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Molecular Glues and Molecular Glue Degraders: Mechanisms, Design, and Therapeutic Applications

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Abstract. Molecular glues and molecular glue degraders appear to be a fast-growing class of therapeutic agents that selectively modulate protein-protein potential interactions and can enhance the selective degradation of proteins. These small molecules are providing the possibility to target proteins that previously thought to be very challenging or inaccessible that are involved in a host of diseases. The present review focuses on describing the basic concepts of molecular glues and the rationale behind the interactions and the general concept that drives their design. Special attention is paid to their uses in cancer therapy, neurodegenerative diseases, and infections therapy. Exploring new therapeutic targets and drugs based on the molecular glue degraders' ability to recognize and bind E3 ubiquitin ligases and promote ubiquitination proteolysis of specific proteins. Furthermore, the review looks at some of the limitations and the difficulties in the creation of these agents, as well as that potential in the field of pharmacogenomics. Thus, future expansion of molecular glue with state-of-the-art technologies including artificial intelligence and CRISPR is expected to extend its therapeutic applicability; evidently a step-up for targeted therapies. In this review, it offers the state-of-art on molecular glue studies and future direction for such work.

Keywords: Molecular Glues, Protein Degradation, Rational Design, Targeted Therapy, Drug Discovery.

1. Introduction

It is the molecular glue that is emerging as an increasingly acknowledged sort of small molecules capable of redefining the prospects and approaches of the drug discovery and targeted/precision medicines. These compounds are capable of either stabilizing or inducing new PPIs, which means that they can affect proteins that have previously been termed 'undruggable.' Molecular glues have provided a new set of targets for therapeutic intervention especially in disease states which have not responded to treatments involving small molecule inhibitors and biologics [1].

This article analyses the various ways in which molecular glues operate, with a focus on their ability to selectively target proteins for degradation by the UPS. This pathway is important for recycling proteins within the cell, and removing damaged or unnecessary proteins, or proteins that are no longer needed as they have been misfolded. Molecular glues operate within this system by encouraging the selective targeting of E3 ubiquitin ligase to the target proteins which is followed by their destruction and therefore affecting critical cellular functions. Protein-specific features and needs for molecular glues' design are strongly rely on the structural and functional information about target proteins and their partners. The continuing improvement of the way to determine high-resolution structures of the macromolecules such as X-ray crystallography as well as the cryo-electron microscopy (cryo-EM) have been the major factors that driven these molecules. Furthermore, the technology of high-throughput screening (HTS) has indeed provided a huge boost in identifying a large number of molecular glues by screening huge and extensive libraries of small molecules against the particular biological system.

In future, application of AI and machine learning plan a significant role in the process of drug discovery and enhancing the design of molecular glues. As such these technologies have the possibility of enhancing the efficiency and accuracy in screening molecular glue candidates. Also,

the therapeutic protection of molecular glues is important in considering the diseases like Alzheimer's, Parkinson's, and Huntington's that are characterized by misfolded or aggregated proteins in the brain. That is, molecular glues lock onto these pathological proteins to provide promising therapeutic strategies for the core causes of such devastating diseases. This review will offer a comprehensive snapshot of the current Research status of Molecular Glue highlighting the difficulties a well as potential advantages of a field that is still progressing at an extremely fast pace.

2. Molecular Glues

2.1. Definition and Concept

Molecular glues are small molecules. They alter the manner in which proteins interrelate. While the conventional small molecules inhibit one target protein, molecular glues make two or more proteins bind to each other. This can form a new protein complex This can form a new protein complex. This new approach allows molecular glues to get at proteins that are off limits to more conventional small-molecule drugs. They can enhance a low affinity interaction to become higher or initiate a new interaction that normally will not occur. It is very useful in medicine since molecular glues can be used to disaggregate toxic proteins or activate fundamental cell processes. There are two main types of molecular glues: The two types of self-antigens are monovalent and bivalent. Monovalent molecular glues linking one protein to another form a monovalent link or one to one link. Bivalent molecular glues can cause a number of proteins to be linked jointly or can hold a set of proteins. This makes the proteins interact more effectively – that is, it makes the proteome work more effectively. Due to this flexibility, molecular glues are a valuable instrument when, for instance, small molecules that would ordinarily be used are inefficient.

2.2. Historical Perspective

The idea of molecular glues has only recently come to the forefront but dates back to key earlier findings in chemical biology. In the end, Thalidomide and its analogs were described as molecular glues because they could bind cereblon protein that further enabled its interaction with transcription factors (specific ones) leading to ubiquitination and then subsequent degradation of these factors. This was one of the major breakthroughs for the community, which demonstrated that molecular glues have a large potential as therapeutics to target proteins formerly known as "undruggable".

