DMD keynote speaker Huib Ovaa on PROTACs: 'We've only scratched the surface.'

'Protein degraders are a revolution'

Pharmaceutical companies are increasingly interested in using the body's own protein degradation system to dispose of disease-causing proteins. Professor Huib Ovaa will be addressing so-called protein degraders or PROTACS during a keynote lecture at the FIGON Dutch Medicine Days.

'In drug development you normally design a compound that fits into a defined binding pocket of a protein, where it modulates the function of that protein', says Huib Ovaa, professor in chemical biology at Leiden University. 'But by using small molecules that activate the body's own protein degrading system, you can completely remove a specific protein. This means you no longer need to target very specific ligand binding pockets.'

This new drug development strategy is called targeted protein degradation, a strategy that is currently booming among pharmaceutical companies. The molecules of their interest are called proteolysis-targeting chimaeras (PROTACs). PROTACs and other protein degraders are the subject of a keynote lecture on small molecules and the ubiquitin proteasome system by Ovaa during the FIGON Dutch Medicine Days.

Ubiquitin flags

'The idea for PROTACs is actually quite old', tells Ovaa. 'Craig Crews and Ray Deshaies came up with the concept around 2003. I remember a chemical biology conference at Yale University when working at Harvard as a postdoc, where Crews had posters of the first PROTAC designs. Those were nice molecules, but they never really worked. It was about 5 years ago that James Bradner (now working at Novartis, ed.) showed that the sedative thalidomide could be used as an important element of effective PROTAC molecules. That was the proof needed to show that the PROTAC strategy could work. Since then this novel approach has become very popular.'

Advantages

So, what are these molecules and why are they promising? A PROTAC is a molecule with two 'hands' that bind to a protein of interest on one side, and to a ubiquitin ligase on the other. 'This induces proximity between the ligase and the target protein, which leads to the latter's ubiquitination', explains Jacques Neefjes, professor of chemical immunology at Leiden University and Ovaa's close colleague. 'The resulting ubiquitin 'flags' are recognized by the proteasome, which will then take in, unfold and degrade the ubiquitinated protein.'

The advantages of this drug approach are clear, according to Neefjes, who is studying the proteasome. 'Making use of the ubiquitin system is very clever; the protein binding ligand is very specific for the target protein, reducing side effects.' Also, after the disease-causing protein is broken down, the bifunctional molecule is released, making it a catalyst: one PROTAC can destroy many proteins.

'They bring into view a new class of drug targets'

Long sought target

PROTACs are called small molecules, but they are bigger than most small molecules on the market. Because of their size they don't fulfill the traditional requirements that pharmaceutical companies have for drug-like small molecules, such as the 'rule of five' (a set of five chemical and physical properties that a compound should have to be active in the human body, for example a defined molecular weight). Ovaa, however, argues that this is amply compensated by their efficiency and catalytic action. 'We are now seeing examples of proteins being degraded that were previously considered to be very hard or impossible to target', he says. 'I think protein degraders are a revolution, as they bring into view a new class of drug targets. And all this has become possible thanks to our understanding of the ubiquitin system.'

In principle almost every disease can be targeted with PROTACs, but cancer and neurodegenerative diseases, like Parkinson's disease, are probably first on the list of priorities. 'They both have very defined and clear targets and previous attempts at targeting them failed', says Neefjes. One such long sought target is

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KRAS, the most frequently mutated oncogene in human cancer. It has the reputation of being almost 'undruggable'.
Ovaa: 'But the PROTAC approach might be able to change that. I have high hopes for it.'
But first things first. This year the very first PROTAC has entered clinical trials. The compound is developed as a treatment for prostate cancer by the company Arvinas, which was cofounded by Crews. The target of this PROTAC is the androgen receptor, a protein that is often upregulated in prostate cancers and is an important target for this type of cancer. Also, Roche, Pfizer, Merck, Novartis and GlaxoSmithKline are heavily investing in the search for new PROTAC designs, as well as for ligands that can be incorporated into such reagents.
The latter is actually one of the drawbacks of PROTACs, according to Ovaa. 'Of the 600 known ubiquitin ligases there are only a handful of ligands that can be used as the targeting 'left and right hands' in these molecules. But as research on these PROTACs is speeding up, we hope to find more ligands soon. Also, we need to further focus on the entry into the cells, as this is tricky for these molecules because of their size.'

Better PROTACs

Ovaa's own research is focused on the ubiquitin proteasome system and how to activate proteasomes. For this he developed another type of protein degradation accelerators: small molecule proteasome activators. Using an assay for proteasome activity he and his team found more than ten compounds that accelerate the degradation of alpha-synuclein, the main protein that aggregates in Parkinson's disease. 'We found that one such activator is a potent p38 MAPK inhibitor. The kinase p38 MAPK inactivates the proteasome by phosphorylating it and by blocking this enzyme you can actuality increase the activity of the proteasome', explains Ovaa. Increasing the activity of the proteasome alone holds a promise for an interesting therapeutic intervention, but there is more. 'We also discovered that such proteasome activators raise the effectiveness of PROTACs', he says. 'So, by using these two molecules in combination you can turn a good PROTAC into an even better PROTAC, or a poor one into a good one. This is good news for the emerging research field.'

'The idea is actually quite old'

Now Ovaa focuses on finding new molecules that can use the ubiquitin system to our advantage. 'It is not easy, because you have to test hundreds of molecules before you hit on something that works, but it is worth it, as I think the potential of this field is huge and unexplored. The ubiquitin system does so many things: it determines protein stability by targeting 'flagged' proteins to the proteasome or lysosome or even towards other cellular pathways. So far we have only scratched the surface. There are still a lot of exciting things to discover and druggable targets to find.' ●