an essential role in the shortened 6-month treatment course. Boosting PZA activity could reduce the emergence of resistance, shorten treatment times, and lead to a reduction in the quantity of PZA consumed by patients, thereby reducing the toxic effects.

Issues

In vitro assessments for PZA are often avoided because of the lack of standardisation, which has led to a lack of effective *in vitro* tools for assessing/enhancing PZA activity.

Options

We have addressed this gap by firstly defining the conditions for PZA assessment in fermenter models that replicate the acidic conditions that PZA is active in[1], and secondly by applying this knowledge to the development of a standardised assays to screen for active molecules and perform further characterisation.

Details/Priorities

The Discovery team at UKHSA, Porton Down, focuses on the discovery and development of therapeutics for AMR, by addressing fundamental questions about drug resistance and antigen discovery through to the preclinical evaluation of novel and existing antimicrobials, in collaboration with Academia, Public Sector, and Industry worldwide. To achieve our goals, the team has developed novel, disease-relevant, defined, growth models, and rare technologies, which range from fermenter models to rapid, modernised, high throughput assays for determining antimicrobial activity.

Outcome

The team has discovered hits that potentiate PZA and are now characterising them and determining their mode of action against *M. tuberculosis*.

Future work

The assay method has been accepted for publication[2].

Benefits

80,000 compounds

Through a collaborative project with industrial partners **we have screened large compound libraries (>80,000 compounds) to find molecules that enhance the efficacy of PZA**, thereby reducing toxicity, and extending its life.

This approach is being applied by the team for the

screening of compound libraries against other AMR pathogens

including *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, *Mycobacterium abscessus*, carbapenem-resistant Enterobacterales, and viral threats such as coronaviruses and CEPI priority pathogens.

We are the only research group in the UK

using a combination of fermentation, molecular methods, and bespoke HTS assays for drug discovery and evaluation in pathogenic bacteria.

Work with VDEC

We work with industry, academia and government. Contact UKHSA today to see how we can help you.

Get in touch: **vdec@ukhsa.gov.uk**

1. Steven T. Pullan, Jon C. Allnutt, Rebecca Devine, Kim A. Hatch, Rose E. Jeeves, Charlotte L. Hendon-Dunn, Philip D. Marsh, Joanna Bacon. "The effect of growth rate on pyrazinamide activity in *Mycobacterium tuberculosis* – insights for early bactericidal activity?" (2016) BMC Infectious Diseases 16: 205
2. Christopher W. Moon, Eleanor Porges, Stephen C. Taylor, and Joanna Bacon. "A microtitre plate assay at acidic pH to identify potentiators that enhance pyrazinamide activity against *Mycobacterium tuberculosis*. (chapter) Antibiotic Resistance Protocols, 4th Edition (2024) Springer Protocols, Humana Press.