PROTEIN DEGRADATION IN A SNAPSHOT

Created by

TPD Targeted Protein Degradation

October 22-24, 2019
Boston, USA

www.proteindegradation.com

WHAT IS INDUCED PROTEIN DEGRADATION?

Protein degradation plays a central role in many cellular functions. Misfolded and damaged proteins are removed from the cell to avoid toxicity. Induced protein degradation is an approach that is 'event-driven', upon drug binding, the target protein is tagged for elimination.[1]

WHAT ARE PROTACS & WHY IS THE BIOPHARMACEUTICAL INDUSTRY SO EXCITED ABOUT THEM?

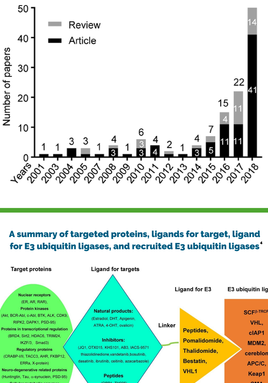
Targeted protein degradation using Proteolysis Targeting Chimeras (PROTACs) has emerged as a novel therapeutic modality in drug discovery. PROTACs mediate the degradation of select proteins of interest (POIs) by hijacking the activity of E3 ubiquitin ligases for POI ubiquitination and subsequent degradation by the 26S proteasome[2]. Inhibitors require sustained protein binding to evoke the intended biological reaction. This can be problematic in the incidence of target overexpression, the presence of competing ligands, or protein mutations that lead to binding resistance. The PROTAC model bypasses these issues by promoting degradation that circumvents the native resistance of proteins against sustained inhibition[3]. PROTACs are also considered as the way forward to finally drug the "undruggable" proteome, including the RAS and MYC oncogenes.

CAN PREVIOUSLY INEFFECTIVE INHIBITORS BE TURNED INTO PROTEIN DEGRADERS?

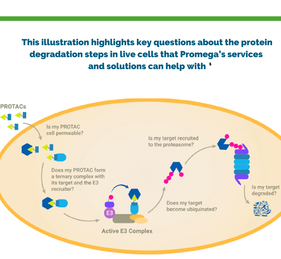
Because PROTACs don't inhibit the target protein's enzymatic activity, but bind their targets with high selectivity, it may be possible to retool previously ineffective inhibitor molecules as PROTACs for next-generation medicines for patients.

A graph view of the publications on the proteolysis targeting chimera (PROTAC) technology

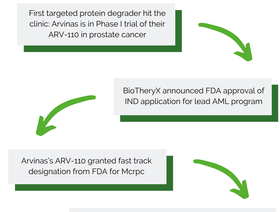
Research articles and reviews on PROTAC were searched from Pubmed (https://www.ncbi.nlm.nih.gov/pubmed). The literatures were presented chronologically from 2011. Numbers up columns indicate the total number of article and review papers.[4]



A summary of targeted proteins, ligands for target, ligand for E3 ubiquitin ligases, and recruited E3 ubiquitin ligases[5]



This illustration highlights key questions about the protein degradation steps in live cells that Promega's services and solutions can help with [1]



2019 Latest Advancements of the Field

First targeted protein degrader hit the clinic: Arvinas is in Phase I trial of their ARV-110 in prostate cancer

BioTheryX announced FDA approval of IND application for lead AML program

Arvinas's ARV-110 granted fast track designation from FDA for Mcrpc

Arvinas received authorization to proceed for ARV-471 to treat patients with locally advanced or metastatic ER+ / HER2- breast cancer to begin in Q3 2019

TPD 2019 Latest Deals & Collaborations

Bayer teamed up with Arvinas in deal worth up to $750 million

C4 Therapeutics and Roche announced a transformation of their strategic collaboration initiated in January of 2016 totaling over $900 million in upfront and milestone payments

Gilead stroked $2.48 billion deal with Nurix to focus on protein degradation

Vertex targeting protein degradation in $1bn Kymera deal

Biogen and C4 Therapeutics entered into strategic collaboration with a potential total of up to $415 million

Boehringer Ingelheim and the University of Dundee have extended their collaboration, building on the success of their ongoing alliance

References:

1. Lai AC, Crews CM. Induced protein degradation: an emerging drug discovery paradigm. Nat Rev Drug Discov. 2017;16(2):101–114. doi:10.1038/nrd.2016.211
2. Paiva SL, Crews CM. Targeted protein degradation: elements of PROTAC design. Curr Opin Chem Biol. 2019;50:111-119. doi.org/10.1016/j.cbpa.2019.02.022.
3. www.bpsbioscience.com/protacs
4. Zou, Y., Ma, D., Wang, Y. The PROTAC technology in drug development. Cell Biochem Funct. 2019; 37: 21– 30. https://doi.org/10.1002/cbf.3369
5. https://www.promega.co.uk/resources/technologies/nanoluc-luciferase-one-enzyme-endless-capabilities/protein-degradation/

TPD Targeted Protein Degradation

October 22 - 24, 2019 Boston, USA

Finally Drug the "Undruggable with Targeted Protein Degradation"

www.proteindegradation.com