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PROTACS – A New Generation of Poorly Soluble and Permeable Molecules for Targeting Proteins

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Introduction

Proteolysis Targeting Chimeras (PROTACs) discovered over 20 years ago, have been classified as molecules beyond rule of five (bRoF), meaning they do not follow the classic Lipinski's rule of five for solubility and bioavailability [1]. In the recent past, they have gained considerable attention as the class of novel molecules for their abilities to selectively target and degrade disease-causing proteins, and to overcome drug resistance [2]. As a matter of fact, the small molecules have been known for targeting only 10–15% of human proteome but other majority of disease-relevant proteins are beyond the reach of certain therapeutic molecules [3]. The invention of new approaches such as Targeted Protein Degradation (TPD), represents a great opportunity in drug discovery to identify potential drug candidates. TPD aims at inducing proteolytic elimination of target protein by programmed quality control machinery inside cells and being involved in a range of ailments including neurodegenerative disorders, immunotherapy, oncology, infectious diseases, multi-drug resistance diseases, among others, as shown in Figure 1 [4].

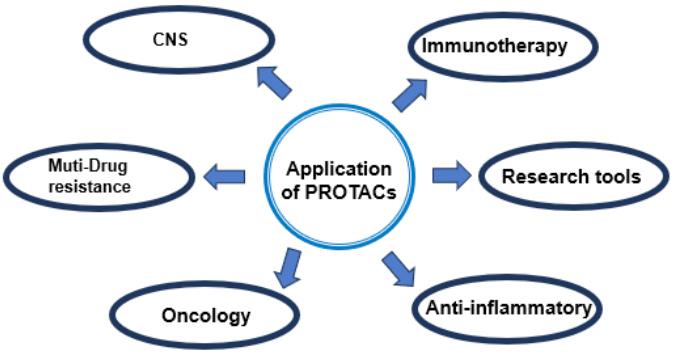

Figure 1: PROTAC applications at the forefront of several diseases.

PROTAC is a bifunctional molecule comprised of a ligand which at one end binds to protein of interest (POI) or target protein, a ligand which at other end recruits and binds to an E3 ubiquitin ligase, and a linker at the center that connects the two functional domains, as shown in Figure 2.

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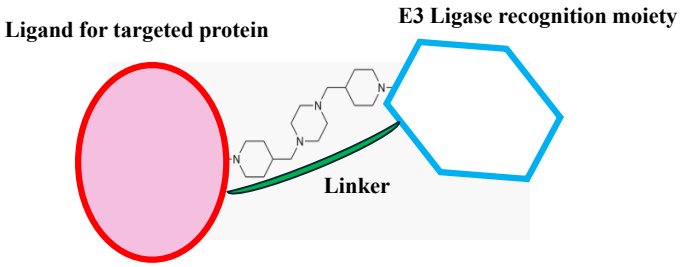

Figure 2: Structure of a typical bifunctional PROTAC molecule.

PROTAC's ligases are based on a Cereblon (CRBN) or a Von Hippel-Lindau (VHL). In recent years, a few of CRBN based PROTACs have entered clinical trials [5]. Table 1 lists a range of PROTAC molecules undergoing in the advanced stages of clinical development. There are no approved marketed drugs. It is evident that these investigational PROTAC molecules in clinical development target Protein of Interest (POI) like Androgen Receptor (AR), Estrogen Receptor (ER), Bruton's Tyrosine Kinase (BTK), and interleukin-1 receptor-associated kinase 4 (IRAK4) associated with ailments like solid tumors, hematological malignancies, autoimmune diseases among other diseased conditions [6].

Table 1: List of selected PROTACS in advanced stages of clinical developments.