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3. Machanism of Action

3.1. Protein-Protein Interaction Facilitation

The molecular glues advertised are those that actively participate in stabilizing the protein interactions. This is to mean that they are able to co-localize proteins that do not normally associate or interact for only a short period. This made them to be distinct from ordinary small molecules; there is absence of such characteristics. In contrast to traditional small molecules where the aim is to modulate or inhibit or activate a particular protein, molecular glues alter how proteins interface. This they accomplish in that they combine with specific locations on proteins so as to cause variations which help to augment the binding of proteins or generate additional loci for binding. It has been established that these modifications produce a range of biological consequences. For example, molecular glues interact with E3 ubiquitin ligases through the process of binding with proteins which are not usually

recognized. This function enables the ligase to attach ubiquitin to the target protein hence degrading it.

3.2. Degradation Pathway: Ubiquitin-Proteasome System

Ubiquitin-Proteasome System (UPS) degrades misfolded, damaged and any unnecessary proteins. It is obvious that it is critical to target this process for the support of proper cell functioning. In proteolytic roles, molecular glues invoke this system to destroy the desired protein of focus in the cell. During the first mechanism of these processes, the glues adhere to the target protein. When one wants to bind a specific protein, a lot of care is taken to ensure that only the target protein is tagged for destruction. Acting as molecular glue in this interaction enhances selectivity: The other proteins are not affected and therefore are not broken down which helps to retain the useful proteins from the degradation process and at the same preventing imbalances within the cell. The presumed advantages of molecular glues are most relevant to cancer therapy because they offer a way for the disease's progression to be halted by eradicating all of the oncoproteins that underlie the disorder.

3.3. Specificity and Selectivity

High specificity in drug development is difficult to achieve. This makes it critical that drugs target the right molecule and do not have off-target effects. Molecular glue contributes to this aspect by inducing very specific protein interactions. Therefore, they are precise. The specificity of molecular glue is further enhanced by good compatibility between the glue and proteins. Target protein structure has a say in designing molecular glues. Scientists use computational modeling and structure-based design so that they can predict the interaction mode for their glue and target well. This also helps fine-tune the glue for high potency at low doses while being selective enough not to bring in non-target proteins. Also important is the environment where molecular glue works in cells; selectivity of glue depends not only on structure but also on this factor of the cell setting. Assays are developed for use in medium-throughput settings, where conditions optimize running six points per doseresponse curve, so that scientists can quickly screen through large numbers of molecules for hit identification before confirming hits via mass spectrometry or other methods later downstream during optimization.

3.4. Emerging Mechanisms Beyond Degradation

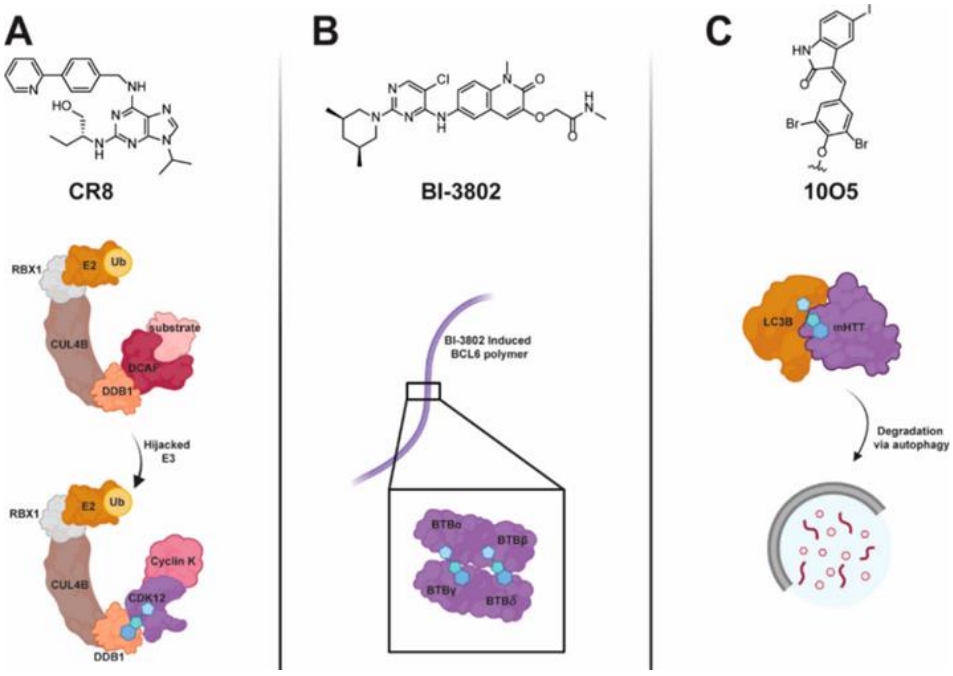

Figure 1. Mechanisms of molecular glue-induced degradation that operate without E3 ligase receptor recruitment [2].

