Int J Med. Public Health. 2022; 12(3):96
A Multifaceted Peer Reviewed Journal in the field of Medicine and Public Health
www.ijmedph.org

Guest Editorial

PROTACs: Opportunities and Challenges Ahead in the Field of Drug Discovery

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Proteolysis Targeting Chimeras (PROTACs) are alternatives to traditional small molecule-based drug discovery techniques that focus on direct regulation of protein activity. Targeted protein degradation in cells by heterobifunctional small molecules has emerged as one of the most promising technologies for modulating a protein of interest (POI). PROTACs connect three chemical elements: POI ligand to an E3 ubiquitin ligase (E3) recruiting ligand with an optimal linker for conjugating these two ligands.[1] PROTACs cause degradation via the ubiquitin-proteasome system (UPS) through proximity-induced ubiquitination of the POI. PROTACs induce target protein degradation at low exposures due to their catalytic mode of action thus making them an attractive platform for cancer therapy and other diseases.

The concept of PROTAC was developed by Raymond J. Desharies, Kathleen M. Sakamoto, Kyungbo Kim, and Craig M. Crews in 2001.[2] Since then, significant progress has been made in developing multiple antitumor PROTACs over the last 20 years, with different subcellular localization.[3] PROTACs due to their unique MOA achieve therapeutic efficacy at a very low dosing regimen compared to small-molecule inhibitors (SMIs) which are used at higher concentrations. With PROTACs there lies a possibility to achieve tumor-specific degradation using ligands for tumor-specific E3 ligases and target "undruggable" proteins like transcription factors (TFs).[4]

Pharmaceutical companies have reported PROTACs targeting proteins related to various disease types. For example, PROTACs targeting B-cell lymphoma 6 (BCL6) were reported by AstraZeneca, Boehringer Ingelheim reported for focal adhesion kinase (FAK), Pfizer developed for Bruton's tyrosine kinase (BTK), and Interleukin-1 receptor-associated kinase 4 (IRAK4) from GSK. More recently Arvinas, Inc., reported, ARV-110 an androgen (AR)-targeted PROTAC that exhibited satisfactory results in phase I clinical trial with high potency against both wild-type and mutants.[5]

As with any new technology, PROTACs have many challenges to overcome. There is an urgent need to establish new pharmacokinetics (PK) and pharmacodynamics (PD) evaluation system for PROTACs as the traditional methods cannot accurately measure their PK/PD properties due to their unique MOA.[6] Developing an assay for effective screening for ligands that can be used in PROTACs for disrupting protein-protein interactions is a major challenge that needs to be addressed. A rational design for developing novel PROTACs is another major hurdle to address as there is limited knowledge on selectivity profiles, degradation mechanisms, and off-target effects in multiple diseases and cell types.[7] There is an urgent need to explore the opportunities provided by PROTACs to address "undruggable targets' as there has been only one reported example of PROTACs targeting undruggable protein.

The scientific community is still in the early stages of the development of PROTACs, and it is expected that this field will continue to develop dynamically. A joint effort combining resources between academia and industry can further the development of this new technology and open a broad way for the discovery of new drugs.

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DOI : 10.5530/ijmedph.2022.3.19

Article Available online
http://www.ijmedph.org/v12/i3

Cite this article : Vadukoot AK. PROTACs: Opportunities and Challenges ahead in the field of drug discovery. Int J Med Public Health. 2022;12(3):96.