Company	Drug Candidate	Target	Indication	Clinical Phase
Arvinas/Pfizer	Vepdegestran (ARV-471)	ER	ER + /HER2- breast cancer	Phase III
BMS	CC-94676 (BMS-986365)	AR	mCRPC	Phase III
BeiGene	BGB-16673	BTK	R/R B-cell malignancies	Phase III
Arvinas	ARV-110	AR	mCRPC	Phase II
Arvinas/Novartis	ARV-766	AR	mCRPC	Phase II
BMS	BMS-986458	KRAS G12D	Lymphoma	Phase II
C4 Therapeutics	CFT1946	BRAF (V600E)	ST	Phase II
Cullgen	CG001419	NTRK	ST	Phase II
BeiGene	BGB-16673	BTK	R/R B-cell malignancies	Phase II
Arvinas	ARV-110	AR	mCRPC	Phase II
Arvinas/Novartis	ARV-766	AR	mCRPC	Phase II
BMS	BMS-986458	KRAS G12D	Lymphoma	Phase II
C4 Therapeutics	CFT1946	BRAF (V600E)	ST	Phase II
Cullgen	CG001419	NTRK	ST	Phase II
Jiangsu HengRui	HRS-5041	ER	MCRPC	Phase II
Jiangsu HengRui	HRS-1358	AR	Breast cancer	Phase II
Kintor Pharma	GT-20029	AR	AGA	Phase II
Kymera	KT-474 (SAR444656)	IRAK4	HS and AD	Phase II
Prelude Therapeutics	PRT3789	BTK	NSCLC, ST	Phase II
Ranok Therapeutics	RNK-05047	BRD4	Advanced ST including DLBCL	Phase II

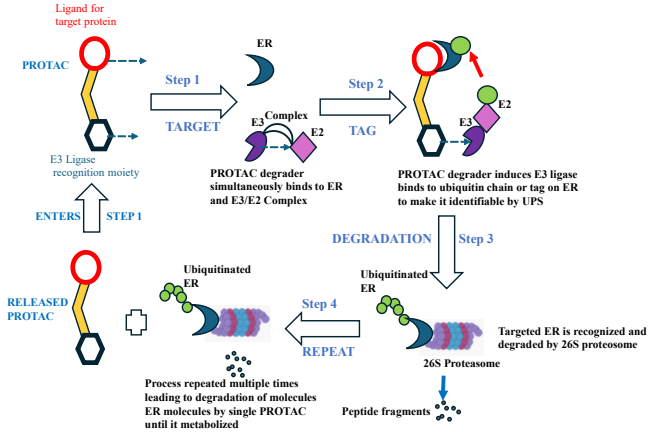

Figure 3: Mechanism of PROTAC on Estrogen Receptor (ER) protein degradation.

PROTAC - Mechanism of action

The chimeric molecule facilitates the formation of a POI–PROTAC–E3 ternary complex, as shown in Figure 3. This structure enables PROTACs to tag with Ubiquitin-Proteasome System (UPS) and degrade target proteins, leading to a promising new approach to drug discovery. In short, PROTAC on initiation in Step 1 targets and forms a ternary complex as POI–PROTAC–E3 ligase (Step 2) and enables Ubiquitin (Ub) transfer of lysine residues to POI. The polyubiquitinated POI is subsequently recognized and degraded by 26S proteasome (Step 3) [7]. Following protein degradation to peptide fragments, PROTAC is recycled back to engage with next POI (Step 4), suggesting it acts as a catalyst to continue with complexation, target degradation and elimination as the cycle continues in Step 1 [8].

Delivery and oral bioavailability of PROTACS

As more molecules being discovered are poorly soluble, PROTACs remain the most challenging new generation of highly insoluble, impermeable large molecules, qualified as beyond Lipinski's Rule of Five (Ro5) [9]. Thus, finding the appropriate technologies for bringing these innovative molecules to clinic poses solubility and bioavailability challenges. PROTACs are unique, complex and large (MW > 800 Da) than traditional small Molecules (MW < 500 Da). So, their permeation through membrane barriers is highly difficult, and often impossible. Those challenges offer an opportunity to explore the most innovative formulation strategies to enhance their solubility, stability, permeability, and hence the cellular uptake.

