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Towards the Rational Design of Monovalent Degraders: Lessons Learnt from Cyclin K Degraders

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Abstract: Monovalent degraders can enhance pre-existing surface complementarity between a target protein and a ligase to induce target degradation *via* the proteasome. For the most part, degraders have been discovered serendipitously and structure-activity relationship (SAR) studies have been limited, making it difficult to rationally design new compounds. Here we discuss how work on the SAR of cyclin K degraders demonstrates that a broad range of compounds can stabilise protein-protein interactions to induce degradation and how it lays the foundation for further monovalent degrader discovery.

Keywords: Cyclin K · Monovalent degraders · Targeted protein degradation

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1. Introduction

Over the past 20 years, targeted protein degradation (TPD) has gained popularity as a novel approach to targeted therapy. This strategy relies on the principle of induced proximity, whereby small molecules are used to bring a protein of interest into range of the cellular quality control machinery resulting in target degradation.[1] In many cases, the regulatory unit is an E3 ligase complex that can ubiquitinate the target protein, resulting in its degradation by the proteasome.[2] Monovalent degraders are small molecules that bind to the protein of interest, inducing its degradation through a variety of mechanisms, such as inducing misfolding or stabilising an interaction with an E3 ligase, without need for direct binding between the small molecule and the ligase. These compounds can also be described as 'molecular glues', an umbrella term that includes immunomodulatory imide drugs (IMiDs), compounds that directly bind to and redirect ligases to degrade various neosubstrates. IMiDs often suffer from unwanted off-target degradation, particularly of zinc finger proteins, which limits their clinical application. Monovalent degraders, on the other hand, are often able to be highly target selective, making them an attractive therapeutic modality. Furthermore, their small size when compared to bivalent degraders such as proteolysis targeting chimeras (PROTACs), enables them to possess more drug-like physicochemical properties. Even with the growing interest, most monovalent degraders have been discovered serendipitously, with little known about how to rationally design compounds with a degradative mechanism of action. Often, monovalent degraders stabilize weak, pre-existing protein-protein interactions.[3] Notable examples include compounds that stabilise interactions between IDO1 and the ligase KLHDC3, and BRD4 and ligase components DCAF11 and DCAF16 (Fig. 1).[4–6] As many proteins are naturally turned over by the ubiquitin-proteasome system, there are likely to be many sets of complementary proteins and ligases whose affinity could be enhanced by addition of small molecules to induce degradation.[7] Despite the promise of this idea, there are still only a handful of targets for which this mechanism has been exemplified, often with only one or two compounds found to induce the effect. If the structural requirements for degradation are highly specific, discovering and optimising new molecules will be challenging. Furthermore, it is unclear if there are general molecular features that can be used to induce degradation of diverse targets that could guide compound design of new degraders. In this work, we analyse the findings of structure activity relationship (SAR) studies on cyclin K degraders in order to understand how readily such compounds can be designed. We highlight that the protein surface complementarity may be the largest factor in determining degradability of a protein, and that promisingly, a broad range of chemical matter is capable of stabilising weak pre-existing protein-protein interactions.

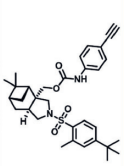
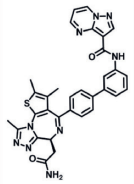
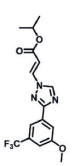
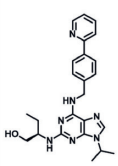
	Monovalent degraders stabilising weak pre-existing target-ligase interactions			
Target	IDO1	BRD4	XPO1	Cyclin K
Example degrader structure				
Ligase recruited	KLHDC3	DCAF11, DCAF16	ASB8	DDB1
Number of reported chemical structures	4	3	2	80+

Fig. 1. Comparison of monovalent degraders stabilising pre-existing target-ligase interactions.

