Is the PROTAC Party Just Getting Started?

A little over five years ago, the biotech world became intrigued with the promise of Antibody–Drug Conjugates (ADCs). Investors poured resources into CDMOs and production capabilities expanded. With the apparent success of ADCs, we now see the next 'hot area' for conjugates as part of the rapidly emerging modality targeting "undruggable" proteins for degradation. PROteolysis-TArgeting Chimaeras (PROTACs) are today to innovators and CDMOs what ADCs were a few years ago, as the next big modality innovation.

Most significantly, it's the science that has advanced. The realisation of key milestones in discovery and development has inspired investors to reconsider their commercial assessments and we are currently entering a new chapter for targeted protein degradation.

For example, the significant technical hurdle of achieving PROTAC pharmacodynamic activity in the central nervous system through oral administration has now been reported. Beyond additional orally bioavailable PROTACs entering the clinic, we note the first positive pivotal Phase III trial and the first new drug applications being filed. What was once speculative is consolidating into an expanding area of opportunity and potentially sometime next year, we will see the first PROTAC FDA approval. In fact, there are now around 90 PROTACs in various phases of clinical trials, with Arvinas alone having six advanced programmes spanning oncology, neurology and beyond, and the field is rapidly expanding in therapeutic indications.

Just this September, Arvinas out-licensed its commercialisation rights for Vepdegestrant immediately post submission of its NDA to the FDA. This has the potential to prime the wider industry for far more late-stage assets and potential deal-making.

We are further encouraged by reports of scientific innovations in linker chemistry/composition, ligase discovery/applications, computational models forecasting ternary complex stability and proteomics-based selectivity profiling, all leading to enhanced PROTAC characteristics such as the aforementioned oral bioavailability and CNS penetration. These combine with refined clinical and regulatory strategies to augment commercial viability.

So, what are PROteolysis-TArgeting Chimaeras (PROTACs) and why might they be a transformative advancement in therapeutic development? At the core of this modality is a fundamental change in the nature of functional intervention. While traditional therapeutics modify the activity of a protein (e.g. enzyme inhibition, receptor agonism or antagonism), PROTACs selectively induce the degradation of the target protein through exploitation of the cell's own ubiquitin-proteasome system. This approach requires the identification of a ligand with sufficient binding affinity for a suitable location on the protein surface; however, there is no strict requirement for binding in a specific location, such as the active site of an enzyme. By eliminating the functional activity of a protein, we open up significant new opportunities in the treatment of cancer, neurodegenerative disorders and other diseases involving dysregulated proteins.

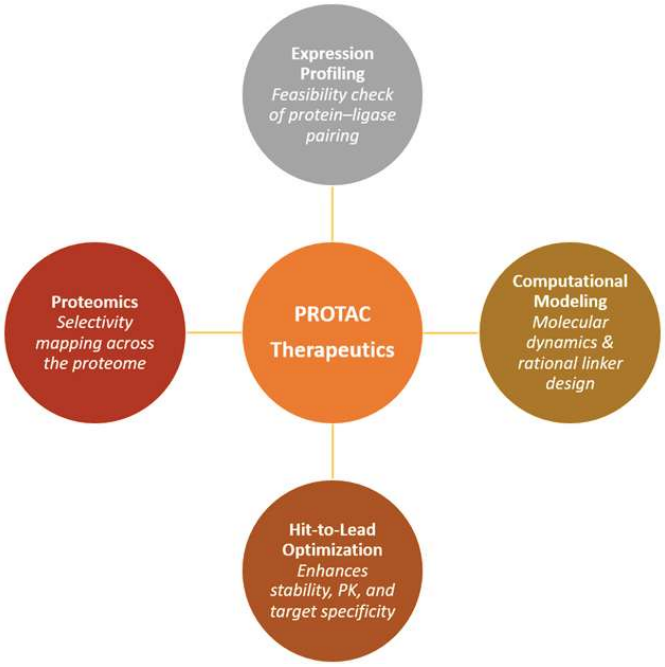
PROTAC molecular structures comprise three parts: a targeting ligand that binds to the protein of interest, a second ligand that engages an E3 ubiquitin ligase and a linker connecting the two. When brought into close proximity by the PROTAC, the E3 ligase tags the target protein with ubiquitin, marking it for degradation by the proteasome. Among the many E3 ligases in human cells, Cereblon (CRBN) and Von Hippel-Lindau (VHL) are most utilised due to their compatibility with small-molecule design and well-characterised interactions.

