Molecular Glues: A New Dawn of Small Molecule Drugs After PROTAC

Currently, **targeted protein degradation (TPD)** is an emerging therapeutic strategy that exerts therapeutic effects by inducing the degradation of pathogenic target proteins. TPD has attracted much attention because of its wider range of action, higher activity, targeting "non-drugable" targets, and overcoming drug resistance. Targeted protein degradation (TPD) is a promising research field, and its emergence has changed the pattern of drug development, opened up new drug targets and drug blueprints, and opened up new avenues for "Undruggable" target drug development.

PROTAC and molecular glues are the two main modes of targeted protein degradation technology based on the ubiquitin-proteasome system (Figure 1). PROTAC induces target proteins to approach ubiquitin ligases by recruiting ubiquitin ligases, resulting in ubiquitination and degradation of target proteins. Molecular glues promote or induce protein-protein interaction (PPI) between E3 ubiquitin ligase and target protein by modifying the surface of ubiquitin ligase, so that the target protein is ubiquitinated and then degraded.

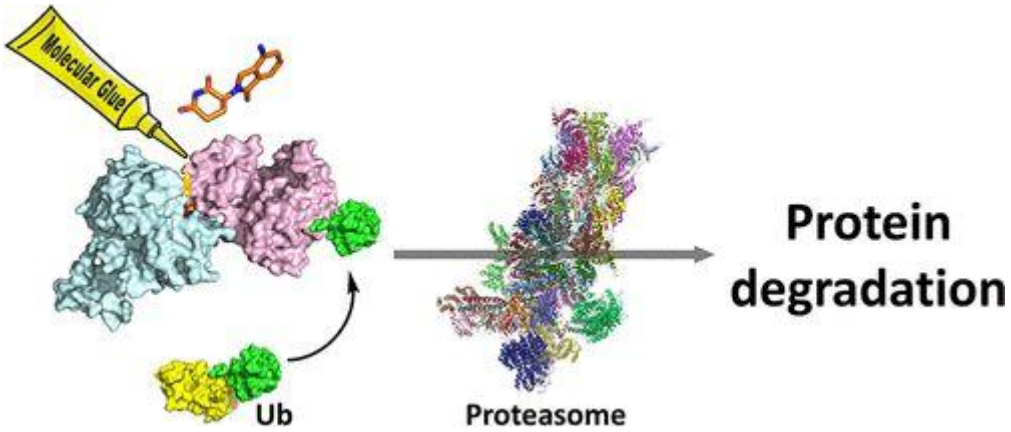

Figure 1. Mechanism of action of molecular glue degraders

The concept of "molecular glue" first appeared in the early 1990s. **The immunosuppressants cyclosporine A (CsA) and FK506 were the first examples of molecular glues.** Studies have found that cyclosporine A and FK506 act in the form of molecular glues. CsA and FK506 could induce the formation of two ternary complexes of cyclophilin-CsA-calcineurin and FKBP12-FK506-calcineurin, respectively. The later immunosuppressant rapamycin can also act as a molecular glue to stabilize the FKBP12-rapamycin-FRB (mTOR) ternary complex. In 2013, researchers first elucidated the mechanism of action of thalidomide analogs as molecular glue degraders. After 2014, molecular glue degraders gradually emerged and gradually developed into the focus of researchers (Figure 2). In recent years, there has been a wave of research and development of molecular gel inhibitors in the medical circle.