Two approaches have been used to overcome those challenges with cell permeability. First, structural optimization of

PROTACs to boost the absorption and bioavailability, and second, use of advanced delivery systems for encapsulation, permeation and efficient cellular uptake. Those delivery vehicles including exosomes, liposomes, lipid nanoparticles, polymeric nanoparticles, amorphous solid dispersions, antibodies, aptamers among others have been used and some technologies will be described in a greater detail [10].

Structural based delivery of PROTACS

Structural flexibility and rigidity of a PROTAC's linker are critical for (i) efficient complexing with POI and E3 ligase on both ends of the molecule, and (ii) enhancing the ubiquitination tagging and subsequent degradation of the POI by proteosome to peptide fragments [11]. These structural modifications of a linker are essential for receptor recognition, cell permeability and desired efficacy via intracellular internalization mechanism initiated through CD36 binding at the membrane outer surface. A fatty acid-based transporter, CD36, has been identified as a membrane receptor for PROTACs for their intracellular uptake [12].

The efforts continue to identify and exploit the structural variations of the linkers to yield stronger bonding with receptors and greater cellular uptake by specific receptor-mediated endocytosis pathway [13]. Flexible linkers, for example, include alkyl chains and Polyethylene Glycol (PEG) which yield more conformational freedom to potentially facilitate and engage with target protein POI and the E3 ligase. In addition, PEG linker can also enhance solubility and permeability of PROTACs. On the other hand, rigid linkers such as alkynes, aromatic or heterocyclic rings like piperazine and triazole) yield defined conformation with stable ternary complex with POI and E3 ligase as opposed to flexible linkers. In addition, these linkers also help improve metabolic stability and pharmacokinetic properties. Table 2 lists a range of rigid and flexible linkers and their targets. In a recent study, Jimenez et al have shown that methyl moiety at the linker can help enhance the oral bioavailability of PROTAC molecules. Using eleven structurally related von Hippel–Lindau (VHL) based PROTAC molecules bearing a methyl group on the linker, it was determined that efflux ratio (ER) was a better predictor of oral bioavailability (%F) than CaCo2 cell owing to its chameleonic folding, influencing ER and F% [14].

Table 2: Shows a list of a few rigid and flexible linkers [13].

Linker type and Composition	Target protein (POI)	E3 Ligase	*DC_{50} (nm)	*D_{max} (%)
Rigid - Piperazine based	BTK	Cereblon	5	>90
Rigid- Cycloalkane based	BRD4	VHL	0.9	>90
Rigid - Triazole based	FLT3	Cereblon	10	>90
Flexible - PEG based	BTK	Cereblon	1-40	>85
Flexible - PEG based	BRD4	VHL	1.8	98
Flexible – Alkyl/PEG based	FLT3	Cereblon	3-292	76-96

*DC_{50} – half maximal degradation concentration *D_{max} - maximum protein degradation level

Nanoparticle based delivery of PROTAC

The drug delivery systems are used to improve PROTAC's solubility and increase exposure by prolonging systemic circulation while protecting from enzymatic degradation, and to achieve the desired bioavailability. The particle size, drug loading, encapsulation efficiency, surface composition and charge, zeta potential, excipient compositions, pH among other factors contribute to stability of nanoparticles. The nano-assemblies like polymeric micellar nanoparticles, mixed micelles, emulsions, nano-emulsions, liposomes, Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and exosomes are all important carriers for effective delivery of PROTACs. Let's take a closer look into a few of them.

