Jean-Claude Muller: Targeted protein degradation

Scientists are looking inside the cell for drug targets

The development of new drugs is dependent on many factors, and one of the most important is being able to identify and reach a target. For years, a key target for drug development has been the G protein-coupled receptor which describes a family of receptors on the surface of cells that help regulate many bodily functions. An estimated 50% of drugs in development, or approved for marketing, are based on GPCRs[1]. Yet this only tells part of the story.

Scientists have also been looking inside the cell to try and understand how proteins function and whether their behaviour might contribute to drug development. This has given rise to research into protein degradation and the subsequent development of small molecule drugs that can intervene in the degradation process. In this article, we review the history and current status of two protein degrader drug groups. They are molecular glues and PROTACs (proteolysis targeting chimera).

History

Protein degradation is a natural process by which cells in the human body break down proteins that are damaged or no longer needed, in order to maintain equilibrium. This is a continuous process that supports the health of cells and ensures that they can carry out their regulatory functions. The process of regulated protein destruction was identified by Aaron Ciechanover and Avram Hershko of the Israel Institute of Technology and Irwin Rose of the University of California, Irvine, US, at the beginning of the 1980s. They discovered that protein degradation is a controlled process that is managed by a molecule called ubiquitin which tags defective proteins and brings them to the proteasome for destruction. The three scientists were awarded the Nobel Prize in Chemistry in 2004 for their discovery[2].

Table 1. FDA approved drugs with molecular glue activity

Drug	Biological Target	Clinical Indication
Cyclosporin	Cyclophilin	Organ transplant rejection
Tacrolimus	FKBP12	Organ transplant rejection
Rapamacyn	FRB domain of mTOR	Organ transplant rejection
Temsirolimus	FRB domain of mTOR	Cancer
Rimiducid	FKBP12/F36V	Graft versus host disease
Thalidomide	CRBN domain	Multiple myeloma
Lenalidomide	CRBN domain	Multiple myeloma
Pomalidomide	CRBN domain	Multiple myeloma
Taxol	Microtubule stabilisation	Solid tumours
Taxotere	Microtubule stabilisation	Solid tumours
Discodermolide	Microtubule stabilisation	Solid tumours

In parallel, another group of scientists, led by Stuart Schreiber, were investigating protein-to-protein interactions but from a different angle. Dr Schreiber, a Harvard University scientist and co-founder of the Broad Institute of Harvard and Massachusetts Institute of Technology, US, pioneered an approach to protein interactions that integrated chemical biology with human biology. Upon arriving at Harvard in 1988, one of his first projects was to investigate the modes of action of three molecules which were immunosuppressants. They were Sandimmune (cyclosporin A), Tacrolimus (FK506) and Sirolimus (rapamycin). Using affinity chromatography, Dr Schreiber's group discovered that cyclosporine A, FK506, and rapamycin displayed similar peptidyl-prolyl isomerase activity and interacted with high affinity with intracellular signalling amongst proteins such as cylophilin, calcineurin and FKBP-12. These proteins were called immunophilins because of their ability to bind to immunosuppressive drugs.

But how could scientists investigate these interactions? The most powerful agents were antibodies. But because of their size, antibodies could only attach to cell-surface receptors. They were unable to penetrate cell membranes. At the time, these newly discovered biological responses triggered by immunophilins could only be understood by hypothesising that the molecules were not just binding one protein, but were acting by competitively binding two different and complementary targets. This then induced an original docking assembly with unexpected biological properties. This research lead to the idea that some 'natural product molecules' resulting from billions of years of natural selection are bifunctional and act by inducing proximity of two proteins.

These natural product molecules became known as chemical inducers of proximity (CIPs)[3]. In 1993, Dr Schreiber coined the term 'molecular glues'. These are small molecules that can recruit protein complexes known as ubiquitin ligases to carry out protein degradation. In the period that followed, several drugs were given a regulatory approval that followed the molecular glue discovery modality but weren't classified as such (see Table 1). These drugs included thalidomide and its analogues and synstab A, a mitosis modulator; discodermolide, a polyketide; epothilone, a microtubule; and indasulam, a cell cycle inhibitor. This raised the possibility that other small molecules could be synthesised to behave like molecular glues.

Monovalent and bivalent molecules

The original molecular glue molecules were monovalent, meaning that they could induce and stabilise protein-protein interactions between a ligase and a target protein leading to biological activity. The ligase is E3, a protein in the ubiquitin system. As described by Nobel laureates Drs Ciechanover, Hershko and Rose, ubiquitin ligases are small regulatory proteins found in most tissues which tag other proteins for degradation.

