Prazer Therapeutics
prazertx.com/science/science.php

Transforming the future of targeted protein degradation with the SPiDEM platform

South Korean biotech Prazer Therapeutics is creating and validating a breakthrough drug discovery and development platform based on targeted protein degradation (TPD) technology to tackle previously undruggable targets in oncology, neuroscience and other therapeutic areas that are not readily addressable with existing TPD approaches.

The onset or progression of many refractory diseases, including neurodegenerative disorders and cancers, is caused by the accumulation of proteins. Targeted protein degradation (TPD) has emerged as a novel therapeutic modality that harnesses intracellular proteasomal and lysosomal protein-degradation pathways for selective elimination of pathological proteins. This approach enables the modulation of proteins that have been difficult to target with conventional small-molecule inhibitors.

While previous TPD approaches have exhibited potential, they have also revealed challenges owing to a narrow range of protein-degrading mechanisms. First-generation degraders, such as molecular glues and proteolysis-targeting chimeras (PROTACs), use a single type of E3 ubiquitin ligase for proteasomal degradation, and are not fully effective against protein aggregates and membrane proteins. Also, there may be potential caveats associated with the use of E3 ubiquitin ligase in an exclusive manner, such as drug resistance and disturbed protein homeostasis.

While new endocytosis- or autophagy-mediated TPD approaches that navigate protein targets directly to proteasomes or lysosomes are being reported, their protein targets may still be limited to soluble proteins, protein aggregates, or membrane proteins. Also, therapeutics leveraging endocytosis-mediated lysosomal degradation, such as lysosome-targeting chimeras (LYTACs), may have penetration issues in the blood–brain barrier (BBB) or tumor microenvironment.

SPiDEM's novel degrading mechanism

Founded in 2019, Prazer Therapeutics' goal is to identify and advance new mechanisms to tackle the challenges faced by the previous generations of TPD therapeutics. Prazer's proprietary TPD platform, selective protein degradation enabling moiety (SPiDEM), allows the rational design and rapid optimization of orally available and BBB-penetrating small molecules. SPiDEM's novel degrading mechanism has potential for enhanced drug-likeness, expanded therapeutic applications, reduced risk of drug resistance and sustained efficacy.

SPiDEM compounds are composed of a target-binding moiety (TBM) and a ubiquitin-recruiting moiety (URM). While the TBM binds to a protein target, the URM is ubiquitinated and induces degradation of the protein target (Fig. 1).

"SPiDEM is expanding the landscape of E3 ubiquitin ligases. The chemical moiety URM is directly ubiquitinated by a broad range of E3 ligases, including the HECT [homologous to E6AP C-terminus]-type as well as the RING [really interesting new gene]-type," said Kyung-Soo Inn, Prazer's CEO.

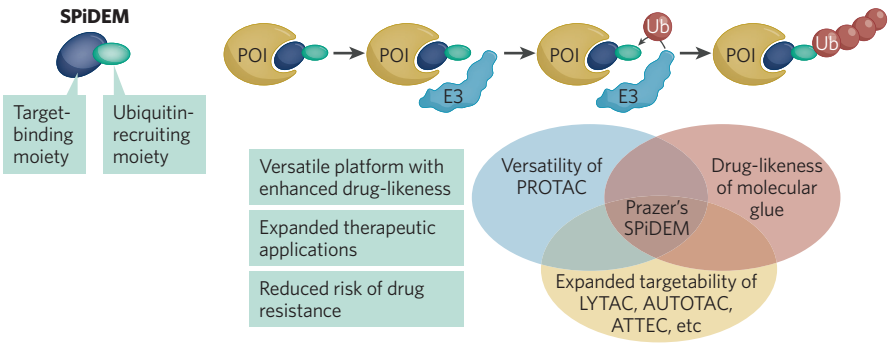

Fig. 1 | SPiDEM offers differentiation from previous targeted protein degradation modalities. ATTEC, autophagosome-tethering compound; AUTOTAC, autophagy-targeting chimera; E3, ubiquitin ligase; LYTAC, lysosome-targeting chimera; POI, protein of interest; PROTAC, proteolysis-targeted chimera; Ub, ubiquitin.

Rational design of SPiDEM degraders

SPiDEM merges the power of molecular glues and PROTACs—druggability and versatility. The small size and linker-free nature of SPiDEMs confer improved pharmacokinetic (PK) profiles comparable to those of molecular glues. In silico analysis comparing over 150 SPiDEM degraders with the bromodomain-containing protein 4 (BRD4) PROTAC, dBET1, showed enhanced drug-likeness, highlighting the potential of SPiDEMs as orally available drugs. Prazer's Tau SPiDEM program also shows promising PK profiles, including enhanced BBB penetration and bioavailability.

Unlike molecular glues, SPiDEM doesn't require phenotypic screening and allows rational design—like PROTACs. SPiDEMs are less dependent on protein–protein interactions than PROTACs because they do not require comprehensive linker optimization.

"We only need to introduce a linker when a TBM binds to the hydrophobic core of a protein target, so that the URM can navigate the solvent-accessible surface for ubiquitination," said Kyung-Soo. "This potentially reduces the hit-to-lead time to as little as two months."

Expanded therapeutic applications

SPiDEM broadens therapeutic applications as it harnesses both proteasomal degradation of soluble proteins and autophagy- and endocytosis-mediated lysosomal degradation of protein aggregates and membrane proteins.

"Prazer's SPiDEM approach expands the application of TPD therapeutics to a broad range of intractable diseases. Our current focus is on Alzheimer's disease, progressive supranuclear palsy, Parkinson's disease, dementia with Lewy bodies, and a variety of cancers," said Kyung-Soo.

Since its founding, Prazer has focused on establishing and optimizing the SPiDEM library to validate it as a platform. The SPiDEM library is composed of over 400 SPiDEM compounds (more than 180 URMs conjugated to TBMs of over 10 protein targets).

Prazer is seeking collaborations that combine the SPiDEM platform technology with partners' expertise to identify and develop novel TPD therapeutics.

"We are open to any type of partnership. We can transform partners' target ligands such as conventional inhibitors, or TPD modalities such as PROTACs, to SPiDEM degraders within six months," said Kyung-Soo. "We are also looking to create synergy with partners to co-develop novel TPD modalities, for example, antibody–drug conjugates using SPiDEM degraders as payloads for cell-specific delivery."

While most TBMs for SPiDEM degraders have been sourced from the public domain, Prazer seeks to develop or co-develop novel target binders in the longer term. Prazer also seeks partners for its in-house programs, such as Tau SPiDEM, which is expected to begin preclinical trials in early 2024.

CONTACT
Heejin Kim, Business Development & Licensing Team Lead
Prazer Therapeutics
Seoul, Republic of Korea
Tel: +82 2 6217 1023
Email: biz@prazertx.com

ADVERTISER RETAINS SOLE RESPONSIBILITY FOR CONTENT