Protein Degraders Take Industry By Storm

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Proteins are essential components of living matter — they function as building blocks for cells and tissues, as well as participate in signaling and practically all biochemical activities. However, each protein operates correctly only for a limited time and is eliminated by molecular machinery after it has reached its “functional shelf life”. To maintain a healthy and functional proteome, cells tightly control protein turnover processes, ensuring that misfolded, damaged, and old proteins exit the game promptly. This sophisticated degradation mechanism was recently hijacked by the drug discovery industry to develop new small molecule therapies — protein degraders.

What is protein degradation?

According to Nello Mainolfi, CEO of Kymera Therapeutics (NASDAQ: KYMR), practically every big pharma player and medium-sized biotech business today has internal R&D research or external collaborations in the field of protein degraders. The boom sparked by these small molecule therapies is due to a number of causes, which we will cover in this article, together with notable companies in the field, and three case studies revealing innovative strategies to go about designing targeted protein degraders.

Small molecule inhibitors (SMIs), one of the most commonly used methods of treating illnesses, have essential limitations. SMIs can currently reach protein targets of only around 20% of the proteome. According to the medical journal EBioMedicine, over 75% of known proteins lack active sites for SMIs binding, which means that traditional therapeutics can't inhibit their function. To overcome the limitations, researchers took a fresh approach to small molecules, turning an old tool into a novel therapy.

The idea began to take shape in the 1990s, when Proteonix, a biotech company, submitted a patent for a bifunctional molecule that targets the ubiquitin-proteasome system (UPS). Even though Proteonix never developed a medication based on the patent, it kicked off two decades of active research in the field. The first Proteolysis targeting chimera (PROTAC) was introduced in 2001, and it consisted of two ligands connected by a flexible linker. The basic chemical architecture of modern PROTACs is the same: one ligand targets the E3 enzyme, which is a component that sends outdated proteins to the proteasome, and another ligand targets a protein of interest (POI) that has to be degraded. A PROTAC binds E3 and POI, bringing them closer to form an induced proximity complex. In some cases, when the proteins align appropriately, the POI gets ubiquitinated, which marks it for degradation by the proteasome.

Another broad approach to protein degradation includes so-called “molecular glues,” an actively growing area of research. In contrast to PROTACs, being relatively large bifunctional small molecules with two active sites and a linker, molecular glues are smaller and more drug-like molecules. The latter bind to an aggregate protein pocket resulting from two separate proteins coming into proximity due to the effect of the molecular glue molecule. While this article primarily focuses on the bifunctional protein degraders, there is an excellent overview of molecular glues in the 2022 C&EN article “Molecular glues are beginning to stick. “

Advantageous therapeutic modality

PROTACs and other targeted protein degraders have an advantage over conventional small molecule inhibitors because of their unique mechanism of action. To maximize the therapeutic potential of SMIs, high and frequent doses are usually needed because one needs a stoichiometric ratio of the SMI and POI (i.e., occupancy-based pharmacology). However, one PROTAC molecule can trigger the breakdown of several POI molecules through the catalytic mechanism. Thus PROTACs require substantially lower concentrations in the cell to achieve efficacy. This phenomenon has the potential benefit of lowering a drug's toxicity and improving its side effect profile. As such, the factor that defines the efficacy of a PROTAC is not the affinity but the kinetics of binding — a measure of how rapidly a PROTAC can bring both targets together to start the process. As a result, chimeras can function by binding to every nook or cranny of a protein, possibly extending the pool of druggable target options.

The race for better degraders

One of the first companies that started commercial development of PROTAC therapeutics is Arvinas (NASDAQ: ARVN). Dr. Craig Crews, a co-founder of the company and a scientist from Yale University, was the one who discovered PROTAC technology in the early 2000s. Almost two decades later, in 2019, Arvinas was also the first to announce that its protein degrader candidates got into clinical trials. Today, the company has a strong portfolio, with two medications, ARV-110 and ARV-471, in Phase 2 clinical trials. Both drugs address solid tumors; ARV-110 acts as a ligand for the Androgen Receptor (AR) in prostate cancer, and ARV-471 targets Estrogen Receptor (ER) in breast cancer. In 2018, the company priced a $120 million IPO. It has several notable collaborations, including Bayer, Certara, and others.