Figure 1: Structural elements of a typical PROTAC molecule

Despite their therapeutic potential, PROTACs introduce specific challenges in drug development. Notably, they often violate Lipinski's Rule of Five, a heuristic used to predict oral bioavailability. Their relatively large molecular size and suboptimal physicochemical properties can also impede membrane permeability and solubility. To mitigate these issues, formulation techniques such as lipid-based carriers and nanoparticle systems are being explored to enhance pharmacokinetic profiles. Simultaneously, medicinal chemists are refining linker structures and optimising E3 ligase affinity to improve bioavailability.

While classical, small-molecule enzyme inhibitors directly block the active site, as noted above, PROTACs operate via a cascade that includes target binding, ternary complex formation with an E3 ligase, subsequent ubiquitination and eventual proteasomal degradation. Each of these sequential steps influences degradation efficiency and must be fine-tuned. Advanced screening tools such as NanoBRET and HiBiT, along with high-throughput methodologies, are essential for evaluating these interactions. Additionally proteomic approaches, particularly mass spectrometry, are employed to monitor degradation kinetics and assess cellular responses.

However, the potential for resistance remains an obstacle, as cells can develop mutations in either the target protein or the



recruited ligase, or reduce the expression of E3 ligases such as CRBN. To address this, researchers are identifying alternative E3 ligases with broader expression profiles. Computational techniques and gene expression analysis aid in selecting appropriate ligase candidates. CRISPR-based functional genomics methods support the elucidation of resistance pathways and inform strategies to enhance PROTAC resilience. Moreover, combining PROTACs with complementary treatments, such as kinase inhibitors or immune checkpoint therapies, is being explored to counteract resistance and bolster clinical outcomes.

As with more traditional therapeutic modalities, PROTAC lead finding and optimisation requires a multi-disciplinary approach. This initiates with expression profiling, whereby researchers verify that both the target protein and chosen ligase are present at levels suitable for degradation. The focus then shifts to design, deploying computational modelling and molecular dynamics simulations to guide the creation of a linker that can bring all three components together in a stable ternary complex. Once a starting molecule is in hand, hit-to-lead optimisation gradually tunes the degrader, improving metabolic stability, pharmacokinetics and target specificity. Medicinal chemists then refine degrader activity while minimising off-target effects.

This process often demands iterative problem-solving. For example, in a recent collaboration, regioisomer formation rates were initially as high as 70% but were cut to below 30% through a careful determination of alternate reagents. Initially, low synthetic yields (≤ 35%) were improved using a combination of One-Factor-At-a-Time (OFAT) and Design-of-Experiment (DoE) approaches. The team also developed highly sensitive analytical methods to identify minute impurities in the linker region and used particle size optimisation, salt and polymorph engineering, and labile protection chemistry to boost solubility and bioavailability. The collective application of these optimisations exemplifies the type of precision problem-solving required to evolve a viable degrader concept into a manufacturable clinical candidate.

Chemical proteomics were also deployed to scan the entire proteome for potential selectivity issues, allowing researchers to address them early in the discovery phase.

To engineer a PROTAC aimed at a cancer-related protein, initial steps involved identifying suitable ligands using both computational simulations and screening platforms. Once promising leads were found, medicinal chemistry refinement improved degradation efficiency and linker design. The drug metabolism and pharmacokinetics (DMPK) team conducted *in vitro* and *in vivo* evaluations, assessing parameters such as solubility, permeability and absorption. These combined efforts culminated in the selection of a candidate for preclinical evaluation, showcasing the value of a coordinated development approach.

The broader field of targeted protein degradation is also rapidly expanding beyond PROTACs, such as molecular glues, antibody-based degraders (AbTACs) and autophagy-targeting chimaeras (AUTACs). While PROTACs are bifunctional conjugates, molecular glues are single molecules that stabilise the interaction between the target protein and the ligase. AbTACs are conjugates that leverage antibody selectivity to direct target proteins to degradation pathways and AUTACs use autophagy for protein clearance. Each approach offers unique advantages, with target choice depending on subcellular localisation, protein turnover and disease context.

So what comes next for PROTACs? Continued work remains to facilitate the optimisation of drug-like properties, broaden the spectrum of applicable E3 ligases and pre-emptively address resistance mechanisms. Parallel exploration of molecular glues, AbTACs and related sub-modalities promises further expansions of therapeutic scope. Through sustained research efforts including cross-disciplinary collaboration, PROTACs offer a powerful means of modulating disease-driving proteins with unprecedented precision.

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Dr. Kenneth Barr holds a PhD in Synthetic Organic/Organometallic Chemistry from Massachusetts Institute of Technology and has pursued his Postdoctoral study in natural product synthesis from the University of Texas. He has over two decades of experience in the areas of drug discovery for both small molecules. Prior to joining Syngene, Kenneth was the Head of R&D Strategic Global Operations at FORMA Therapeutics, where he was responsible for driving research effectiveness through the optimisation of internal and external R&D research efforts, providing alliance management for key CRO relationships.