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From Inhibition to Destruction – Kinase Drugs Found to Trigger Protein Degradation

For decades, kinase inhibitors have been a mainstay of cancer therapy, designed to switch off enzymes that fuel uncontrolled cell growth. But new research shows that these drugs often go further: they can also cause the very proteins they target to be dismantled by the cell, making them yet another tool for the emerging field of Targeted Protein Degradation (TPD). In a new study published in *Nature* (DOI 10.1038/s41586-025-09763-9), scientists at CeMM and AITHYRA, both institutes of the Austrian Academy of Sciences in Vienna, and the IRB in Barcelona, with partners across Europe, the US and China, have now mapped this effect systematically, uncovering a widespread but overlooked phenomenon in pharmacology.

Protein kinases are the molecular switches of the cell. They control growth, division, communication, and survival by attaching phosphate groups to other proteins. When these switches are stuck in the "on" position, they can drive cancer and other diseases. Not surprisingly, kinases have become one of the most important drug target families in modern medicine: today, more than 80 kinase inhibitors are FDA-approved, and nearly twice as many are in clinical development.

These drugs were designed to block enzymatic activity. But a new study led by CeMM, the Research Center for Molecular Medicine (Vienna), the AITHYRA Institute for Artificial Intelligence in Biomedicine (Vienna), and the Institute for Research in Biomedicine (Barcelona), together with partners across Europe, the US and China, reveals a surprising twist: kinase inhibitors can also accelerate the degradation of the very proteins they target. The findings, published in Nature, show that drug-induced degradation is not a rare quirk but a common and potentially exploitable feature of kinase inhibitor pharmacology.

A systematic look at an overlooked phenomenon

Hints that inhibitors might destabilize their targets had surfaced before, but the scope and mechanisms were unclear. To address this, the researchers systematically profiled 98 kinases with a library of 1,570 Inhibitors, monitoring protein abundance over time. The result was striking: 232 compounds lowered the levels of at least one kinase, with 66 different kinases affected.

Some of these cases followed the known route of the so-called "chaperone deprivation", where inhibitor binding prevents the stabilizing chaperone HSP90 from protecting its client kinases. But many others did not. Instead, the team discovered a shared mechanistic principle: inhibitors can push kinases into

altered states through changes in activity, localization, or assembly, which are naturally unstable and therefore cleared more quickly by the cell's own proteolytic circuits.

"Inhibitor-induced degradation turns out to be surprisingly widespread," says Natalie Scholes, senior postdoctoral researcher at CeMM and first author of the study. "Our data show that small molecules don't just block kinase activity; they can shift proteins into conformations that the cell recognizes as unstable. That means inhibitors can double as degraders, adding a whole new layer to how these drugs work."

Three case studies, one unifying principle

To dissect these mechanisms, the researchers focused on three kinases with very different fates: The researchers illustrated this principle with three examples: one kinase (LYN) was eliminated within minutes once an inhibitor tipped its natural stability switch; another (BLK) was broken down only after being released from the cell membrane into the cytosol by a membrane-bound protease complex; and a third (RIPK2) was cleared after forming large protein clusters that the cell recognized and removed through its recycling machinery. Together, these cases illustrate a broader rule: inhibitors can "supercharge" endogenous degradation pathways, nudging kinases into unstable states that the cell's quality-control machinery removes.

"This study demonstrates that degradation is not an anomaly but part of the pharmacological spectrum of kinase inhibitors," says Georg Winter, Director at the AITHYRA Institute for Biomedical AI, adjunct Principal Investigator at CeMM and senior author of the study. "Understanding this dimension could help us design better drugs that don't just silence kinases but remove them altogether—and in some cases, it may explain unexpected effects of existing therapies."

Pictures attached
Photo: First author Natalie Scholes and senior author Georg Winter (© Barbara Bachmann / CeMM)

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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 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, 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 of the Austrian Academy of Sciences** 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. With a generous donation from the Boehringer Ingelheim Foundation, the Austrian Academy of Sciences (OeAW) is hosting AITHYRA in Vienna.
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