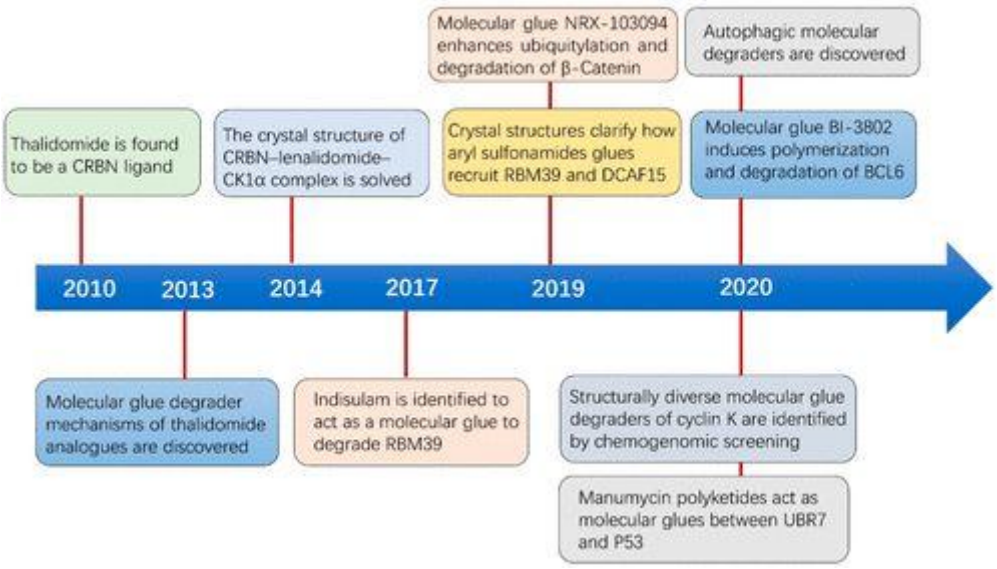

Figure 2. Development history of molecular glues

With the "continuous warming" in the field of targeted protein degradation, molecular glue degraders have become the focus of many pharmaceutical companies around the world. A number of ubiquitin proteasome-based molecular glue degraders have achieved positive research results and have been approved for clinical studies. **Thalidomide and its derivatives (lenalidomide and pomalidomide)** have immunomodulatory, anti-inflammatory and anti-tumor effects and have been approved by the US FDA for the

treatment of **multiple myeloma** and other diseases. In the follow-up mechanism study, it was accidentally found that **thalidomide and its derivatives also act as molecular glue degraders**, and promote the ubiquitination and degradation of substrate proteins by inducing the PPI of CRBN and substrate proteins (IKZF1/3, etc.).

Molecular glues and PROTAC

Although both molecular glue and PROTAC are bifunctional protein degraders, they have different mechanisms of action and structural features (Figure 3). PROTAC is a heterobifunctional degrader that interacts with both E3 ubiquitin ligase and target protein, inducing the target protein to approach E3 ubiquitin ligase, leading to ubiquitination and degradation of the target protein. The **molecular glue is a small molecule degrader**, which can only interact with the ligase (more frequently) or the target protein, by inducing or stabilizing the PPI between the E3 ubiquitin ligase and the target protein to form ternary complexes that induce ubiquitination and degradation of target proteins.

