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Drug discovery: New method identifies E3-specific degraders for targeted therapies

For many years, the team of Principal Investigator Georg Winter at CeMM has been researching the development of Targeted Protein Degraders: a new generation of drugs that achieve greater therapeutic success through the targeted degradation of harmful, pathogenic proteins. In their current study, published in the Journal of the American Chemical Society (JACS), the researchers present a new method for the identification of molecules that act as degraders and thus could be used as therapeutic drugs.

(Vienna, 31 January, 2023) The latest generation of drugs relies on targeted degradation of damaged or pathogenic proteins. This involves the use of chemical molecules that link a damaged, pathogenic protein to the cellular waste disposal system, a so-called E3 ubiquitin ligase. This approach is also called "Targeted Protein Degradation (TPD)". The JACS study overcomes an important limitation in this field, as currently known degradation molecules only bind to a handful of E3 ligases, thus limiting the therapeutic options and potential. Georg Winter, Principal Investigator at CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences, explains: "There are about 600 E3 ligases in a human cell. We are looking for a way to find a suitable degradation molecule, for as many of these E3 ligases as possible. This may open up new therapeutic pathways, especially for patients whose therapy is no longer effective due to drug resistance." In their study, first author Alexander Hanzl from Winter's group at CeMM and his colleagues demonstrate a method that makes it possible to find suitable degrader molecules specifically for a particular E3 ligase. "Let's assume that in a certain type of cancer, one of the 600 E3 ligases is particularly abundant. Then it would be of great advantage to find a degrader that can recruit exactly this E3 ligase and thus specifically treat the cancer cells," Hanzl said.

Self-degradation mechanism of the E3 ligase makes degrader recognizable

The researchers have built upon the knowledge that cullin-RING-E3 ligases have a regulatory "self-degradation" mechanism. Hanzl and Winter show how adding degraders can rescue this auto-degradation under specific conditions. This ultimately allows the identification of new, E3 ligase specific degradation molecules. "Within six days, about 10,000 molecules can be screened for their

mode of action as degraders for a specific E3 ligase," Hanzl says. Georg Winter adds:
"With more and more clinical studies on the efficacy of degraders, it is becoming apparent that, over time, therapy resistance differing from previously described resistance mechanisms in therapies with traditional inhibitor-based drugs can emerge. It is therefore even more important to be able to recruit as many E3 ligases as possible in order to pursue new therapeutic approaches. With our study, we take a step in this direction and present the first scalable approach for finding E3 ligase selective degradation molecules."

Significantly increase efficacy

Currently, numerous degrader drugs are being tested in clinical trials, and some are already available to patients, particularly for various blood cancers. "Traditional therapeutics, which take the approach of blocking an isolated function of a protein, only reach about 20 percent of our proteins. The other 80 percent do not have a suitable binding site and thus cannot be targeted. The new generation of drugs using targeted protein degradation can potentially significantly increase this ratio and perhaps reach up to 80 percent of proteins in the future," says Winter. To overcome emerging resistance, it is further important to be able to recruit as many E3 ligases as possible with degraders and thus ensure the "removal" of damaged proteins. The presented results demonstrate a method that enables the identification of degraders for specific E3 ligases, to advance the development of improved therapies.

Photo: Alexander Hanzl, Georg Winter, © Laura Alvarez, CeMM

The study "E3-Specific Degrader Discovery by Dynamic Tracing of Substrate Receptor Abundance" was published in the Journal of the American Chemical Society on 5 January 2023, DOI: 10.1021/jacs.2c10784

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Georg Winter obtained his PhD from the Medical University of Vienna, working on elucidating the mechanism of action of anti-neoplastic drugs under the supervision of Prof. Giulio Superti-Furga at CeMM. He specialized in proteomics as well as chemical-genetic approaches to identifying drug resistance mechanisms and on mechanistically elucidating synergistic drug combinations. After his PhD, he continued his training in chemical biology and worked as a postdoctoral fellow with James Bradner at the Dana Farber Cancer Institute of Harvard Medical School. There, he developed a

pharmacological solution for target protein degradation and applied this strategy to the study of leukemic gene regulation. Since 2016, Georg Winter has been a Principal Investigator at CeMM. His lab develops methods and applies them to target protein degradation to understand and block oncogenic transcriptional circuits. To this end, the Winter lab combines phenotypic drug screens, chemical genetics, and drug target identification approaches with holistic measurements of global gene activity and genome structure. The goal of Georg Winter's research is to combine basic research on gene regulation and the ubiquitin-proteasome system with functional genomics and chemical compound development to develop novel and personalized therapeutic paradigms.

The CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences is an international, independent, and interdisciplinary research institution for molecular medicine under the scientific direction of Giulio Superti-Furga. CeMM is oriented towards medical needs and integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, and rare diseases. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.
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