New investigations reveal other manners how molecular glues function. Some interact with signaling pathways in that they can stabilize specific protein-protein interfaces. Some assist in the formation of multi-protein complexes that are needed for transcription or repair of DNA injury, as shown in **Figure 1**[2]. These implications entail those molecular glues are capable of performing another function apart from degrading proteins. In cancer treatment the molecular glues could enhance the potency of the tumor suppressor proteins. This they achieve by stabilizing interactions between co-activators and this would help bring back or rather reinstate normal functioning in the cell. In diseases such as Alzheimer's, molecular glues may prevent amyloid proteins from forming aggregates and hence slow the progression of the disease. If further details are grown, various kinds of molecular glues can be used for other treatments. These discoveries prove that molecular glues are useful for reaching the target site in drug development. It could offer treatment for many illnesses in ways that are different from the traditional methods.

4. Design Pathways of Molecular Glues

4.1. Rational Design

To create molecular glues, one has to understand the structure and the purpose of the target proteins. Very particular attention is paid to the ways in which proteins and their partners recognize each other [3]. They sometimes employ resolution methods such as X-ray crystallography or cryo-EM. All these tools assist in identifying regions where the small molecules can serve as a connector between proteins and make them bind together. It is very crucial to predict how well a molecular glue will bind. Tagging designs that come up with suitable molecular glues to those that can be removed easily is crucial. In molecular level one, scientists employ computer models to model interactions in the atomic level. These models allow them to effectively simulate many a molecule. They are as follows: To ascertain which of them favours protein interactions most. When they have set their eyes on a fine-looking candidate, they polish it. The molecule can be changed by design or synthesis of a new molecule and then a test is conducted. They enhance its mechanical properties, its ability to sort out what is permissible and how it interacts in the body. As has been described, it is a cycle of improvement. They begin with a concept, that they experiment, and make improved. So each stage takes molecular glue nearer to being efficient and secure. It is a slow-moving process and meticulously done but it is always in a seek for how to make the glue better.

4.2. Screening Methods

Molecular glues can be identified through the high throughput screening (HTS). It is a fast method and it can screen a large number of small molecules within a short duration of time. Ten thousand to millions of molecules are being screened in cells for particular targets. Another aspect in the HTS is the so-called Reporter Assays. When proteins collide, they generate something that we may liken to light. If the compound gives a good signal, it is a 'hit'. Tunes that are hits are checked and developed as well. One other method is fragment-based fashion. Some fragments of the molecules are used in the testing to identify whether they demonstrate binding affinity to the target protein selections. If a fragment operates well, then it is related to other fragments or strengthened to throw better molecular adhesives. To use HTS is like going for a search of books in an enormous library and choosing the most wonderful books. Scientists then try to identify the best, and then proceed to develop those, in order to enhance their characteristics [4].

4.3. Structure-Activity Relationship (SAR) Studies

SAR studies that help make molecular glues better in the same way that structure-function relation aid the understanding of workings of proteins and protein interactions. In analyzing the properties of the glue, researchers determine what the variations in structure do to the functional properties. They work the design and change it to make it more efficient, still having to filter it. In many of these studies, high-resolution data are available. Structure elucidation methods such as X-Ray

crystallography for instance, explain how a glue molecule interacts with a protein, or which of the atoms or groups form the target.

4.4. Challenges and Future Directions

The major problem of the molecular glues is the ability to direct the glue towards desired protein. They must not impact on other proteins in such a way that will disrupt the normal functioning of the cells. This entails knowledge of how protein collaborate in cells. Some of them are difficult to hit due to the fact that they are intracellular and highly conserved including transcription factors or RNA-binding proteins. These proteins also cannot be characterized by the presence of the so-called binding sites. To combat this, researchers are starting to use innovative approaches such as allosteric modulation or employing this concept of novel structures. AI and, more specifically, machine learning will continue to play a more significant role in the design of molecular glues [5]. These technologies can analyzed bulky data within the shortest time possible. They can discern patterns and can foresee the method by which a glue might function. It accelerates the process of finding both which in turn could pave way for new therapies.

