

REVIEWER'S REPORT

Manuscript No.: IJAR -58254

Title: TARGETED PROTEIN DEGRADATION WITH PROTACS IN CANCER THERAPY: MECHANISMS, CLINICAL ADVANCES, CHALLENGES, AND FUTURE PERSPECTIVES.

Recommendation:

Accept as it is

Accept after minor revision.....

Accept after major revision

Do not accept (*Reasons below*)

Rating	Excel.	Good	Fair	Poor
Originality		Good		
Techn. Quality	Excellent			
Clarity	Excellent			
Significance	Excellent			

Reviewer's ID: Dr. Sumathi

Detailed Reviewer's Report

- 1. PROTACs (Proteolysis Targeting Chimeras) are a revolutionary class of small-molecule drugs that harness the cell's natural disposal system to completely eradicate disease-causing proteins rather than just inhibiting them.**
- 2. Targeted protein degradation (TPD) is a drug design strategy that uses small molecules (like PROTACs and molecular glues) to chemically tag and destroy disease-causing proteins. Instead of just blocking a protein's active site, this method forces the cell's natural recycling systems to permanently eliminate the target, effectively "drugging the undruggable."**
- 3. TPD leverages the body's innate waste-disposal systems—primarily the ubiquitin-proteasome system (UPS) and the autophagy-lysosome pathway. Unlike traditional enzyme inhibitors, which require continuous binding and high drug concentrations, degraders work catalytically: one molecule can tag and destroy many target proteins, allowing for lower doses and sustained effects.**
- 4. The ubiquitin-proteasome system (UPS) is the cell's primary pathway for degrading damaged, misfolded, or unneeded proteins. It**

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maintains cellular health by tagging targets with a molecular label called ubiquitin and shredding them into harmless amino acids, a process vital for regulating the cell cycle, gene expression, and immune responses.

- 5. Cancer therapy refers to treatments designed to eliminate, shrink, or control cancerous tumors and cells. Oncologists tailor approaches based on the type and stage of cancer, often combining different modalities like surgery, chemotherapy, radiation therapy, immunotherapy, or targeted therapy.**
- 6. Molecular glues are small, monovalent molecules that bind to a protein and alter its surface, inducing it to "stick" to another protein it wouldn't normally interact with. By forcing these unnatural interactions—usually with a cellular enzyme—they can inactivate disease-causing proteins or hijack the cell's natural garbage disposal system to destroy them.**
- 7. Drug discovery is the complex process of identifying and developing new candidate medications. It typically begins with target identification and hit discovery, and culminates in clinical trials to ensure human safety and efficacy. Modern research heavily utilizes artificial intelligence and genomics to accelerate drug screening and design.**
- 8. Key words are excellent.**
- 9. Significant points excellent.**
- 10. Result part can be made tables and graphs.**
- 11. Research topic is medically important one.**
- 12. Summary points also be included.**
- 13. Can be continued to explore more things in molecular docking level.**
- 14. After a small changes good to publish in your journal.**