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2. Discussion

The first cyclin K degrader, CR8, was identified in 2020 by Słabicki *et al.* having originally been developed as a cyclin dependent kinase (CDK) inhibitor.[8] Their work demonstrates that CR8 binds to the CDK12 active site and stabilises complex formation with DNA damage-binding protein 1 (DDB1), an adaptor protein of the CUL4 E3 ligase complex, resulting in degradation of CDK12's partner protein, cyclin K, as well as CDK12 itself. This mechanism of degradation is unique, as E3 ligases usually engage a target through a substrate receptor such as cereblon.[9] Here, the need for a substrate receptor is bypassed, with CDK12 acting as a pseudo-substrate receptor and placing its partner protein in proximity to be ubiquitinated and subsequently degraded. CDK12 and DDB1 have an endogenous affinity of ~ 50μM that does not result in cyclin K degradation, but which is stabilised ~1,000 fold in the presence of CR8. Hence this compound is stabilising a weak pre-existing interaction between a protein and a ligase. The solvent-exposed 2-pyridyl group was shown to be essential for strengthening this interaction, filling a pseudo-cleft formed between CDK12 and the DDB1 β-propeller domain. Shortly after, Mayor-Ruiz *et al*. reported further cyclin K degraders based on a new scaffold but similarly featuring solvent-exposed aromatic groups.[10] Previously, monovalent degraders stabilising basal protein-protein interactions were rare in the literature and often remained as isolated examples. Since their initial discovery, there have been over 10 publications denoting novel cyclin K degraders, making it one of the most well studied targets in this context. With such a large dataset in hand, and having conducted our own previously reported SAR studies,[11] we herein analyse the literature on cyclin K degraders in order to extract key findings that can guide further monovalent degrader discoveries.

2.1 *Structural Features of Cyclin K Degraders*

Many chemically diverse compounds have been shown to have cyclin K degradation activity (Fig. 2).[12–15] When analysing the dataset, the compounds fall across a broad range of molecular weights and cLogP values without a clear trend towards particular molecular properties. Encouragingly, this means that many of the degraders satisfy Lipinski's rule of five and possess drug-like properties.[16] Looking specifically at the solvent-exposed group, also termed degradation motif, we find that there are some loose trends in features inducing degradation. Work by Kozicka *et al.* produced 28 crystal structures exemplifying the interaction between CDK12, DDB1 and various degraders.[17] These structures highlight the importance of forming a π-cation interaction between the degradation motif and DDB1 Arg928 residue. As a result, the solvent-exposed group was thought to be limited to aromatic moieties. However, subsequent studies, including our own, have shown that non-aromatic groups are capable of stabilising this interaction, potentially by forming a weak hydrogen bond to Arg928 instead (Fig. 3). However, the phenyl group directly

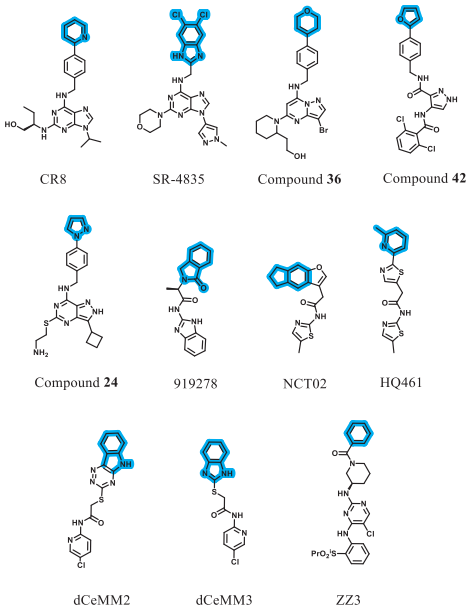

Fig. 2. Structures of cyclin K degraders published in the literature, with the solvent-exposed group, or 'degradation motif', highlighted in blue.

below the degradation motif may compensate for the lack of solvent-exposed aromaticity. Smaller groups, such as 5-membered rings, were also used to successfully induce degradation despite not optimally filling the cleft. This establishes that the solvent-exposed group does not have to be perfectly optimised for the pocket, likely due to the surface compatibility of CDK12 and DDB1 priming the interface. Groups which were predicted by docking experiments to extend beyond the confines of the pseudo-pocket were not capable of triggering cyclin K degradation. Therefore, the ideal size and electronic properties of the solvent-exposed group are expected to be determined by the protein-protein interface, and the trends established for cyclin K degraders may not be transferrable to new targets. This further establishes the importance of understanding the mechanism of degradation for new monovalent degrader projects. If the ligase responsible for degrading a target can be identified, this could facilitate structure-based drug design using experimental or predicted crystal structures to identify residues to target for interactions.