Founded in 2012, Nurix Therapeutics (NASDAQ: NRIX) is another pioneer in the protein degradation space. The company has two protein degrader candidates in the Phase 1 clinical trial, oral small molecules NX-2127 and NX-5948, both for alleviating B-cell malignancies. Targeted protein modulators also represent the company's pipeline for immuno-oncology and drug-enhanced cell therapy programs. A notable resource in Nurix's hands, their DELigase Platform enables the company to discover candidates in the E3 ligases realm using the immense power of DNA-encoded libraries of small molecules, a known technology to explore ultra-large chemical spaces. DELigase Platform allows the Nurix team to identify small molecules that can either decrease or increase protein levels – processes they refer to as Targeted Protein Modulation.

Nurix Therapeutics went public in 2020, banking a total of $209 million, followed by a recent post-IPO equity deal of around $40 million.

Another known player in the protein degradation space is Kymera Therapeutics (NASDAQ: KYMR), which was founded in 2015.

Case Study

Identifying High-Impact Tissue Sparing E3 Ligases and Their Binders

The company has programs that target IRAK4, IRAKIMiD, STAT3, and MDM2, each of which centers on a critical signaling node within the IL-1R/TLR, JAK/STAT, or p53 pathways. The most advanced program is the IRAK4 degrader, KT-474, which is in Phase I clinical trials for treating immunology-inflammation diseases such as hidradenitis suppurativa and atopic dermatitis. The IRAKIMiD degrader, KT-413 aims to treat MYD88-mutated diffuse large B cell lymphoma. Kymera is also developing selective STAT3 degraders for treating hematological malignancies and solid tumors, as well as autoimmune diseases and fibrosis. KT-333 is a first-in-class STAT3 protein degrader currently in Phase I clinical trials. Finally, their MDM2 degrader program aims to treat hematological malignancies and solid tumors. KT-253, a highly potent MDM2 degrader, unlike small molecule inhibitors, can suppress the MDM2 feedback loop and can rapidly induce apoptosis with brief exposures.

Kymera Therapeutics debuted on IPO in 2020, raising more than $170 million. The company has several R&D collaborations, with a notable $150 million Sanofi deal in 2020, promising to bring an additional $2 billion or more, should things work out as planned.

Massachusetts-based C4 Therapeutics (NASDAQ: CCCC) does not only focus on target discovery and PROTACs development but also potential protein degrader optimization strategies. C4's small molecule degrader CFT7455, a treatment designed to target DNA-binding protein IKZF1/3 in multiple myeloma

patients, received an orphan drug designation from the FDA in August 2021. CFT7455 Phase 1/2 Trial in Multiple Myeloma and Non-Hodgkin's Lymphomas was Initiated in June 2021, with top-line clinical data results expected this later year. The biotech went on IPO in 2020, raising more than $200 million.

Roivant Discovery is the drug discovery engine for Roivant Sciences (NASDAQ: ROIV).

Case Study

QUAISAR Computational Platform for Designing Targeted Protein Degraders

The company is approaching the discovery and design of novel small molecules and protein degraders using its *QUAISAR* computational platform, which combines physics-based simulations and machine learning to address biologically and genetically validated, but previously intractable protein targets. The company has an impressive technological stack, comprising quantum mechanics, thermodynamics, molecular simulation, artificial intelligence, and supercomputing infrastructure.

Roivant Sciences has a diversified business strategy and more than $2 billion in total funding via IPO and post-IPO financing rounds.

