

Breakthrough in understanding role of enzyme in disease

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Researchers at the University of Dundee have uncovered the mechanism of an important human enzyme that plays a role in the development of debilitating diseases including cancer, dementia and diabetes.

Professor Daan van Aalten and his team at the University's College of Life Sciences have been studying how proteins in the cell are regulated by an unusual chemical modification called O-GlcNAc.

The team have now explained the inner workings of the enzyme O-GlcNAc transferase (OGT), which is the master regulator of O-GlcNAc in the cell. Inappropriate levels of O-GlcNAc are known to exist in some forms of [cancer](#), diabetes and [dementia](#).

"The reaction of this enzyme is important for keeping proteins in the cell in a healthy state, and when this is misregulated you get diseases," explained Professor van Aalten. "We knew that OGT is a very, very important enzyme and without it cells are not viable, but that was previously all that was really known about the workings of it. Now we understand how this enzyme works we can make inhibitors against it.

"This [protein](#) is essential for human function, but also plays a role in diseases such as cancer, [diabetes](#) and dementia. If you have an inhibitor you can tune down the activity of the enzyme rather than removing it altogether, and in that way probe its role in [disease progression](#)"

"This paper sets the groundwork for designing inhibitors that can be used to probe the role of O-GlcNAc in these different diseases. For example, we will be able to look at how bringing O-GlcNAc back to normal levels affects tumour progression.

"We will be able to study the role of it in live, healthy cells and on models of these diseases to see whether there is any [therapeutic effect](#) from

inhibiting this enzyme. We can only do this when we have an inhibitor, and we can only develop an inhibitor now that we understand the structure and mechanism of the enzyme."

The research, which was funded by the Wellcome Trust, is published today in the latest edition of the *Nature Chemical Biology* journal.

Provided by University of Dundee

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