Researchers target undruggable cancers

October 19 2017

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A new approach to targeting key cancer-linked proteins, thought to be 'undruggable," has been discovered through an alliance between industry and academia.

The study published in *Nature* shows that two novel and specific small-molecule inhibitors developed by the research teams can bind to and deactivate an enzyme that controls the stability of the p53 tumour

suppressor protein. This deactivation allows p53 to be turned on, putting the brakes on cancer growth.

The majority of cancers have a faulty or inactive p53 which allows them grow out of control. But despite its important role in cancer, attempts to target p53 directly have hit a number of dead ends. To get around this problem the researchers in this alliance looked at a specialised system, the ubiquitin-proteasome system, which regulates the turnover of a range of proteins, including p53.

Focusing on one enzyme in the system, USP7, the researchers were able to show how the two inhibitors exploit a unique binding site in the enzyme. This leads to a cascade of effects that ultimately reactivate p53.

The multidisciplinary research collaboration was brought together by Cancer Research UK's Therapeutic Discovery Laboratories and included scientists at FORMA Therapeutics Inc (USA), the Universities of Oxford and Liverpool, and the MRC Laboratory for Molecular Biology in Cambridge.

Dr Andrew Turnbull, one of the lead researchers at the Cancer Research UK Therapeutic Discovery Laboratories, said: "Our study shows that we can target these 'undruggable' proteins by specifically targeting the enzymes that control them. Combining this revelation with detailed three-dimensional structures of these enzymes, and their potential targets, means this could be the starting point to develop drugs that target them and the proteins they control."

Professor Benedikt Kessler, who was part of the study alliance at Oxford's Target Discovery Institute along with Dr Adan Pinto-Fernandez, added: "By extending this drug discovery approach, we hope to open up ways to target other proteins that drive cancer, as well as those that cause other chronic diseases such as neurodegeneration and

immunological disorders."

The full paper, 'Molecular basis of USP7 inhibition by selective small molecule inhibitors', can be read in *Nature*.

More information: Andrew P. Turnbull et al. Molecular basis of USP7 inhibition by selective small-molecule inhibitors, *Nature* (2017). DOI: 10.1038/nature24451

Provided by University of Oxford