Cedilla Therapeutics, located in Cambridge, is working on a new way to target protein degradation. Instead of bringing UPS components to a protein of interest, it looks for unrecognized allosteric binding sites for ligands that can destabilize protein structure. Destabilized proteins are degraded by inner cell mechanisms and no more extended function in a cell.

The nature of the ubiquitin degradation process functions only inside cells and not in the intracellular matrix –is a restriction that PROTACs have yet to overcome. As a result, PROTAC molecules are unable to reach targets that are outside of cells. However, lysosome-targeting chimeras, or LYTACs, are a new option for targeted protein breakdown. PROTACs and LYTACs have similar structures and modes of action. However, the latter connects target proteins to the transmembrane receptor CI-M6PR at the cell surface. Creating a trimeric complex between a POI, a receptor, and an LYTAC causes the protein to be degraded by protease enzymes in the lysosome.

Cedilla raised a total of $139 million from a group of investors, including Casdin Capital, Boxer Capital, RA Capital Management, and others.

Another player in the LYTAC space is San Francisco-based Lycia Therapeutics, which focuses on the applications of lysosomal targeting chimeras in three main areas: hardly-druggable membrane or circulating proteins, diseases that are driven by protein aggregation, and diseases in which

autoantibodies play a role. In 2021, Eli Lilly tapped Lycia's LYTAC platform to develop therapeutics for immunology and pain in a $35 million pact, with up to $1.6 billion in promised biobucks.

Lycia Therapeutics raised a total of $120 million from several investors, including Eli Lilly. RTW Investments LLC, Versant Ventures, and others.

Finally, there is a new player rapidly building its presence in the protein degradation space — Celeris Therapeutics, a biotech company founded in 2021 in Gras, Austria, and headquartered in Silicon Valley, California.

Case Study

Application of AI-driven Xanthos Platform for Designing Protein Degraders

In February 2022, Celeris Therapeutics entered a research collaboration with Merck KGaA, enabling the latter to use Celeris's graph-based artificial intelligence (AI) platform for discovering and designing novel small molecule binders and bifunctional degraders. Just two months later, Celeris Tx also partnered with Boehringer Ingelheim to allow the pharma giant use AI platform Celeris One to generate novel proximity-inducing compounds to degrade pathogenic proteins agreed upon with Boehringer.

The company has received $6 million to date from several venture capitalists, including R42, APEX Ventures, Pace Ventures Enigma, i&i biotech, and Longevitytech.fund.

INTERVIEW: Targeted Protein Degradation: a New Approach to Small Molecule Therapeutics

The early discovery and clinical race in the targeted degradation space are becoming tenser, with other active players advancing their candidates, including pharmaceutical giants Bristol Myers Squibb and Novartis, as well as a cluster of smaller biotechs, including Dialectic Therapeutics, Foghorn Therapeutics, Captor Therapeutics, Amphista Therapeutics, Cullgen, Monte Rosa Therapeutics, NeoMorph, and others.

Bright future ahead for targeted protein degradation

The continuation of intense scientific research on protein degraders broadens the scope of this modality's prospects. Third-generation controllable PROTACs that can be regulated by visible and UV light are being developed, and new targets appear — including RNA-binding proteins and DNA-binding proteins. While more than 600 E3 ligases have been discovered in human cells, only a few have been verified for PROTAC use. For instance, degraders with ligands for cancer-and tissue-specific E3 ligases will improve the selectivity of potential therapeutic candidates while lowering toxicity and side effects.

However, there is still much work to be done in this field, as some protein degrader characteristics have to be improved. Chimeras are more significant than traditional small-molecule pharmaceuticals, which have an impact on cell permeability. This could pose difficulties in the case of oral delivery, as well as hamper migration across biological boundaries to treat central nervous system illnesses.

- Arvinas
- C4 Therapeutics
- Cedilla Therapeutics
- Celeris Therapeutics
- Kymera Therapeutics
- Lycia Therapeutics
- Nurix
- Roivant Sciences