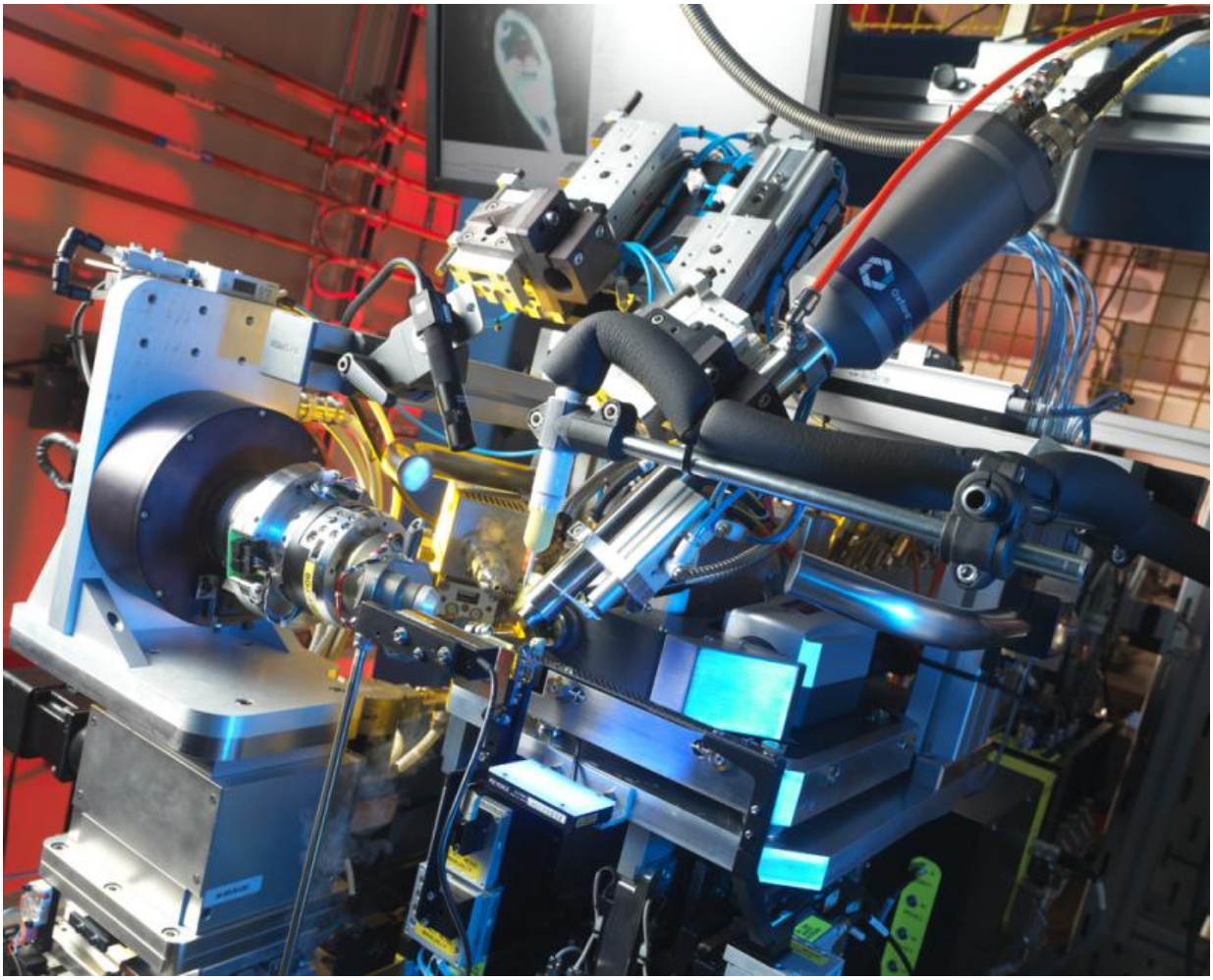
Solved structure of S. pneumoniae enzyme could lead to new antibiotics

December 1 2015



The high tech machinery on MX beamline I04. Credit: Diamond Light Source

Scientists have used the UK's synchrotron science facility, Diamond Light Source, to solve the structure of a key enzyme in Streptococcus pneumonia (the pneumococcus). These bacteria cause a range of respiratory infections, including sinusitis, bronchitis, ear infections, pneumonia, meningitis and septicaemia.

Respiratory infections are one of the biggest killers in the western world, and pneumococcal infections can range from mild to potentially deadly. Children and older people are most at risk, as well as those with compromised immune systems.

Scientists from Diamond and the University of St Andrews have used crystallographic techniques on the synchrotron's MX beamlines to uncover the structure of NanC, a type of enzyme known as a 'neuraminidase'. These enzymes help the bacteria to grow and spread and are an important target for future antibiotics.

S. pneumoniae bacteria contain up to three neuraminidase enzymes, Nan A, B and C. The scientists have already uncovered the structure of the other two neuraminidases – A and B – and the discovery of the NanC structure is the final step in identifying how these enzymes work to sustain S. pneumoniae and how they could be targeted and disabled, thus destroying the bacteria.

Martin Walsh is deputy life sciences director at Diamond and lead author on the study. He comments: "With the structure of NanC, we now have a vital new piece of the puzzle which informs wider research into drug design and equips us to better tackle the pneumococcus in all its forms. The next step will be for scientists to use this structural information to aid in the design of inhibitors of the pneumococcus neuraminidases which could lead to new treatments for pneumococcal disease."

There are approximately 90 distinct pneumococcal serotypes and, although not all cause disease, this makes treatment challenging. An effective conjugate vaccine has been available since 2001. The vaccine targets 7 serotypes and has significantly reduced the invasive pneumococcal disease burden in the first world, especially for the vulnerable: the very young and old. This has recently been augmented by the introduction of a 13 serotype conjugate vaccine.

However there has been a rise in antibiotic resistance in serotypes not covered by this conjugate vaccine and we are seeing previously non-infectious serotypes increasing in virulence. This makes treatment of pneumococcal pneumonia and less severe illnesses such as otitis media more difficult to manage. And so finding new approaches to combat pneumococcal disease remains a high priority.

Because the pneumococcus rely on neuraminidases for survival, drugs that shut off these enzymes could aid new ways to treat infections. This approach is already used for influenza virus: both Tamiflu and Relenza target influenza neuraminidase which prevents the virus infection spreading but, as yet, no equivalent drugs exist for bacterial infections.

The Diamond group's findings show that NanC does not function exactly like Nan A and B, so future antibiotics will have to work broadly enough to attack all three neuraminidases .

Garry Taylor, Professor of Molecular Biophysics and Deputy Principal of the University of St Andrews, said: "With a fuller understanding of the structure and function of S. pnemoniae's three neuraminidase enzymes, we're now better equipped to design next-generation antibiotics for some of the world's most prevalent and deadly respiratory infections."

More information: C. David Owen et al. NanC: Structural Insights

into the Specificity and Mechanism of a Sialidase that Produces a Sialidase Inhibitor , *Journal of Biological Chemistry* (2015). DOI: 10.1074/jbc.M115.673632

Provided by Diamond Light Source