Polymeric nanoparticle based delivery systems

Polymeric nanoparticles have been used in delivery of a range of therapeutics across all modalities. Self-assembled as aggregates in aqueous solutions, they act as solubilizers and stable carriers as micelles, nanospheres, nanogels, or drug conjugates for transporting drugs through membranes, yielding enhanced cellular uptake and bioavailability [15]. Those carriers or excipients are amphiphilic in nature, meaning they possess both hydrophilic and lipophilic moieties in the same molecule. Examples include poloxamers, polyethylene glycol, polycaprolactone, polyethylene oxide, poly (lactide-co-glycolic acid) PLGA among others. PROTACs for their unique structural features having both ends different, one end receptive to ER binding and other end receptive to E3 ligase binding, have shown promising preclinical outcomes in polymeric nanoparticles [16]. In a study, ARV-825 upon encapsulation in interior core of polymeric nanoparticles comprised of PEG-b-PLGA (2 kD:11.5kD) showed high drug efficiency (ca. 99%) and smaller particle size (ca. 89 nm) and with prolonged half-life [17]. In vivo data suggests higher cytotoxicity, higher pancreatic tumor suppression and killing via apoptosis by upregulating caspase 3 and downregulating of BRD4 and c-Myc proteins. Like PLGA, other co-polymers like mPEG-b-poly-dl-lactic acid (mPEG-PDDLA) self-assembled as polymeric micelles and used for targeting glioma through Blood Brain Barrier (BBB) permeation. For instance, mPEG-PDLLA micelles encapsulated with a novel PROTAC ARV-825 molecule with uniform particle size of 26 nm, showed over 96 h of controlled release, and led to apoptosis through BRD4 degradation as compared to free ARV 825. Other polymeric micelles have been used for targeted delivery of drugs for treating drug resistance tumors. Cimas et al. used antibody conjugated NPs [18]. For example, PROTAC MZ1 was loaded in stable polymeric micelles (ca. 114 nm in size) comprised of Polylactic Acid (PLA) and Polyethyleneimine (PIE) and prepared by nanoprecipitation, wherein the nanoparticle surface was conjugated via carbodiimide chemistry with transtuzumab, an antibody targeting Herceptin-2 (HER-2) receptor for breast cancer. In vitro data showed an extended release over 12 h and enhanced cytotoxic effect with increase cell death via apoptosis against SKBR2 and BT474 cancer lines as opposed to free drug. Gao et al. have demonstrated that micellar POLY-PROTAC derived from click chemistry via disulfide linkage of drug molecule with the backbone of an amphiphilic di-block copolymer, synergistically induce cell death by apoptosis upon combination with Photodynamic Therapy (PDT) in mouse xenografted with MDA-MB-231 breast cancer [19]. Ma et al investigated the PEG conjugating Folic Acid (FA) (PEG-FA) coupled with EGFR-targeting PROTAC via a disulfide bond against xenograft tumor in mice and found that polymeric micelles enhanced tumor-specific targeting proteolysis by BRD4 degradation [20]. Taken together, the polymeric micelles outperformed free PROTAC by demonstrating an excellent in vivo anti-tumor efficacy, and significantly improving tumor targeting in xenograft mice. These results in due to longer circulation and enhanced tumor penetration, lead to higher BRD4 degradation activities causing cell death via apoptosis and hence enhanced survival rate.

Lipid nanoparticles - Liposomes

Liposomes are comprised of inner hydrophilic and out hydrophobic regions where the drugs molecule can be encapsulated depending upon the structure of drugs. For large molecules like PROTACs (MW >800 Da), the hydrophilic moieties can reside in inner aqueous core, and the hydrophobic moieties can interact with the fatty acid within the bilayer. Thus, encapsulation of PROTAC within the liposomes enhances stability and protects it from degradation by enzymes, thus minimizing the non-specific interactions with biological systems and reducing adverse effects [21]. Ku et al. demonstrated that PROTAC molecules GNE-01 and GNE-02 formulated in cyclodextrin-liposomes versus in solutions, showed 80-fold and 23-fold enhancements in efficacy, respectively [22]. In another example, ARV 825 PROTAC co-formulated with docetaxel in liposomes showed enhanced antitumor activities through dual mechanisms of protein degradation of BRD4 and chemotherapy with tumor suppression by 57.4% [23]. Other examples like recombinant bioPROTAC demonstrate the potential complexing with cationic and ionizable liposomes to effectively encapsulate PROTACs like ARV 825 in lipid bilayer to help maximize anticancer efficacy while reducing side effects through targeted delivery of POI [24]. The smaller particle size (ca. 105 nm) and electrostatic charge (ca. +26 mV) on liposomes enable selective accumulation in tumors via Enhanced Permeation and Retention (EPR) mechanism, resulting in potent inhibition of melanoma cell lines.

