

One Drug, Two Cleanup Crews: A built-in backup for targeted protein degradation

Targeted protein degradation has become one of the most promising strategies in modern drug discovery, enabling scientists to eliminate disease-causing proteins instead of merely blocking them. Now, researchers at CeMM, AITHYRA (both Institutes of the Austrian Academy of Sciences), and CeTPD have discovered that a single small molecule can recruit not one, but two independent protein disposal systems at the same time. This dual mechanism introduces a built-in redundancy that could make future degrader therapies more robust and less vulnerable to resistance. The findings, reported in *Nature Chemical Biology* (DOI: [10.1038/s41589-026-02224-y](https://doi.org/10.1038/s41589-026-02224-y)), expand the design principles of targeted protein degradation and open new avenues for more resilient medicines.

Most drugs work by inhibition: they block a protein's activity but leave the protein itself intact. Targeted protein degradation takes a fundamentally different approach, harnessing the cell's own quality-control machinery to remove proteins entirely. To do this, degrader molecules bring a target protein into proximity with an E3 ligase—an enzyme complex that labels proteins for destruction by the proteasome. This strategy has transformed drug discovery, particularly because it allows researchers to tackle proteins that are difficult to inhibit directly and to eliminate not only their enzymatic activity but also their structural functions.

A new layer of control in protein degradation

Until now, however, most degraders have relied on a single ligase. This creates a vulnerability: if cells lose or alter that pathway, for example through mutation or adaptation in cancer, the drug can become ineffective. Overcoming this limitation has been a central challenge in the field.

In their new study, researchers from Georg Winter's Group at CeMM Research Center for Molecular Medicine and AITHYRA (both Institutes of the Austrian Academy of Sciences), together with Alessio Ciulli's group at the Centre for Targeted Protein Degradation (CeTPD), investigated a small molecule designed to degrade SMARCA2/4, the central ATPase subunits of the BAF chromatin remodelling complex, which is frequently implicated in cancer. They uncovered an unexpected mechanism: Rather than relying on a single E3 ligase, the compound was able to engage two distinct systems. Both pathways could independently drive the degradation of the target protein, and only when both were disabled the process came to a complete halt.

Two pathways, one purpose

This dual engagement effectively creates a molecular backup system. If one degradation pathway is compromised, the other can still ensure that the protein is removed. Such redundancy is rare in drug mechanisms but common in biology, where it serves to increase robustness and resilience.

The researchers also uncovered how this mechanism works at the molecular level using a combination of genetic, biophysical and structural deconvolution techniques. The compound facilitates the formation of a highly specific complex with one E3 ligase and the target protein. At the same time, the molecule can also recruit another E3 Ligase, providing an alternative route to achieve the same outcome.

Fine-tuning the cell's disposal machinery

Strikingly, this system is not fixed. The researchers showed that even small changes in the chemical structure of the compound can shift its preference from one ligase to the other. Likewise, subtle genetic changes in the ligases themselves can influence which pathway is engaged. This means that ligase recruitment is not only dual, but tuneable.

“By enabling a single molecule to engage multiple degradation pathways, we can introduce redundancy into targeted protein degradation,” says Georg Winter, co-corresponding author of the study, Life Science Director at AITHYRA and Adjunct Principal Investigator at CeMM. “This could help overcome one of the key limitations of current degrader therapies, namely their susceptibility to resistance.”

“This is an incredibly important development.” Professor Alessio Ciulli, co-corresponding author of the study and Director of the CeTPD, said, “The structural detail we have been able to obtain here is remarkable. We can see precisely how this small molecule creates a new molecular handshake between proteins that would not normally interact. Because we can chemically tune which enzyme is doing the heavy lifting, medicinal chemists have a new avenue to explore when designing the next generation of cancer drugs. The collaboration between our two groups has once again proven to be a powerhouse for fundamental discovery.”

The implications extend beyond a single target. Drug resistance remains one of the most formidable obstacles in cancer therapy, often arising when cells adapt to circumvent the mechanisms that drugs rely on. By distributing activity across multiple degradation pathways, dual-ligase strategies could make it significantly more difficult for cells to escape treatment.

More broadly, the study expands the conceptual framework of targeted protein degradation. It suggests that future drugs may not only be designed for specificity, but also for resilience – capable of maintaining their function even as biological systems change. In doing so, it points toward a new generation of medicines that are not only powerful, but durable by design.

Pictures attached

Photo: Co-Corresponding author Georg Winter (left) and co-first author Dmitri Segal (right). © Wolfgang Däubler / CeMM

Graphic: Cryo-EM structure of the complex between DCAF16 (red), DDB1(Δ BPB) (purple), DDA1 (orange), and SMARCA2 BD (green), glued by compound 1 (gray). © Dmitri Segal
The Study “Dual E3 ligase recruitment by monovalent degraders enables redundant and tuneable degradation of SMARCA2/4” was published in *Nature Chemical Biology* on 12 May 2026. DOI: 10.1038/s41589-026-02224-y

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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 Maria Rescigno. 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, rare diseases and aging. The Institute's research building is located on the campus of the Medical University and the Vienna General Hospital.

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The **AITHYRA Research Institute for Biomedical Artificial Intelligence** was founded in September 2024 and will combine the best of academic, corporate, and start-up worlds, and will have a mixture of AI and life science experts. In the ultimate expansion state, AITHYRA is envisioned to have 10-14 junior and senior research groups, as well as many global collaborators, very substantial computational and experimental infrastructure, and a state-of-the-art AI-driven robotic lab. AITHYRA is an institute of the Austrian Academy of Sciences (ÖAW) and was established with generous funding from the non-profit Boehringer Ingelheim Foundation.

www.oeaw.ac.at/aithyra

The **Centre for Targeted Protein Degradation (CeTPD)**, University of Dundee, was established in 2023 and is directed by Professor Alessio Ciulli. It brings together chemists, structural biologists, and cell biologists working to understand, design and develop the next generation of targeted protein degradation and induced-proximity therapeutics.

www.dundee.ac.uk/cetpd

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