5. Molecular Glue Degraders

5.1. Concept and Definition

Molecular glue degraders represent a big leap in medicine [6]. While ordinary molecular glue is intended to merely 'glue' proteins together, these degraders are designed to 'un-glue' particular proteins. This idea began quite as an accidental observation regarding certain slim particular small molecules that aided in the interaction of proteins for the degradation of other proteins. This has gradually metamorphosed into a completely different type of treatment. These degraders harness the body's inner mechanisms to, essentially, expel unwanted proteins from the cells. Molecular glue degraders employ the UPS to recognize and degrade proteins.

5.2. Mechanism of Action

They function in a way that they link E3 ubiquitin ligases with the target proteins. Once the target proteins are tagged, they are degraded in the presence of proteasome complex. This method is well applicable in the determination of proteins, particularly those with hard to identify active sites. Molecular glue degraders employ the UPS to recognize and degrade proteins. They function in a way that they link E3 ubiquitin ligases with the target proteins. Once the target proteins are tagged, they are degraded in the presence of proteasome complex. This method is well applicable in the determination of proteins, particularly those with hard to identify active sites.

5.3. Design Strategies

Designing molecular glue degraders starts with finding the right target protein and an E3 ubiquitin ligase that a small molecule can connect, as illustrated in **Figure 2** [7]. The aim is to create a degrader that makes a strong and specific bond between these proteins. This process starts with knowing a lot about the target protein and the E3 ligase. This knowledge helps scientists guess how well a degrader will work before making and testing it. High-throughput screening (HTS) is also used to find possible degraders. Hits from HTS are then improved through structure-activity relationship (SAR) studies. These studies involve making small changes to the degrader to improve how well it breaks down the target protein, ensuring the best results for treatment.

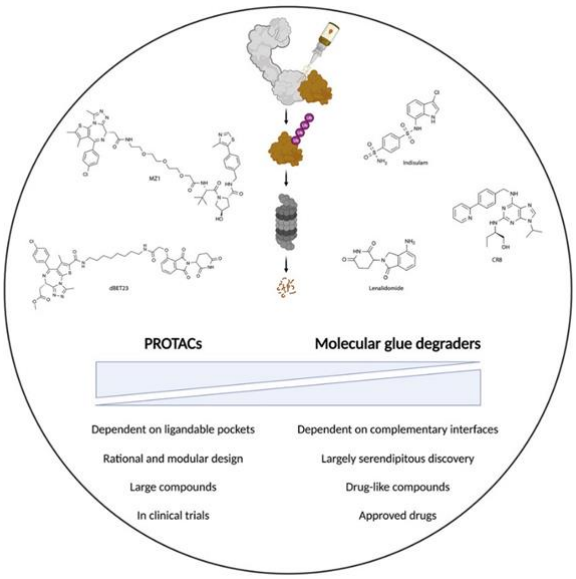

Figure 2. Illustration of how protein surface variations impact the design and functionality of molecular glue degraders [7].

5.4. Challenges and Limitations

The process of designing molecular glue degraders begins with the identification of the target protein and E3 ubiquitin ligase that puts converge and the small molecule can bind. The idea is to develop such a degrader which forms a tight and highly selective interaction with these proteins. This process begins with a lot of information about the target protein and the E3 ligase of interest. This knowledge assists scientists estimate the performance of a degrader before creating one and then manufacturing it for testing. It is also employed to seek for possible degraders. The hits from HTS are further optimized through structure activity relationship studies. These studies entail modifying some parameters within the degrader slightly so as to enhance the efficiency of degradation of the requisite protein [8].

5.5. Applications in Therapeutics

Molecular glue degraders are having medicinal chemistry research done on them for various therapeutic applications, especially in oncology. These degraders can in cancer treatment be employed to reduce oncoproteins that cause the formation and sustenance of tumors. For instance, molecular glues that target the degraders of the BET proteins have past good outcomes, especially in preclinical studies. Apart from oncology, molecular glue degraders could be utilized in neurodegenerative diseases because they can degrade proteins associated with progressive diseases[9]. For instance, degraders designed to target tau proteins could help in releasing toxic neurons' aggregates, thus slowing down or stopping progression of neurodegenerative diseases. In addition, roles in the treatment of infectious diseases owing to the destruction of vital proteins within a virus or bacteria, thereby stopping their replication, could be attributed to molecular glue degraders.