In a separate investigation, Vartak et al. used Precirol Ato5, Captex 300 and decanoic acid to formulate ARV-825, a PROTAC loaded in PEGylated Nanostructure Lipid Carriers (NLC) [25]. The resulting NLC with particle size of 56 nm and with high drug loading and stability, showed an effective lung tumor inhibition and cell death or apoptosis via BRD4 degradation and c-Myc suppression. Chen et al. have demonstrated that a synthetic lipid 80-O14B encapsulating PROTAC ARV-771 pre-fused with POI and E3 ligase receptors in LNPs at 61% significantly improved the cellular uptake and permeability with 90% reduction of BRD4 level within 24 hours with respect to free PROTAC [21].

Self-emulsifying drug delivery systems (SEDDS)

SEDDS have been used in formulation of BCS II and IV molecules and have been approved in several approved drugs [26]. Like other approved molecules, studies suggest that PROTAC is self-emulsified in an oil/surfactant based emulsifying system. Comprised of oils, surfactants and cosurfactants, these assemblies can encapsulate and help protect PROTAC in the interior hydrophobic core by self-emulsifying in the aqueous solutions to tiny oil droplets (o/w micro/nano-emulsions), resulting larger surface area for enhancing the solubility and bioavailability of molecules. The compositions of the ingredients in SMEDDS/SNEDDS including oils, surfactants and co-surfactants are critical for producing smaller particles with large surface area to enhance stability and oral bioavailability by protecting in gastrointestinal tract [27]. In a study, ARV-825 encapsulated in SNEDDS comprised of dimethyl acetamide, medium chain triglycerides, and polyoxyl 35 castor oil, upon self-emulsification to particle size of 45 nm and zeta potential of -3.78 mV in aq. solution, showed a significant increase in solubility; 66-fold in fed state and 300-fold in fasted state simulated gastric fluid while maintaining supersaturation without any precipitation. In vivo data suggests that ARV-825 in SNEDDS is highly effective against BRAF inhibitor resistance melanoma cell. Further evaluation of ARV-825 in SNEDDS suggests that it acts as a substrate for CYP3A4 but not for Pgp efflux pump [28]. Saraswat et al. evaluated ARV-825 in combo with vermurafenib, a BRAF inhibitor in NANOVB, a self-emulsifying lipid-based system that significantly improved the solubility and oral bioavailability of drugs. In vivo data in mice showed a significant tumor inhibition resulting an increased in survival rate, likely caused by reducing the expression of BRD4 and Ki -67 proteins [29].

