New knowledge will boost fight against superbug

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A breakthrough in the fight against drug-resistant infections is one step closer following the discovery of the structure of NDM-1: a vicious form of bacteria that is currently resistant to the most powerful antibiotics available.

Medical Research Council (MRC) scientists at the Research Complex at Harwell (RCaH) in Oxfordshire, led by director Professor Simon Phillips, have produced a model of NDM-1 that will now enable researchers and pharmaceutical companies to progress towards potential new treatments.

The research is published today in the online journal *Acta Crystallographica Section F: Structural Biology and Crystallization Communications*.

In recent years there has been growing concern that the usefulness of antibiotics could be coming to an end as the bacteria that cause disease become increasingly resistant to these drugs. Annually, over 25,000 people in the EU die of bacterial infections that have been able to outsmart even the newest antibiotics. The challenge to find new drugs that can overcome these superbugs is urgent and ongoing.

The name NDM-1 relates to a particular enzyme carried by the resistant bacteria, called New Delhi Metallobetalactamase-1. This enzyme has the ability to break-up or 'hydrolyse' an antibiotic and make it ineffective.

NDM-1 is especially feared as it is resistant to one of the more powerful groups of drugs, carbapenem antibiotics, which are seen as the last line of defence against bacterial infection. By understanding the structure of the NDM-1 enzyme, scientists can now learn more about how it works.

Professor Simon Phillips, director at the Research Complex at Harwell, explains: “Knowledge of the enzyme structure is the first step in understanding how the superbug works and leads the way to the design of drugs that might prevent its action.”

The NDM-1 or ‘New Delhi’ modified superbug came to prominence in the latter half of 2010 and is believed to have entered the UK via patients travelling back from countries like India and Pakistan, where they had exploited cheaper surgery options such as lower-priced cosmetic surgery.

While there have only been around 70 cases of the infection recorded in the UK so far, there is no doubt of the importance of this new discovery for saving lives in the future.

Professor Phillips adds: “NDM-1 is a serious threat to human health. The enzyme it carries is able to degrade many forms of antibiotic and render them useless. In addition, the gene for NDM-1 can be passed between different bacteria so can spread rapidly in the population and generate drug resistance in different diseases. Our MRC-supported work is providing information to allow the development of new drugs as fast as possible.”

Professor Sharon Peacock, a member of the Medical Research Council Infections and Immunity Board, says: “The MRC continues to push forward new frontiers of medical research by supporting fundamental research in the laboratory to tackle serious bacterial infection. Identifying the structure of NDM-1 is a crucial step towards ensuring

that drug development is based on a sound understanding of the mechanisms of bacterial resistance to antibiotics."

Professor Phillips and his research group were able to react to the news of the emergence of NDM-1 quickly at the RCaH because of its proximity to other key research facilities in the discovery process. The MRC-funded Oxford Protein Production Facility-UK, which is based within the RCaH, rapidly prepared samples of the enzyme based only on its genetic sequence. The structure was determined by crystallography carried out at the neighbouring Diamond Light Source.

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