Novel paradigm in drug development: Understanding resistance mechanisms to targeted protein degradation

Targeted protein degradation (TPD) is a new paradigm in drug discovery that could lead to the development of new medicines to treat diseases such as cancer more effectively. A recent study by researchers at CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences reveals global and drug-specific cellular effectors needed for TPD. The results have now been published in the scientific journal Molecular Cell.

(Vienna, 22 August 2019) Traditional medicines mostly function as inhibitors, attacking the disease-relevant proteins that cause cancer, by binding to their accessible pockets. Following this strategy, only ~20% of all proteins are chemically addressable, leaving some of the most relevant targets inaccessible to therapeutic development.

Targeted protein degradation (TPD) is a novel approach in drug development that could overcome this limitation, and currently represents a promising therapeutic strategy towards, for example, cancer treatment. TPD is based on small-molecules, generally called "degraders", which induce the degradation of proteins by re-directing ubiquitin E3 ligases towards the protein we aim to eliminate. In other words, utilizing the cell's Ubiquitin Proteasome System (UPS), which is our body's natural way of seeking out and destroying damaged proteins.

Until now TPD had been mostly studied from a structural perspective. Georg Winter's laboratory at CeMM focused on identifying and mechanistically understanding genetic determinants of sensitivity to small-molecule degraders. "*We selected a representative set of five degraders, which hijack different ubiquitin E3 ligases to degrade proteins of clinical relevance, such as BRD4, CDK9, or GSPT1. Conducting resistance screens, we were able to identify genes that determine the efficacy of targeted protein degradation*", explains Cristina Mayor-Ruiz, CeMM postdoc and co-first author of the study.

The data obtained identify central UPS regulators as essential for degrader efficacy. "*When those proteins are perturbed, ubiquitin E3 ligases lose their ability to flexibly assemble and disassemble in response to cellular needs. Instead, they start tagging themselves for destruction in a process called auto-degradation. As a consequence, the tested degrader drugs fail to destabilize their target proteins and are ineffective in blocking cancer cell growth*", elaborates Martin Jaeger, CeMM PhD student and second co-first author of the study.

The research conducted by Cristina Mayor-Ruiz, Martin Jaeger et al. combining functional genomics and quantitative proteomics is the first study that comprehensively dissects cellular determinants of mechanistically different small-molecule degraders, bringing new light into their rational design.

"*Now that degraders are entering the clinic, understanding potential resistance mechanisms may inform on ways to overcome it. The modulator gene-networks that we have identified can serve as biomarkers to support patient stratification, but also teach us a lot about fundamental aspects of the regulation and dynamics of the protein degradation machinery*", says Georg Winter, CeMM Principal Investigator.

The study "Plasticity of the cullin-RING ligase repertoire shapes sensitivity to ligand-induced protein degradation" was published in *Molecular Cell* on 22 August 2019. DOI: DOI: 10.1016/j.molcel.2019.07.013

Authors:
Cristina Mayor-Ruiz, Martin G. Jaeger, Sophie Bauer, Matthias Brand, Celine Sin, Alexander Hanzl, André C. Mueller, Jörg Menche, Georg E. Winter

Funding:
The study was funded by the Austrian Academy of Sciences. Cristina Mayor-Ruiz was supported by an EMBO long-term fellowship (EMBO-LTF ALTF 676-2017) and Martin Jäger was supported by a Boehringer Ingelheim Fonds (BIF) PhD fellowship.

Georg Winter, PhD, obtained his degree 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 Research Center for Molecular Medicine of the Austrian Academy of Sciences. He specialized on proteomics- as well as chemical genetics approaches to identify drug resistance mechanisms and synergistic drug combinations. He continued his training in chemical biology, working as a postdoctoral fellow with Dr. James Bradner at the Dana Farber Cancer Institute/Harvard Medical School. He innovated the first generalizable pharmacologic solution to in vivo target protein degradation (Winter et al., Science 2015). He was recruited as a CeMM Principal Investigator in 2016 where his research is now focused on using the unique molecular pharmacology of targeted protein degradation to understand and disrupt aberrant gene control in human cancers. Georg Winter (co-) authored 29 manuscripts including publications in Science, Nature, Nature Chemical Biology, Nature Genetics, Elife and Molecular Cell. Dr. Winter's contribution to the field of targeted protein degradation was acknowledged via multiple prices and awards, including the Eppendorf Award 2019 and the Elisabeth Lutz Award of the Austrian Academy of Sciences.

The mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna.
www.cemm.oeaw.ac.at

For **further information** please contact

Laura Alvarez
Social Media and Communications Manager

CeMM
Research Center for Molecular Medicine
of the Austrian Academy of Sciences
Lazarettgasse 14, AKH BT 25.3
1090 Vienna, Austria
Phone +43-1/40160-70 057
Fax +43-1/40160-970 000
lalvarez@cemm.oeaw.ac.at
www.cemm.at