Solid dispersion-based delivery systems

Amorphous Solid Dispersions (ASD) remain the most versatile technology for improving the solubility and oral bioavailability of challenging molecules stemming from high melting and high logP [30]. Requiring a compatible polymer with drug in organic solvent(s), ASD can be scaled up on a range of spry dryers available commercially. Several drugs have been approved as ASDs [31]. In spite of a widely used SD technology, not all molecules are compatible due to their inherent higher crystallinity and melting, and poor solubility, therefore, technologies other than ASD have also been used. Polymers like Soluplus®, Copovidone, HPMCAS, Povidone, Poloxamers, Eudragit, high molecular polyethylene glycols among others are used as polymeric carriers. With the invention of bR05 molecules like PROTACs in recent years, some of these polymers have also been used in solid dispersions with the aims to increase solubility, permeability and bioavailability of those molecules. Screen et al. evaluated a PROTAC, identified as AZ1-4, in HPMCAS and Copovidone in ASD powder. In vitro dissolution data with 20%-40% drug loading of AZ1-4 I in HPMCAS and Copovidone showed over several fold increase in solubility as compared with pure API [32]. The DSC data suggests that glass transition temperature (T_g) increased with increasing drug concentrations in the polymers. In a recent study, Postges et al. evaluated ARCC-4, an Androgen Receptor (AR) based PROTAC at 10% and 20% drug loading in HPMCAS and Eudragit® L100-55 enteric polymers and observed a pronounced enhancement in supersaturation without precipitation under non-sink dissolution conditions [33]. In contrast, the mesoporous silica failed to demonstrate the enhanced supersaturation of ARCC-4 despite an increase in solubility, underscoring the importance of polymer-drug entanglement and interactions in stabilizing the drug in supersaturation. In a separate study, Hoffman et al. evaluated MS4078, a novel PROTAC molecule and observed a significant enhancement in supersaturation without precipitation at 10% drug loading in ASDs comprised of Soluplus® and Eudragit® EPO, prepared by spray drying [34]. The data suggests that supersaturation of MS4078 in ASD increased over 70-fold with respect to an amorphous API. This increase in solubility is due to inherent wettability of Soluplus® which improved dissolution kinetics. Polyvinyl alcohol-based polymer was also evaluated for improving solubility and stability of a crystalline ARV-10 and an amorphous SelDeg51 polypeptide at 30% loading in solid dispersions. In vitro data showed an improvement in supersaturation solubility of both molecules. The stability of SelDeg51 remains unchanged following spray drying as confirmed by activity assay of the polypeptide [35]. Zhang et al. also evaluated a PROTAC at 5%, 10%, 20% and 40% drug loading in HPMCAS, Soluplus® and Eudragit®, prepared by solvent evaporation. Increasing concentration of drug to 40% led to poor dissolution but adding sodium lauryl sulfate improved the dissolution [36].

Conclusion and future perspective

PROTACs in the recent years have generated a great deal of interest due, in part, to unique bifunctional structures capable of identifying and binding the target proteins at one end and ligase E3 at opposite end. The linker at the center could play an

important role in allowing enough length and flexibility to reach out the accessibility of the two opposite ends to proteins and enzymes. Thus, finding the optimal structures of PROTACs has been subject to a continued interest. Furthermore, the delivery of those large molecules (MW>800 Da) apparently has been even more challenging due to their poor solubility and permeability, and thus efforts continue to increase permeation and cellular uptake to enhance the oral bioavailability as apparent from the recent clinical studies of several PROTACs [13] and yet the approval of those molecules is still further on the horizon.

This review article sheds an understanding about different technologies for formulation and delivery of those molecules. Among those include polymeric nanoparticles, Self-Emulsifying Drug Delivery Systems (SEDDS), lipid nanoparticles and liposomes, and amorphous solid dispersions among others all showing a phenomenal progress on PROTACs over the years, but the hurdle continues to achieve the desired outcomes for targeting specific proteins and finding the appropriate drugs for treatment.

Ascendia's enabling platforms offer opportunities to tackle not only the small and large molecules but also the PROTACS. Its AmorSol®, an amorphous based technology can help design the smarter and better formulation for ASDs yielding the desired outcomes for enhancing oral bioavailability. Likewise, for oral liquids, its EmulSol® technology might be extended to formulate and deliver the appropriate solution in SEDDS/SNEDDS, yielding enhanced oral bioavailability by selection of Generally Accepted as Safe (GRAS) excipients, polymers and solubilizers. LipidSol®, for example, for its unique lipid assemblies, LNPs and liposomes could be extended for lipophilic PROTACs bearing both hydrophilic and hydrophobic entities. PROTACs co-delivered with chemotherapeutic agents underscores the importance of combination therapy for drug resistance cancers by accelerating synergistic anti-tumor effects while reducing drug toxicity. With its previous experiences with PROTACs coupled with the expertise in enabling technologies and state-of-the-art cGMP aseptic and non-aseptic ISO cleanrooms, Ascendia can help expedite the formulations undergoing early and late phases of clinical development.

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