Major achievement enables precision drug design for inherited learning disabilities, other neurological diseases

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Scientists have used the UK's national synchrotron science facility, Diamond Light Source, to make a discovery that could pave the way for more effective, targeted drugs to treat inherited learning disabilities and other neurological diseases. UK-based Heptares Therapeutics, the pioneering structure-guided drug discovery and development company, has mapped the structure of a protein linked to the genetic disorder Fragile X Syndrome, a major cause of inherited learning disabilities, as well as to autism, depression, anxiety, addiction and movement disorders. Understanding the structure of this protein means a new generation of targeted medication could be fast on the heels of drugs currently undergoing clinical trials to treat the symptoms of these diseases.

The level of detail required for this work could only be achieved using the intense synchrotron light produced at Diamond Light Source, the UK's synchrotron science facility based on the Harwell Science & Innovation Campus in Oxfordshire. Around 3,500 scientists a year use this light to study samples, and its intensity allows them to visualise on a scale that is unobtainable in their home laboratories.

Diamond Light Source produces a light 10 billion times brighter than the sun allowing scientists to study proteins at an atomic level. Using Diamond, Heptares scientists shone this intense light through pure protein crystals placed in the "beamline", a specialist lab, and for the

first time determined the 3D structure of the protein mGlu5 (metabotropic glutamate receptor 5), part of a family of receptors that controls brain activity. Heptares' research, published today in the journal Nature, outlines a detailed understanding of mGlu5 and how it is affected by a drug which has been evaluated in clinical trials to treat Fragile X symptoms and other neurological disorders.

Using these findings, Heptares has enabled the development of a 'new generation' of targeted medication for diseases linked to this family of proteins with improved effectiveness over drugs currently in trials. Scientists from Heptares have already used the structural information to discover molecules that lock into a "pocket" identified inside the protein during this latest study.

Dr Fiona Marshall, Chief Scientific Officer at Heptares, believes this discovery has the potential to transform the treatment of a range of serious diseases involving mGlu5: "Drugs currently in clinical trials could be on the market within about five years' time, however, with the knowledge gathered in this study we could have a 'new generation' of precisely designed and more effective drugs within about ten years. Being able to use the world-leading microfocus X-ray crystallography beamline (I24) at Diamond Light Source to understand how the protein reacts to different drugs at an atomic level is invaluable in the success of research into these diseases."

In the past, drug design has been largely the product of trial and error. Drugs would be developed and then tested until they had the desired effect. Because scientists lacked a comprehensive understanding of why and how the drugs were working, this approach could lead to unwanted side- effects.

By visualising mGlu5 at the atomic level, Heptares was able to identify a "pocket" in the structure. Computer technology is allowing scientists to

design a drug to fit precisely into this pocket. This targeted drug would only affect the receptor with the pocket identified, reducing the chance of side effects.

Prof Andrew Harrison, Diamond's Chief Executive, comments, "Heptares is currently the biggest annual industrial user of Diamond. This is testament to our unique facilities and the success they have had in the past using techniques only available in the UK at Diamond. Whilst the majority of the research undertaken at Diamond is done by academia, currently 5% of the overall experimental time is purchased by 70 regular industry customers. They are using Diamond to advance R&D programmes across a range of sectors including pharmaceuticals, biotechnology, chemicals, oil and engineering. The synchrotron is playing a major role in keeping a strong R&D base in the UK and promoting highly advanced innovation within a range of businesses from British SMEs to global companies such as GSK and Rolls-Royce."

Fiona Marshall, Chief Scientific Officer at Heptares, concludes, "Publishing this research in Nature will provide scientists with a new understanding about the function of this protein and help facilitate the design of some important new drug treatments. Here at Heptares, we are applying this structural knowledge to a range of proteins known to be important in serious diseases to create a new generation of targeted medication. Diamond will continue to play an important role in our future research."

More information: Andrew S. Doré et al. Structure of the class C GPCR metabotropic glutamate receptor 5 transmembrane domain, 2014, *Nature* dx.doi.org/10.1038/nature13396

Provided by Diamond Light Source