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Advancing targeted protein degraders: leveraging CMC strategies for rapid IND submission and bioavailability solutions

In the rapidly evolving pharmaceutical landscape, targeted protein degraders (TPDs) represent a significant leap forward. TPDs offer a novel therapeutic modality with the potential to address disease-causing proteins that have traditionally been difficult to target with conventional small molecules

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During the past two decades, since the concept of utilising the ubiquitin-proteasome system to degrade target proteins was introduced, targeted protein degradation has transitioned beyond academic research to industrial application.

Numerous companies are now advancing preclinical and early clinical development programmes, illustrating the growing interest and potential of this approach, explains Jinling Chen, Ph.D., Senior Vice President, Head of Pharmaceutical Development and Manufacturing at WuXi STA (a subsidiary of WuXi AppTec).

The promise of targeted protein degraders

Among TPDs, proteolysis-targeting chimeras stand out as a promising class. Proteolysis-targeting chimeras are bifunctional molecules composed of two active moieties connected by a linker.

One moiety binds to the target protein whereas the other recruits an E3 ubiquitin ligase, leading to ubiquitination and subsequent degradation of the target protein by the proteasome.

This mechanism allows proteolysis-targeting chimeras to degrade proteins rather than merely inhibiting their function, providing a promising strategy to tackle undruggable targets.

Case study: accelerating targeted protein degrader development

Project overview: A recent proteolysis-targeting chimera development project showcased significant achievements in speed and bioavailability enhancement, ensuring early delivery.

The project team's primary objective was to prepare material for an investigational new drug (IND) submission and supply clinical trial material for a first-in-human (FIH) clinical study within 14 months.

By addressing key development and manufacturing challenges, the team exceeded expectations and achieved IND readiness in just 12 months.

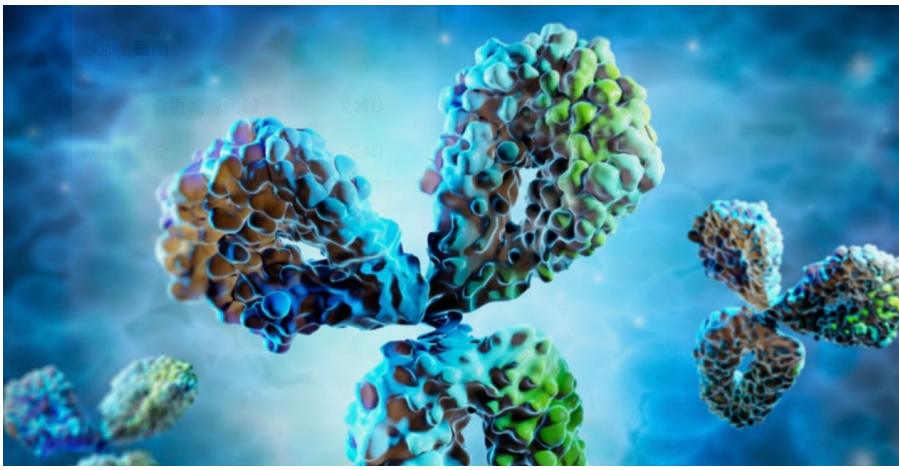
Key challenges and innovative solutions: The initial synthetic route for this molecule comprised 24 steps with an overall yield of just 0.3%. The molecule's complex 3D stereostructure further complicated crystallisation, making it difficult to produce high-purity material meeting the required specifications.

Additionally, with a molecular weight of approximately 800, it exhibited extremely low oral bioavailability (BA) of 0.9% owing to its poor aqueous solubility.

There were also three steps in the synthesis process that involved a palladium (Pd) catalyst, raising safety concerns. Overall, the steps involved a cost of more than $1 million to make 1 kg of the active pharmaceutical ingredient (API).

To address these issues, extensive literature research and discussions among WuXi STA's experts, including chemists and the biocatalysis team, led to a redesigned synthesis route that reduced the number of steps from 24 to 16.

> *"This not only made the entire synthetic process safer and more economical … but also sped up the production of the drug substance."*



Biocatalysis was chosen for its ability to produce intermediates with high chiral purity without requiring expensive supercritical fluid chromatography (SFC) separation.

By eliminating the need for two noble metal catalysis steps, biocatalysis significantly improved both efficiency and cost-effectiveness.

High-throughput crystallisation screening was employed to develop a process that achieved the desired purity and yield. Based on form stability and solubility data, two solvent systems were selected for further optimisation, leading to the final crystallisation process.

Spray-dried dispersion (SDD): On the formulation side, while drug substance work was ongoing, the bioavailability enhancement technology platform was employed to select the most effective drug delivery technology.

Various approaches were evaluated, including spray-dried dispersion (SDD), hot melt extrusion, nanodispersion and liquid formulations.

SDD technology emerged as the most effective way to improve the bioavailability of this molecule. Subsequently, the formulation team further optimised the SDD formulation composition and process, developing an enhanced tablet formulation with a 30-fold increase in bioavailability, making it highly viable for human use.

Detailed breakdown of project phases

The initial phase involved early stage process development and formulation development. The complex synthetic route was carefully analysed, and a detailed plan was formulated to streamline the synthesis process.

The project team focused on redesigning the synthesis route to enhance efficiency and yield. By incorporating biocatalysis and high-throughput crystallisation screening, the team successfully reduced the number of synthetic steps and improved the overall yield.

In parallel with the drug substance team, the drug product team conducted a comprehensive screening of bioavailability enhancement technologies.

The development of an optimised spray-dried solid dispersion played a crucial role in overcoming the bioavailability challenges associated with this molecule. The optimised formulation was developed into a tablet form, ensuring the TPD molecule was suitable for human use.

The final phase involved the production of clinical trial material.

Achievements

By leveraging an integrated Chemistry, Manufacturing and Controls (CMC) platform and advanced enabling technologies in both API process development and formulation, the project team successfully delivered clinical trial material for first-in-human dosing within a 12-month timeframe.

This rapid progression to IND submission demonstrates the efficiency of parallel workstreams and collaborative problem-solving, overcoming significant challenges in targeted protein degrader molecule development.

The project not only addressed complex synthetic hurdles but also improved bioavailability, highlighting the potential of TPDs to target previously undruggable proteins.

As these molecules move from preclinical to clinical stages, they represent a promising breakthrough in the field of targeted protein degradation, signalling a new era in disease treatment.