6. Applications of Molecular Glues in Disease Treatment

Nonetheless, molecular glues and their degraders have enormous therapeutic promise underpinning important challenges and limitations to be resolved for the therapeutic advancement. An issue especially important for such degraders is selectivity, as they are designed to affect only the proteins of interest while leaving all others untouched. This is comparatively easier said than done and requires a thorough understanding of cells' protein interactomes as well as a lot of planning to obtain high specificity. Another profound barrier is the ability of creating resistance: some of the existing

solutions require a long time to bring the DOI to a level where resistance cannot be developed any more.

6.1. Cancer Therapy

The cancer cells or other diseased cells might evolve to become less sensitive to molecular glue degraders and instead grow the more potent receptors for the degraders by a change of their genes or by relating to some elements of the UPS [10]. To avoid this, there is debate on different approaches including, dealing with multiple sites on a protein, or combination therapies. Molecular adhesive degraders are currently in the investigational stage for a variety of therapeutic indications, but are most strongly represented in oncology. In cancer therapy, these degraders can be employed to degrade oncoproteins which facilitate tumor genesis and survival. BET family of protein molecular glue degraders have been found to possess the potential to treat cancer because they have elicited positive outcomes in preclinical studies. In addition to oncology, molecular glue degraders are hoped to benefit from neurodegenerative diseases in which it is possible to utilize a molecular glue degrader in targeting other types of proteins involved in disease progression, for instance misfolded or aggregated proteins [11].

6.2. Neurodegenerative Diseases

Neurodegenerative diseases mainly result from aggresomes and inclusion bodies of misfolded or aggregated proteins that provoke dysfunction, apoptosis or necrosis of neurons. Molecular glues are different because they actually target and eliminate these neuropathogenic proteins. tau proteins found in the neurons of the affected part of the brain develop neurofibrillary tangles in Alzheimer's disease. These molecular glues to clear tau might help to minimize the formation of these toxic structures that are so characteristic of this ailment and thus halt the progression of dementia. This strategy is a step forward from most of the conventional therapies where the emphasis is solely on the management of symptoms and not on the protein abnormality cause. This therapeutic strategy is especially significant, as usually this disease is considered und treatable, and the current conservative strategy includes the use of only dopamine agonists and sympathomimetics.

6.3. Infectious Diseases

Erlicher et al. state that molecular glues are also under investigation as therapeutics for various diseases including those of parasitic origins. As the molecules or compounds that promote the degradation of the functional proteins in viruses or bacteria, molecular glues could offer an innovative concept for fighting infections. For example, the use of molecular glues against viral proteases or polymerases, means that these proteins will degrade rapidly and the virus will be non-infective. Molecular glues that target certain proteins in bacteria, whereby they catalyze formation of biofilms and resistance to antibiotics, would be useful in the case of treatment of bacterial infections which are antibiotic-resistant. This strategy is most useful in combating MDOs where conventional antibiotics have proven to be useless most of the time.

6.4. Personalized Medicine and Future Prospects

Thus, the prospects for the use of molecular glues are rather great, especially in the context of creating highly effective personalized medicine. Recent development in the fields of genomics and proteomics assists in conspecific molecular glue targets and gives a better approach to treating patients. If cancer subtypes exist where different subtypes are caused by distinct genetic alterations, then molecular glues can be developed that selectively bind to a patient's specific oncoprotein. Such an individual-based approach could enhance the value of treatment since it would target the molecular basis of the disease. More so, research on molecular glues as a concept is still progressive, and so, certain usage and application domains in this field have not yet been explored. The future solutions also envision the wide use of fresh technologies, including screens based on CRISPR and artificial intelligence in the development of molecular glues with higher target selectivity and efficacy.

7. Conclusion

Molecular glues and molecular glue degraders are likely a radical change in the fields of drug discovery and therapeutic targeting intercession. These small molecules are able to modulate protein-protein interactions and selectively degrade disease-causing proteins and are innovative approaches to targets that were believed to be difficult to 'drug'.

Science has developed the molecular adhesives that are very selective when attaching to proteins. To do this, they employed rational design and high-throughput screening or HTS and other related techniques. This kind of molecules are rather versatile and used in a great number of therapies. This goes a long way to show how essential they are as a novel class of therapy. In the years to come, as science advances further, especially the areas of the structural biology, computer modeling, as well as artificial intelligence, the molecular glues are likely to be further developed and their application extended.

In future it appears very promising to study how molecular adhesives operate, as well as using strategies of a targeted therapeutic approach. It is possible to employ molecular glues for other diseases and it is also possible to combine them with other technologies. Its future is looking very bright indeed for the field. Molecular glues might find a place for themselves in new treatments, and bring light to those who suffered from illness that once could not be managed.

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