Table 2. Late-stage clinical candidates acting as molecular glue or PROTACs					
Companies	Drug	Modality	Targeted Protein	Clinical Stage	Clinical Indication
Arvinas/Pfizer	Vepdegestrant	PROTAC	ER+/HER2	Phase 3	Breast cancer
BMS	CC94676/BMS 986365	PROTAC	Androgen Receptor	Phase 3	Oncology
BMS	Iberdomide	Mol Glue	Ikaros/Aiolos	Phase 3	Multiple myeloma
BMS	Golcadomide	Mol Glue	IKZF1/3	Phase 3	Oncology
BMS	Mezigdomide	Mol Glue	Ikarios/Aiolos	Phase 3	Oncology
BeiGene	BGB 16673	PROTAC	BTK	Phase 2	Oncology
Sanofi/Kimera	SAR 444656	PROTAC	IRAK4	Phase 2	Atopic dermatitis/Hidradenitis suppurativa
Kintor Pharma	GT 20029	PROTAC	Androgen Receptor	Phase 2	Lymphoma
Prelude Therapeutics	PRT 3789	PROTAC	SMARCA2	Phase 2	Oncology
Kangpu Biopharma	KPG 818	Mol Glue	IKZF1/3	Phase 2	Oncology
Kangpu Biopharma	KPG 121	Mol Glue	CK1a/IKZF1.3	Phase 2	Oncology

Table 3. Deals involving molecular glue technologies			
Licensee	Licensor	Clinical Indication	Year of deal
Pfizer	Arvinas	Oncology	2018
BMS	Celgene	Oncology	2019
Sanofi	Kimera	Immunology	2020
Boehringer Ingelheim	Proxygen	Oncology	2020
Novartis	Orionis Biosciences	Non identified targets	2020
Novartis	Dunad Therapeutics	Four targets	2021
Pfizer	Arvinas	Breast cancer	2021
Merck KGaA	Proxygen	Mutiple targets	2022
Roche	Orionis Biosciences	Oncology and CNS	2023
Merck MSD	Proxygen	Mutiple targets	2023
Biogen	Neomorph	Alzheimer's and Immunology	2024
Novartis	Arvinas	Prostate cancer	2024
Astellas	Axcelead DDP	Not specified	2024
Blueprint Medicine	Vantal	Three unspecified targets	2024
Pulmatrix	Culgen	*	2024
Novo Nordisk	Neomorph	Oncology	2025
Eli Lilly	Magnet Biomedicine	Oncology	2025
AbbVie	Neomorph	Oncology and Immunology	2025
Gilead	Leo Pharma	Inflammatory diseases	2025
* Merger of companies			

The molecular glue mechanism is not the only way to target and degrade proteins however. A second molecule called PROTAC was identified in 2001 and performs a similar function. PROTACs are bivalent small molecules consisting of two ligands connected via a linker. One ligand engages an E3 ubiquitin ligase and the other binds to the protein tagged for degradation. Together the monovalent molecular glue molecule and the bivalent PROTAC are rich sources of new assets for drug development.

Molecular glue molecules are attractive because they have a good membrane permeability and adequate pharmacokinetic properties. PROTACs are slightly larger, with a molecular weight of between 700 and 1000 daltons. At the same time, PROTACs have the potential to reach a broad range of proteins, according to their developers.

In 2015, Raymond Deshaies, a US biochemist and cell biologist, then a professor at the California Institute of Technology, declared that a 'gold rush' towards molecular glues and PROTACs was about to start. He later joined Amgen Inc where he helped develop a PROTAC programme called the induced proximity platform. One of the projects is a PROTAC targeting the SMARCA2 protein for degradation in lung cancer. The hope is that the drug will be able to block lung tumour cell growth while sparing normal cells.

Additionally, Amgen is looking to expand its protein degradation programme to RNA by developing RNA-targeting chimeric molecules. These would work in a similar fashion to PROTACs but bind to RNA molecules instead of proteins and bring them to RNA degrading enzymes for destruction[4].

In the last decade there has been a slow but steady interest in the technology. This has been assisted by the concept of precision medicine which has risen to the top of large pharma's research and development agenda. Efpia, the European pharmaceutical industry federation, highlights precision medicine because it is based on the molecular mechanism of diseases. "Precision medicine targets treatments to patients who are most likely to benefit from them," it says[5]. Academic journals now refer to PROTACs as targeted protein degraders.

The industry leaders

Arvinas Inc, a US biotech based in New Haven, Connecticut, is one of the most active companies in the protein degradation space. It has nine PROTAC programmes in its pipeline, of which six are in oncology and immuno-oncology, and four are in neurology. Three of the programmes are in the clinic, the most advanced of which is a candidate treatment for estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer (ER+/HER2-). The molecule is called vepdegestrant.

