Targeted protein degradation

Section for Organic and Medicinal Chemistry

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Competence Center Drug Discovery

In the fast-paced world of drug discovery, Targeted Protein Degradation (TPD) is a game-changing innovation. Moving beyond traditional small molecule inhibitors, TPD offers a novel approach to selectively eliminate proteins once deemed "undruggable". Initially focused on intracellular targets, especially in cancer, TPD is now expanding to include extracellular and membrane-bound proteins, representing a significant leap forward in treating a broader spectrum of diseases such as neurodegenerative disorders and autoimmune conditions.

The power of PROTACs

At the core of this technology are PROteolysis TArgeting Chimeras (PROTACs), which have revolutionized drug discovery since 2001. These bivalent molecules simultaneously bind to the protein of interest (POI) and an E3 ligase, facilitating the ubiquitination of the POI for subsequent degradation by the proteasome (see Figure). PROTACs have effectively targeted a variety of proteins, such as transcription factors and nuclear receptors, crucial in breast and prostate cancers. PROTACs for nuclear receptors and kinases are advancing in clinical trials, while PROTACs targeting aberrant proteins offer hope for the treatment of neurodegenerative diseases like Alzheimer's and Parkinson's. While PROTACs have revolutionised intracellular protein targeting, efforts are now extending to extracellular and membrane-bound proteins, which play crucial roles in a variety of diseases.

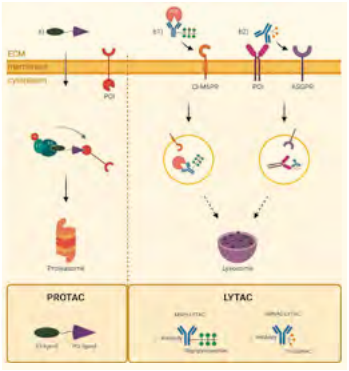
LYTACs: Beyond Proteasome-Based Degradation

Beyond PROTACs, several alternative strategies have emerged for targeting proteins, including those that bypass the proteasomal pathway. For instance, LYsosome TArgeting Chimeras (LYTACs) have been developed to specifically target extracellular and membrane-bound proteins (see Figure). LYTACs direct these proteins to lysosomes for degradation, offering new therapeutic avenues for diseases like Alzheimer's. They have demonstrated potential in crossing the blood-brain barrier to degrade β-amyloid and target challenging proteins such as solute carriers and apolipoprotein E4, with promising implications for neurodegenerative diseases and cancer.

Our contribution at the Competence Center Drug Discovery

The journey of TPD is not without its obstacles. Despite its transformative potential, the field faces several challenges, including suboptimal pharmacokinetics, poor oral bioavailability, and issues with cellular permeability. Moreover, drug-induced toxicity and resistance related to E3 ligase activity remain ongoing concerns. The event-driven mechanism of TPD agents necessitates meticulous management of off-target effects and recovery periods.

Nevertheless, the future of TPD is bright. Ongoing research and clinical trials continue to push the boundaries of what is possible, driving the field towards new horizons. As TPD evolves, it promises to revolutionize disease management by targeting previously inaccessible proteins and enhancing therapeutic outcomes. With emerging technologies and strategies, TPD is set to become a cornerstone of precision medicine, offering unprecedented opportunities to address a wide range of diseases.



Taken from Dimanthi Pliatsika, Cindy Blatter, Rainer Riedl. Targeted protein degradation: current molecular targets, localization, and strategies. Drug Discovery Today, 2024, 104178. doi.org/10.1016/j.drudis.2024.104178

In the Medicinal Chemistry Research Group at our Competence Center Drug Discovery, we are currently being funded by the SNSF through a SPARK project in our search for PROTACs against challenging targets in the context of cancer therapy. The syntheses of the PROTACs have been successfully completed, now the biological evaluation in collaboration with the molecular biology research group in our CC Drug Discovery is on the agenda. ■

Neue Projekte

Atmospheric Aging Impacts on Particles for Cirrus Cloud Seeding
Dauer: 01.03.2024–28.02.2027
Projektpartner: Eidgenössische Technische Hochschule Zürich ETH; University of Toronto; National Autonomous University of Mexico; Simons Foundation

Evaluation of the potential of targeting the IFN1 pathway
Dauer: 01.04.2024–31.03.2025
Projektpartner: SNF

Coffee B
Dauer: 01.04.2024–30.04.2024
Projektpartner: Delica AG

Evaluation of the potential of PROTACs
Dauer: 01.04.2024–31.03.2025
Projektpartner: SNF

BRIDGE Small Molecules against Leukemia
Dauer: 01.04.2024–31.03.2028
Projektpartner: SNF; Universität Bern; Inselspital Bern

National Competence Center of Research Catalysis
Dauer: 01.08.2024–31.12.2028
Projektpartner: SNF; Eidgenössische Technische Hochschule Zürich ETH; Ecole polytechnique fédérale de Lausanne EPFL; Universität Bern; Universität Basel

Weiterbildungsangebote ICBT siehe Seite 9 unten