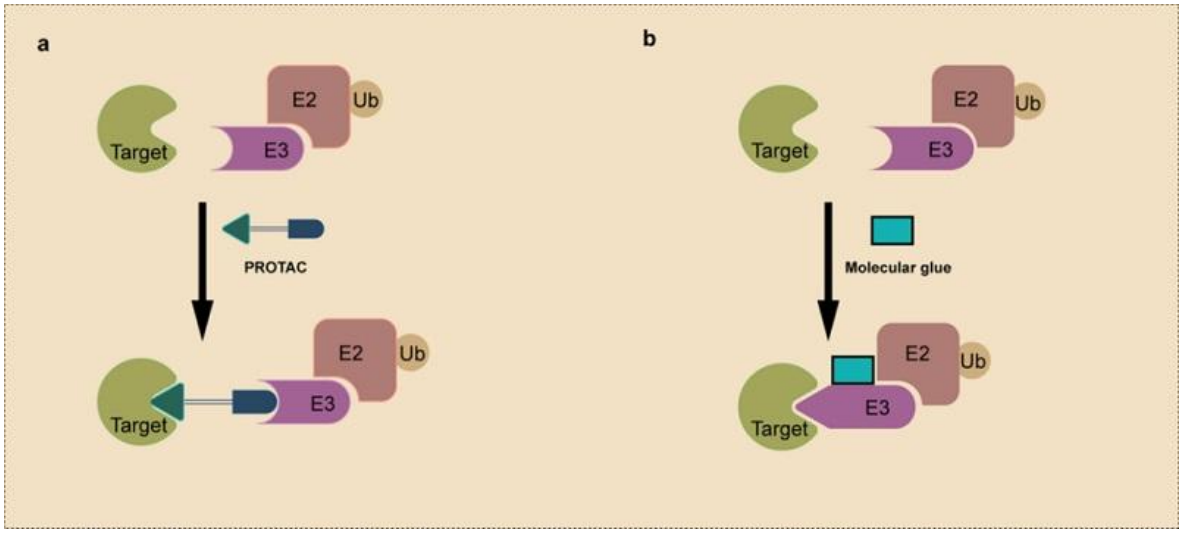

Figure 3. Schematic diagram of the structure of molecular glue and PROTAC

In addition, the target proteins and molecular mechanisms of PROTACs are predictable and can be rationally designed according to the binding mode of ligands to target proteins.

However, the discovery of molecular glues is very accidental, and there is a lack of systematic discovery methods and reasonable design strategies. Molecular glues cannot be obtained through large-scale screening of components like PROTAC, which makes drug design based on molecular glue more difficult, so few molecular glue degraders have been discovered so far.

The advantage of molecular glue is that it can degrade non-ligand-bound proteins by promoting the PPI between ubiquitin ligase and target protein, showing a therapeutic effect superior to that of small molecule drugs. However, PROTACs usually have high molecular weight (MW), poor cell permeability and pharmacokinetic (PK) characteristics, which hinder the development of PROTACs in clinical therapy. Molecular glue has lower molecular weight, higher cell permeability and better oral absorption, which conforms to the "Five Rules for Drugs" and shows better druggability (Figure 4). The molecular glue strategy provides a new research idea for drug development in the field of targeted protein degradation.

Table 1. Comparison of Molecular Glues and PROTACs

	molecular glue	PROTAC
mechanism	binds E3 or target protein induces PPI	binds target and E3
target protein	to be determined	predictable
discovery strategy	historically serendipitous discovery	rational design
feature	monovalent	bivalent
linker	without linker	with linker
molecular weight	lower	higher
rule of five	typically within	beyond
binding pocket in the target protein	nonessential	required

Figure 4. Comparison of molecular glues and PROTACs

Research and development strategy of molecular glue degraders

Molecular glue degrader is a very ideal targeted therapy drug, and its clinical effect is also very potential. However, drug discovery based on molecular glue is very contingent, which makes the development of molecular glue drugs very limited.

1. Obtained from the transformation of kinase inhibitors

In 2020, Benjamin L. Ebert's research group discovered that CR8, a cyclin-dependent kinase CDK inhibitor, is a new molecular glue degrader by systematically mining the database and screening with CRISPR-Cas9 technology (Figure 5). Among them, CR8 bound to CDK can induce CDK12/cyclinK to directly form a complex with CUL4/DDB1, thereby bypassing the substrate receptor DCAFs, enabling cyclinK to be ubiquitinated and degraded by the proteasome system.

