New method for determining protein structure has major implications for drug development

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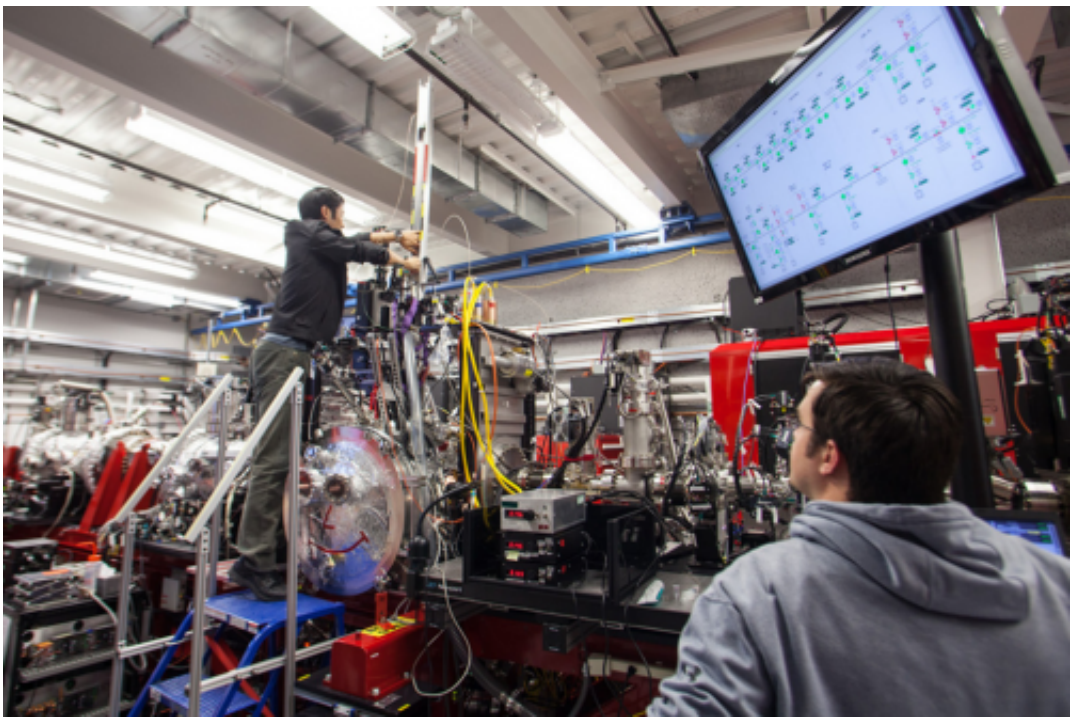

Researchers Wang and Nelson.

Research involving scientists from Trinity College Dublin has led to a major breakthrough that could streamline the process used to determine the structure of proteins in cell membranes. This will have major implications for drug-related research because almost 50% of drugs on the market target these proteins.

Proteins in cell membranes are vital for the everyday functioning of complex cellular processes. They act as transporters to ensure that specific molecules enter and leave our cells, as signal interpreters important in decoding messages and initiating responses, and as agents that speed up appropriate responses. But to understand how they work, and how drugs can be made to target them, it is vital to determine their precise atomic 3-D structure. A major challenge is the production of large membrane protein crystals used in this pursuit.

A research group led by Professor of Membrane Structural and Functional Biology at Trinity, Martin Caffrey, developed a high-throughput method for growing membrane protein crystals that makes use of the 'Lipid Cubic Phase' (LCP). The LCP uses a fat-based media to grow these crystals in.

The crystals are then transferred to specialised circular arenas in which they interact with X-rays emitted by charged particles that race around at close to the speed of light. Scientists later examine the precise pattern left by scattered X-ray particles after they have collided with the crystals to determine their precise structure. Professor Brian Kobilka was awarded his share in the 2012 Nobel Prize in Chemistry, in part for work that made use of the LCP.

Recently, a new method for determining membrane protein structures that uses an X-ray-free laser showed great promise. However, it required huge numbers of protein crystals to generate a clear picture of their structure as only 1 in 10,000 was hit in a way that produced useable data. In the breakthrough, Professor Caffrey, as part of a large team of scientists, used the fat-based LCP media in which the protein crystals were grown to jet them across the laser at a relatively slow pace. This slower pace translated into a vastly improved 'hit rate', which in turn provided a more efficient profiling of the protein structure.

The scientists used a major drug target as their membrane protein of interest in this study. Abbreviated as '5-HT_{2B}', this protein is a cell receptor for serotonin, which is often linked to happiness and the feeling of well-being. The scientists were able to determine the receptor structure to good resolution, as well as showcasing the vastly improved hit rate and ability to grow crystals in the medium in which they are delivered to the laser, which confers further method-related benefits.

Professor of Membrane Structural and Functional Biology at Trinity, Martin Caffrey, said: "This work represents a major breakthrough and a landmark in the membrane structural and functional biology field. Because the data were collected under conditions that were free from radiation damage, and because the research was conducted at a temperature of 20 °C, which is physiologically useful, the solved structure provides a more reliable representation of how the receptor appears within the body."

Provided by Trinity College Dublin