Discovery raises possibility of treating neurological disorders

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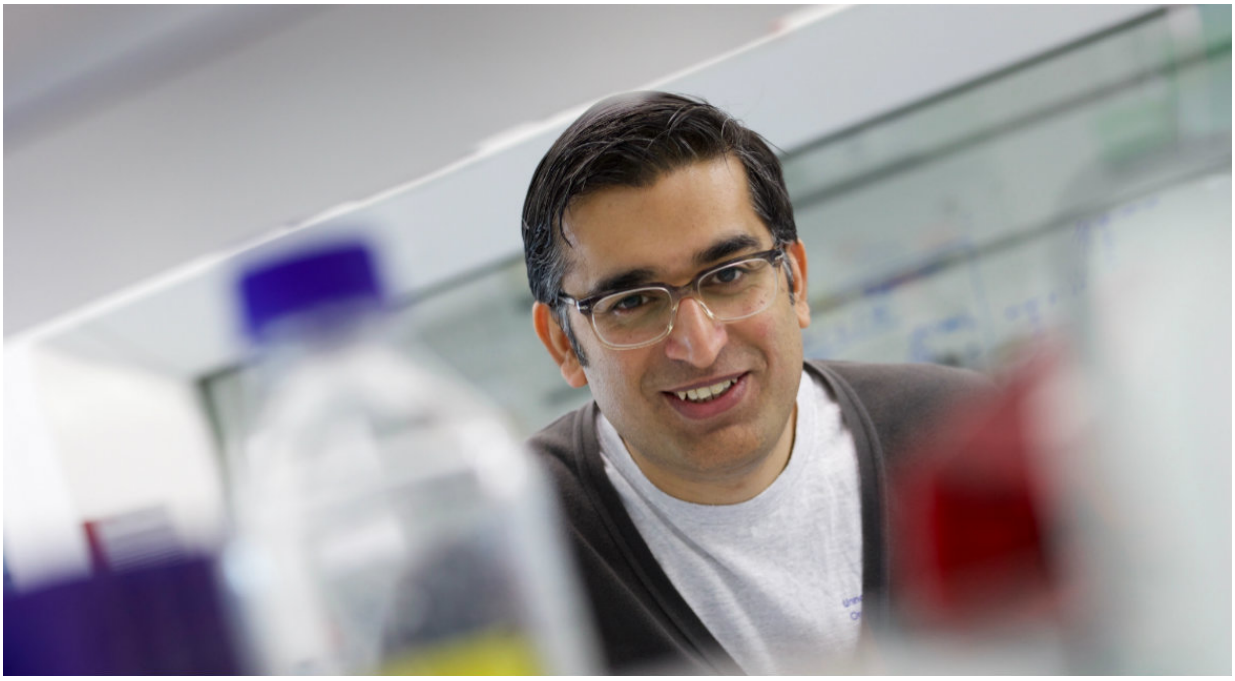

Credit: University of Dundee

The discovery of a novel class of enzyme in human biology by scientists at the University of Dundee has opened a new area of research that could benefit patients suffering from a range of neurological disorders.

These disorders include the acquired neuropathies associated with chemotherapy and diabetes, both of which are on the rise and

significantly affect patient quality of life. The researchers say there is also potential for slowing the progression of a range of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

In a paper published in the journal *Nature*, Dr. Satpal Virdee and colleagues describe the novel class of E3 enzyme known as MYCBP2, which works in a different way from other, similar, enzymes and offers new potential for drug targets.

Dr. Virdee said, "These findings are very striking and there is real tangible potential for developing drugs for a range of neurological conditions."

The MYCBP2 enzyme is one of over 700 E3 enzymes in every human cell which are involved in a process called ubiquitylation, a fundamental regulator of human biology. Dundee is one of the world's leading centres for research into ubiquitylation.

The E3 enzymes have been identified as highly promising future drug targets for diseases including cancer, autoimmune disorders and neurodegeneration.

Dr. Virdee and colleagues in the Medical Research Council Protein Phosphorylation and Ubiquitylation Unit (MRC-PPU) in the University's School of Life Sciences found that MYCBP2 operates in a unique way, selectively transferring ubiquitin to the chemically distinct amino acid threonine. This `tagging' of threonine amino acids with ubiquitin unlocks a new area of cellular biology.

Dr. Virdee said, "Textbooks will tell you that ubiquitylation is a modification of lysine residues. Although there have been a handful of reports describing non-lysine ubiquitylation, a human E3 ligase with non-lysine activity has remained elusive so this is a very significant finding

with fundamental underpinnings.

"MYCBP2 also works differently from other E3 enzymes. Uniquely, the enzyme has two active sites and relays the ubiquitin molecule between them. This opens up new strategies for modulating its activity for therapeutic benefit, as it has been shown that putting the brakes on MYCBP2 could benefit patients suffering from a range of neurological disorders.

The Virdee lab made the discovery that MYCBP2 is a mechanistically novel class of E3 by applying chemical biology technology known as activity-based protein profiling. Activity-based protein profiling requires a chemical probe molecule that is tailored towards a particular enzyme class. The Virdee lab successfully developed activity-based probes for E3 ligases.

Dr. Virdee said, "We hope this finding illustrates the importance of funding long-term interdisciplinary research and I am grateful to the MRC unit for allowing my lab to do just that. The probes are great because they don't have a biased assumption of what an E3 ligase should be. They also tell us when E3s are switched on or off so we are hoping we can use this feature to understand other E3s which might be involved in disease-relevant processes."

The probes irreversibly attach to E3 enzymes that have a specific type of activity. The Virdee lab added their probes to human cell extracts and identified all the proteins that were modified with their probe by mass spectrometry. Unexpectedly, MYCBP2 was labelled.

Kuan-Chuan Pao, a Ph.D. student in the Virdee lab who was involved in probe conception through to this striking biological discovery, said, "It's kind of a dream come true moment for a Ph.D. student to see that your daily hard work really contributes to some huge discovery that expands

our knowledge toward life science.

"In addition, as a trained chemist, it's been my goal to bridge chemistry and biology, exemplified by the chemical probes we use to answer or solve biological questions. We hope we can use this powerful platform to accelerate drug discovery in the near future and in the meantime, discover more exciting new biology."

This study was carried out in collaboration with Professor Daan van Aalten (University of Dundee) and Kay Hofmann (University of Cologne).

Professor Dario Alessi, Director of the MRC-PPU, said, "I would like to congratulate Dr. Virdee and his team for this curiosity-driven discovery. This is certainly one of the most astonishing breakthroughs made in our MRC Unit since I have been its Director and opens the door to an unexplored area of biological research that may have strong links to better understanding human disease."

More information: Activity-based E3 ligase profiling uncovers an E3 ligase with esterification activity, *Nature* (2018). nature.com/articles/doi:10.1038/s41586-018-0026-1

Provided by University of Dundee