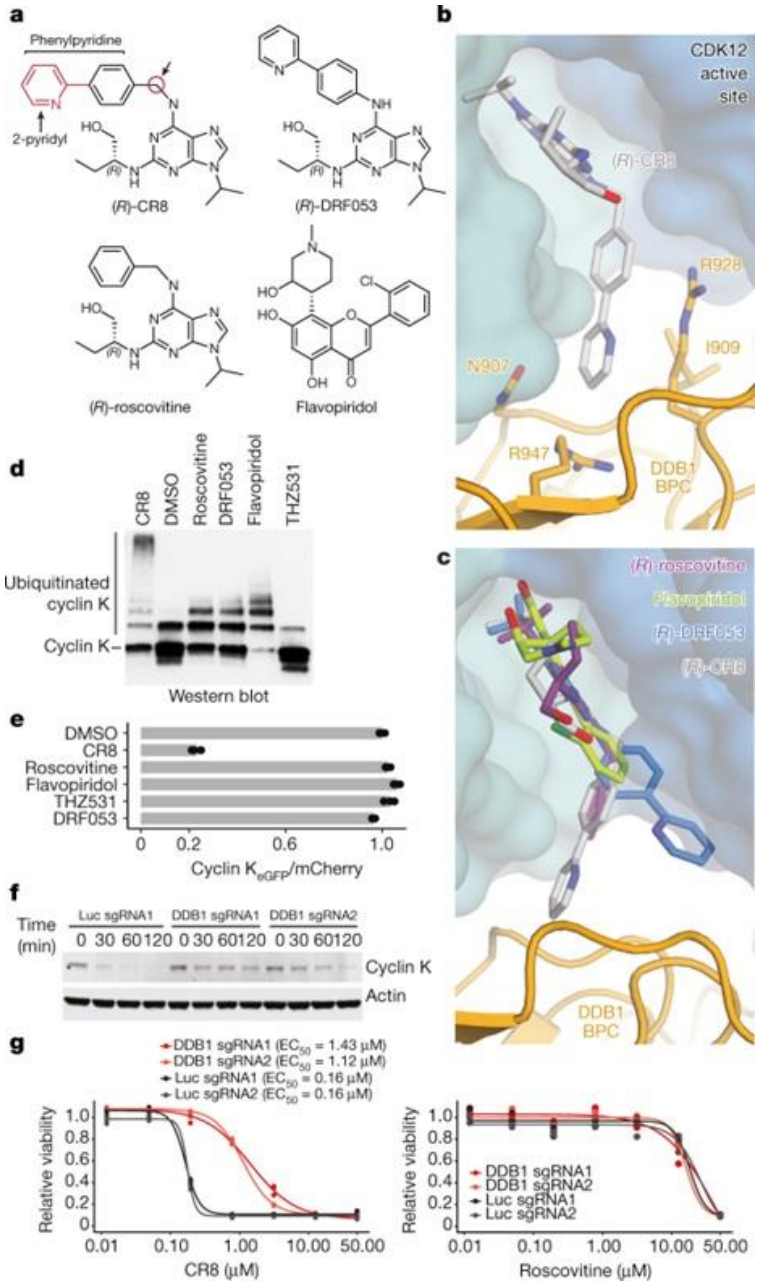

Figure 5. CR8 molecular glue degrader and bioactivity evaluation

2. Phenotype-Based Screening Strategies

In 2020, Georg E. Winter's team discovered a new RBM39 molecular glue degrader-dCeMM1 (Figure 6) through phenotypic chemical screening. dCeMM1 acts by redirecting the activity of CRL4 DCAF15 ligase, ubiquitinating and degrading target proteins RBM39.