In the literature, monovalent degraders for other targets tend to feature more lipophilic solvent-exposed groups. This is well exemplified for BCL6 degraders developed within our own group and others, which feature a solvent-exposed dimethylpiperidine and lose activity when swapped for a more hydrophilic dimethylmorpholine.[18,19] Other types of degraders – such as hydrophobic tag compounds, selective estrogen receptor degraders (SERDs) and selective androgen receptor degraders (SARDs) have also

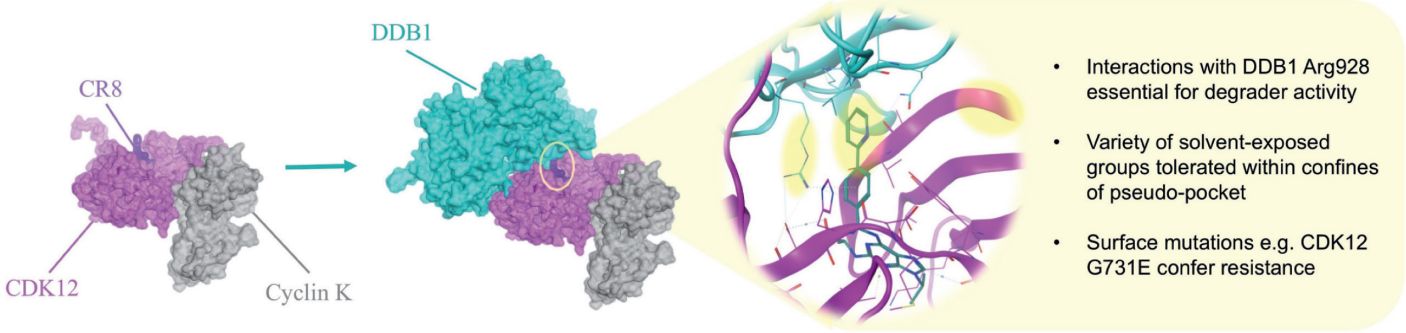

Fig. 3. Surfaces of CDK12, cyclin K and CR8 (left, PDB: 6TD3) showing large surface overlap between DDB1 and CDK12 strengthened by CR8. Key interactions between the two proteins are highlighted (right).

notably featured lipophilic degradation motifs, suggesting some shared features between mechanisms.[20] In the case of cyclin K degraders, there has also been a trend towards more lipophilic degradation motifs, with both our work and Kozicka's demonstrating that addition of polar groups, such as hydroxyls, to the aromatic degradation moiety reduced or abrogated cyclin K depletion. Thus, there may be some molecular features, such as lipophilic solvent-exposed groups, that are more likely to trigger target degradation. This may be related to the tendency for lipophilic groups to be buried rather than solvent exposed. Exposed hydrophobicity can mimic protein misfolding, cause conformational shifts or even result in engagement of other proteins to subsequently rebury the hydrophobic groups.[21] These learnings provide a good starting point for compound design to increase the probability of discovering new degraders. With direct-to-biology approaches enabling the generation and screening of large compound libraries, we will likely see more inhibitors with additional solvent-exposed groups demonstrating degradation activity.[22]

2.2 *Decoupling Inhibition and Degradation*

When looking to optimize cyclin K degraders, one approach has been to increase the CDK12 binding potency. In our work, we attempted this through moving to the more potent pan-CDK inhibitor dinaciclib. Incorporating the solvent-exposed 2-pyridyl group to this scaffold resulted in a compound that was 100-fold more potent at inhibiting CDK12 than CR8 (K_d value of 4nM compared to 400nM) but that only led to a modest 4-fold improvement in cyclin K degradation potency (DC_{50} of 10nM compared to 46nM). This implies that CDK12 binding is not the only determinant of degradation potency. This was further exemplified by Kozicka *et al.* who demonstrated that compounds with minimal CDK12 binding affinity, such as HQ461 and dCeMM2 (IC_{50} >10 μM by LanthaScreen), could still stabilise the CDK12-DDB1 complex formation with EC_{50} values of 43nM and 83nM respectively.[17] Thus, it may be possible to tune out the unwanted inhibition of the other CDKs, which have been linked to dose-limiting toxicities, while maintaining degradation of cyclin K.[23] This further suggests that the surface complementarity between CDK12 and cyclin K is a key driver of this degradation event, rather than the compound itself, with minimal correlation between binding and degradation (Fig. 4). Thus, when designing new monovalent degraders, choosing targets with known ligase interactions may be more important than the availability of potent target binders. Additionally, if the binder has low inhibitory activity, this renders deconvolution of the effects of inhibition *vs* degradation less challenging.