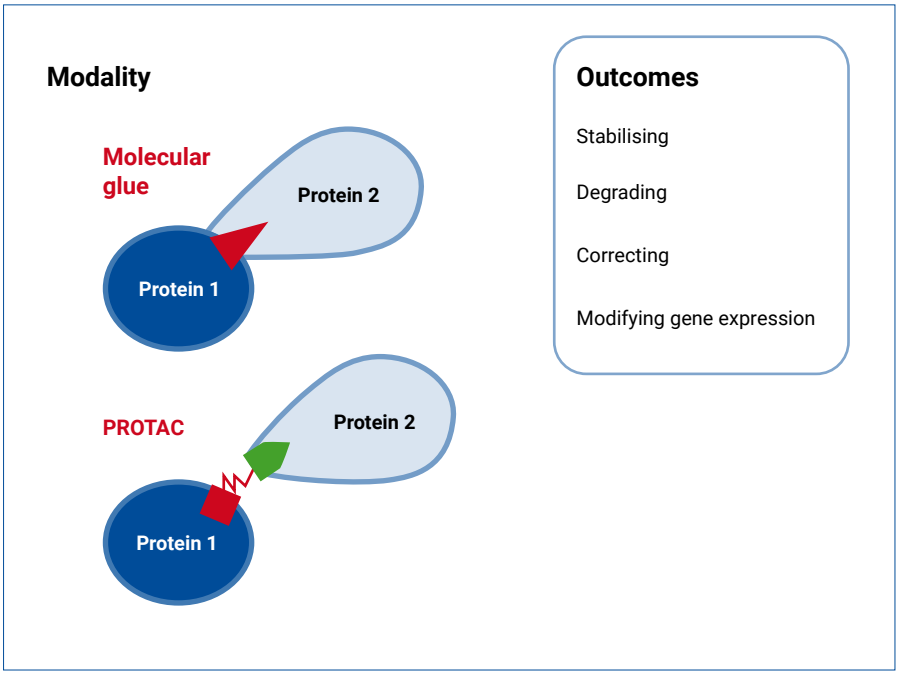
On 11 March, Arvinas and its partner Pfizer Inc reported topline results from a Phase 3 trial of vepdegestrant which showed the drug had reached its progression-free survival endpoint in the estrogen receptor 1-mutant population. However it did not meet the endpoint in the intent-to-treat population. Despite the mixed result, Arvinas pointed out that vepdegestrant was the first PROTAC degrader to show a clinical benefit at Phase 3. Four weeks later, the company reported positive data from a Phase 1 study of one of its neuroscience assets. This is a PROTAC being developed for Parkinson's disease. The molecule was shown to be safe and was able to cross the blood-brain barrier. The target is leucine-rich repeat kinase 2 (LRRK2), a protein that has been implicated in both Parkinson's disease and progressive supranuclear palsy.

Separately on 20 March, Boston, US-based Monte Rosa Therapeutics Inc reported Phase 1 results from MRT-6160, a programme partnered with Novartis and aimed at immune mediated diseases. MRT-6160 is a molecular glue agent targeting a protein called VAV1. In 70 individuals and across five ascending doses, the candidate drug degraded VAV1 by greater than 90% in the subjects' T cells. Monte Rosa also disclosed that it has decided to further develop, on its own, MRT-2359, another molecular glue, which degrades the translational termination factor GSPT1, a protein which is overexpressed in castration-resistant prostate cancer.

One of the biggest players in the field is Bristol Myers Squibb Co which has both molecular glue and PROTAC molecules in development. Its late-stage candidate drugs are listed in Table 2. The company calls its PROTAC-like molecules ligand-directed degraders. In addition, it is developing degrader antibody conjugates. BMS has noted that with targeted protein degradation, its researchers can harness the cell's own machinery to degrade several new classes of proteins that were previously considered 'undruggable'.[6]

The list of heretofore undruggable targets is long. According to a 2024 edition of *Science Bulletin*, an academic journal published in China, more than 80% of proteins linked to a disease cannot be targeted by current treatments. Some examples are transcription factors, the tumour protein p53 and the tau protein.

Targeted protein degradation opens the door for reaching previously undruggable intracellular targets. These include diseases in oncology, immunology and more recently neurological diseases. Modifying the landscape of a protein surface by inducing proximity can trigger multiple biological consequences which go far beyond the simple degradation of targeted proteins (see cartoon).



Additionally, it has been established that molecular glues have a similar potential as gene editing to rewire the circuitry in cells at the level of proteins. As such, they can also correct malfunctioning protein complexes and even modify gene expression, thus opening unchartered territory.

One way to assess the importance of a new concept is to measure the number of deals using the technology between large pharma companies and biotech enterprises. The analysis starts with the monetary value of the deals, but also the companies involved. Current protein degrader deals involve Pfizer in collaboration with Arvinas and Novartis in collaboration with Monte Rosa Therapeutics. In addition, BMS and Amgen are active in the field. It is now clear that protein degradation is attracting a wide range of drug developers.

References:

1. Wikipedia, Biological target, referencing Lundstrom K, An overview on GPCRs and drug discovery, *Methods in Molecular Biology*, 2009. **2.** The Royal Swedish Academy of Sciences, Nobel Prize in Chemistry for 2004, 6 October 2004. **3.** Teng M et al, The rise of degrader drugs, *Cell Chemical Biology,* 17 August 2023. **4.** Amgen Inc, https://www.amgen.com/stories/2023/11/any-target-every-time. **5.** Efpia, Precision medicine, https://www.efpia.eu/about-medicines/development-of-medicines/precision-medicine/. **6.** Bristol Myers Squibb Inc, Protein degradation resources, https://www.bms.com/media/media-library/scientific-media-resources/understanding-protein-degradation-and-resources.html.

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