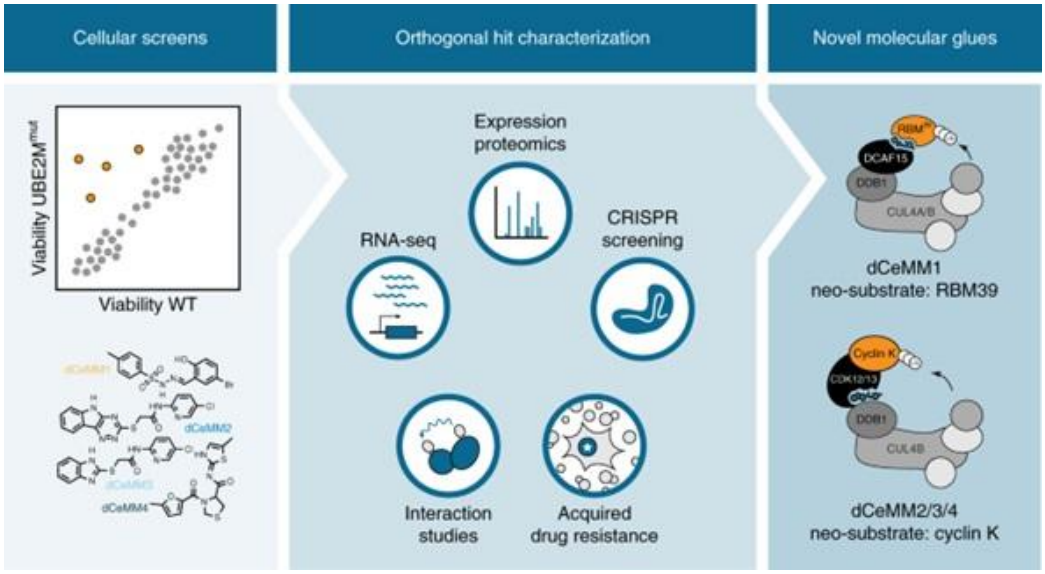

Figure 6. Discovery of RBM39 molecular glue degraders

3. The strategy of new use of old drugs

The strategy of reusing old drugs is one of the important means of drug discovery. Compared with the research and development of new drugs, the new use of old drugs has the advantages of low cost and short time consumption. Thalidomide and its analogues are immunomodulatory imides approved by FDA in the United States for the treatment of multiple myeloma and other diseases (Figure 7). The researchers found in follow-up mechanism studies that these drugs are also molecular glues. They can bind to the highly conserved tri-tryptophan cavity on CRBN and form E3 ubiquitin ligase complexes with damaged DNA-binding protein-1 (DDB1) and Cul4A type E3 ubiquitin ligases, which subsequently induces ubiquitination and degradation of target proteins such as IKZF1/3, CK1α and SALL4.

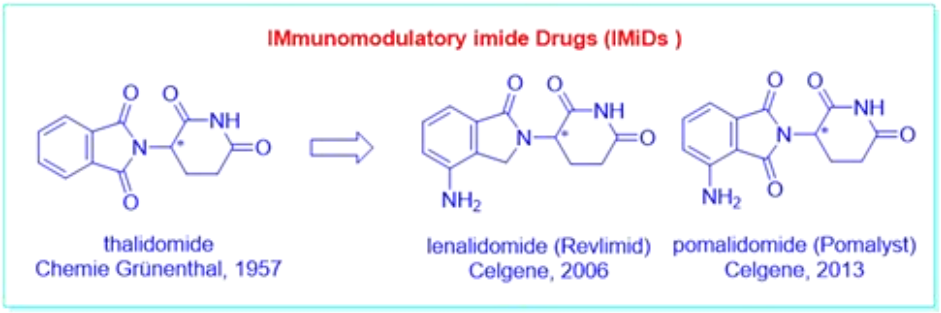

Figure 7. Chemical structures of thalidomide and its derivatives

Indisulam is a potential small-molecule anticancer drug developed by Eisai Pharmaceuticals. But in recent studies, Indisulam was also found to be a molecular glue (Figure 9), which can enhance the protein-protein interaction between DCAF15 and a new substrate protein (RBM39), and induce ubiquitination and degradation of the target protein RBM39.