2.3 *Invoking Other Mechanisms of Degradation*

Despite the large quantity and structural diversity of cyclin K degraders, only one mechanism of degradation has been discovered. This may suggest that for a given protein, only specific degradation mechanisms will be accessible, perhaps pre-determined by the protein structure. For example, in our work we appended an adamantane group to the CR8 scaffold to exploit the hydrophobic tag mechanism that has been used to degrade targets such as Her3 and EZH2.[24,25] Although this has proven successful for other targets, this motif did not induce cyclin K degradation; however, no further analogues of this nature were explored and the compound was not tested for direct CDK12/13 degradation. Further work is required to explore if other mechanisms could be invoked. It has also been demonstrated that the mechanism used to degrade cyclin K may not be applicable to other targets. For instance, CR8 is also able to bind to CDK9 with similar affinity, however it cannot induce complexation of this protein with DDB1 or degradation of its partner protein, cyclin T.[8] This is somewhat surprising as CDK9 and CDK12 are closely related, sharing 45.5% sequence homology. Lv *et al*. demonstrated that mutating the CDK12 Glycine 731 residue, located at the DDB1 interface, to glutamic acid or arginine was sufficient to abrogate cyclin K degradation, suggesting a high sensitivity to differences in surface residues, and strengthening the idea that degradation mechanisms may be highly specific to the target.[26]

3. Conclusions and Outlook

The cyclin K-CDK12-DDB1 system represents one of the most well studied degrader systems, providing unique insights into the molecular features required to induce degradation. Changes to both the scaffold and the solvent-exposed group are well tolerated, showing potential for optimisation to improve potency or PK properties. The ability to dial down CDK inhibition whilst retaining potent cyclin K degradation may be advantageous as it limits the effects of toxicity associated with inhibition of other CDKs. This also demonstrates that potent inhibitor scaffolds are not necessarily required to induce degradation. Promisingly, it has been shown that the interaction interface between the target and ligase does not have to be perfectly optimized in order to gain degradation activity. Thus, despite difficulties in rationally designing degraders, with a large compound library, it may still be possible to identify such compounds. Currently, it is still unclear how large a compound library would be required to find a degrader for a new target, and it is likely that this varies depending on the target. Shaum *et al.* recently designed a 3,163-compound library searching for ENL degraders and found one hit, suggesting that libraries of thousands of compounds may be required.[27] When using a