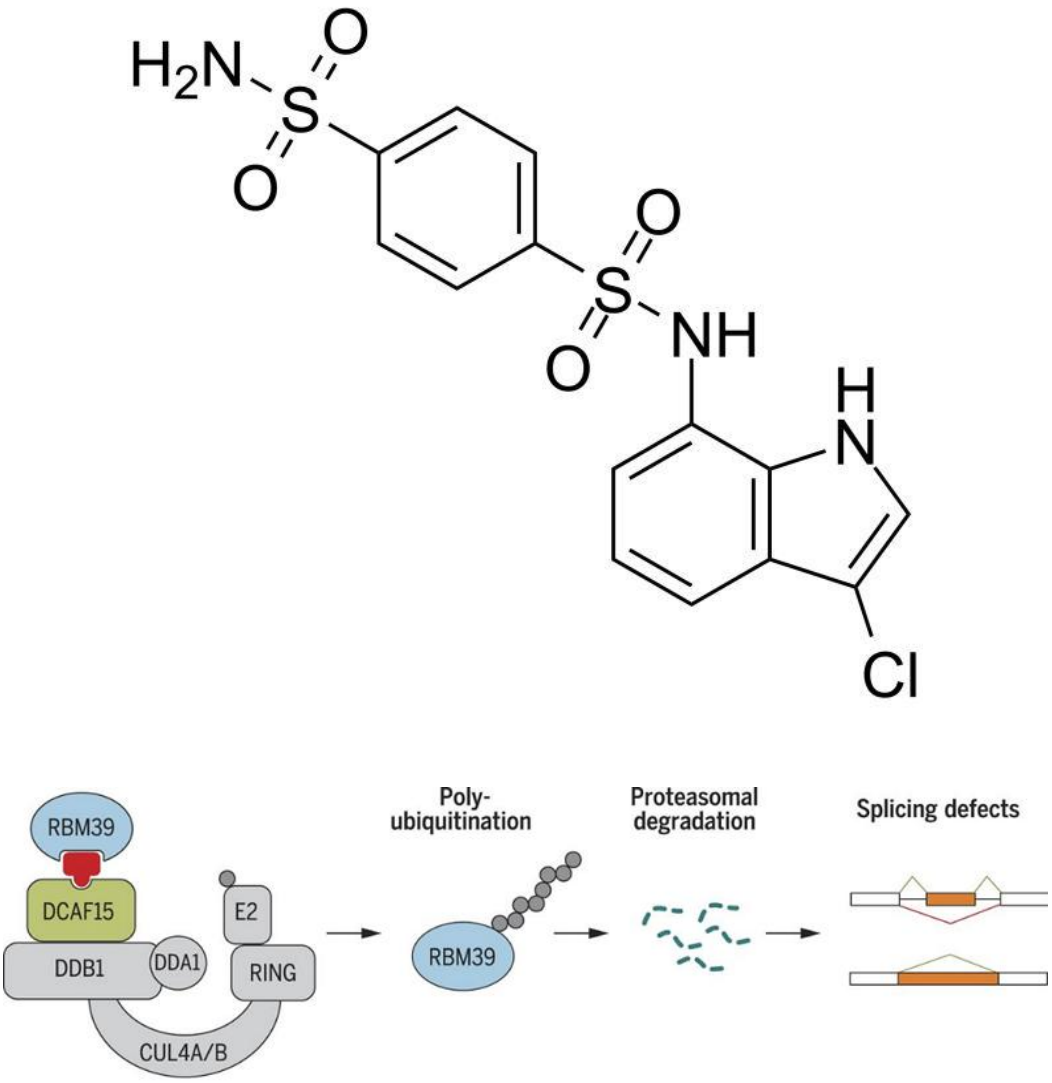

Figure 8. Chemical structure and mechanism of action of Indisulam

Conclusion

Targeted protein degradation (TPD) is becoming a promising therapeutic strategy in the development of new drugs. The discovery of molecular glue-mediated proximity-induced protein degradation technology reveals new biological mechanisms and new therapeutics. At present, drug research and development based on molecular glue is still in its infancy. The discovery of molecular glue drugs is a serendipity, and there is no strategy for rationally designing molecular glue degraders. Therefore, there is an urgent need to develop some reasonable structure-based molecular glue drug discovery technologies. In conclusion, a full understanding of the molecular mechanisms, structural biological characteristics, and medicinal chemistry information of molecular glue degraders will play an increasingly important role in translating targeted protein degradation strategies into practical clinical applications.

The commonly used linkers in the development of PROTACs are PEGs, Alkyl-Chain and Alkyl/ether. **Biopharma PEG** is a reliable PEG supplier provides multi-functionalized PEG derivatives as PROTAC linkers to customers all over the world .

References:

[1]. The CDK inhibitor CR8 acts as a molecular glue degrader that depletes cyclin K. 10.1038/s41586-020-2374-x

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