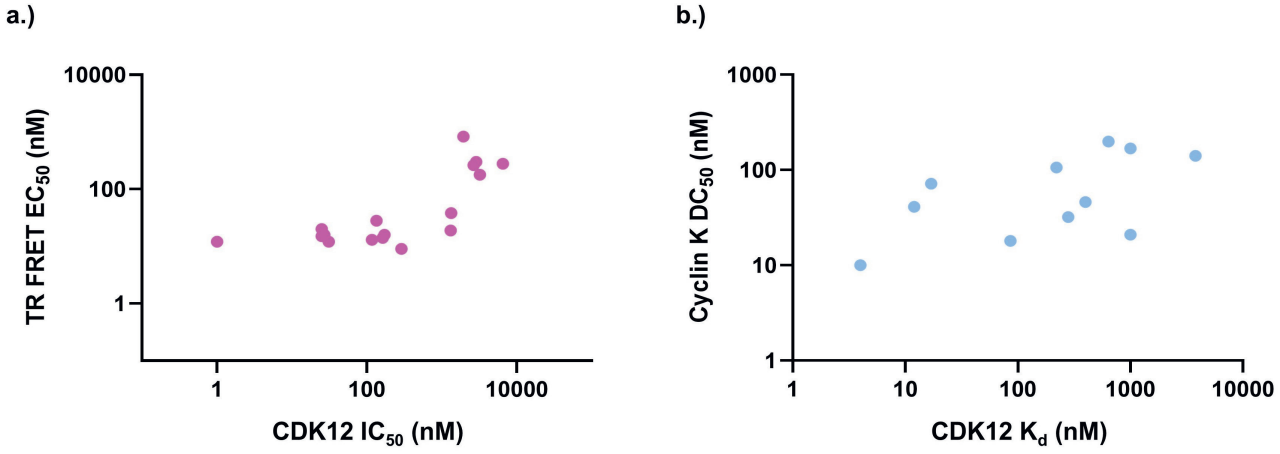

Fig. 4. a.) Comparison of CDK12 IC_{50} (Lanthascreen) against EC_{50} for the cyclin K/CDK12/DDB1 complex (TR-FRET). Data taken from Kozicka *et al*.[17] b.) Comparison of CDK12 Kd (KINOME*scan*) against cyclin K DC_{50} (quantified from western blot). Data from Thomas *et al.*[11]

comparable size library, they also found a handful of hits against BRD4, of which two were reconfirmed by resynthesis. Similarly, Parker *et al*. screened a library of undisclosed size with a hit rate of <1% for BRD4 degraders.[28]

The lack of structural specificity required to convert an inhibitor into a cyclin K degrader suggests that the innate surface complementarity between CDK12 and DDB1 is the largest determinant of the ability to degrade cyclin K, which is further confirmed by the inability of other closely related CDKs to engage this degradation mechanism. Choosing a target that is primed for degradation may be an important factor to consider when searching for new degraders, as the protein-protein interaction surface is far larger than the area occupied by the ligand. It has been demonstrated that the interaction between DDB1 and CDK12 is composed of 79% protein-protein interface, with a much lower proportion of contacts between the protein and CR8.[29] This contrasts with ligase-binding molecular glues such as pomalidomide and thalidomide, where the protein-protein interface represents only 52 - 68% of the total interaction surface. As the degrader composes a greater proportion of the interface, the resulting SAR is often steeper for these compounds, further increasing the difficulty in their optimisation.[29] Consequently, the next hurdle may be devising screening methods, which could be experimental or virtual, to identify proteins and ligases with basal affinity that can be exploited. As there are over 600 E3 ligases, each with the potential to target around 20,000 proteins, unpicking ligase-target relationships remains an unsolved problem.[30] Experimentally, groups have tried to identify cullin RING ligase (CRL) targets by looking at the proteins stabilised by treatment with pan-CRL inhibitor MLN4924, or by looking at proteins stabilised by CRISPR knockouts of different ligase components.[31] However, throughput is still limited, and redundancy in the ligase system may lead to false negatives.

With the growing repertoire of computational tools, we have an increased ability to model protein-protein interactions to look for surface complementarity virtually. For example, AlphaFold-Multimer, is a recent platform enabling the prediction of 3D protein complexes. Despite this, it is still computationally demanding to use these platforms to screen for protein-ligase interactions. Suiter *et al.* predicted that modelling ~600 human E3 ligases against the 20,000 human proteins using AlphaFold-Multimer would require approximately 1,369 years of graphics processing unit (GPU) time.[30] Cyclin K degraders also teach us that we should not limit the scope to E3 ligase substrate receptors alone, as in this case the ligase adaptor protein DDB1 can also be hijacked. Another obstacle is the limited accuracy of AlphaFold-Multimer and other protein-protein interaction models. The creators of AlphaFold-Multimer reported that it was able to predict heteromeric interfaces in 70% of cases, yet it could only produce high accuracy predictions in 26% of cases.[32] Furthermore, additional work is required to understand if these platforms are capable of accurately detecting weak, transient interactions between proteins and ligases which could be stabilised by a degrader. Currently, *in silico* screening strategies may be challenging to implement but with the rapid improvements in computing power and continual development of new platforms, it is likely that virtual screening tools will become increasingly relevant in degrader discovery.

Success in using the CDK12-CR8-DDB1 crystal structure to predict tolerated solvent-exposed groups suggests that the SAR may be specific to this interface and thus these results might not be transferrable to new targets. For new targets, protein-ligase modelling could be used to generate ideas of groups capable of forming interactions between the two. Whilst we are still not at the stage of rational compound design, incorporating solvent-exposed groups to target binders has proven to be a promising technique for discovering new degraders, with work by Nomura *et al*. demonstrating that solvent-exposed covalent warheads can also be utilized to recruit E3 ligases and trigger target degradation.[33] Through a combination of computational tools, large compound libraries, and high throughput screening approaches, there are sure to be further monovalent degrader discoveries in the near future.

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