Scrip
Pharma Intelligence

Scrip's Rough Guide To Targeted Protein Degradation

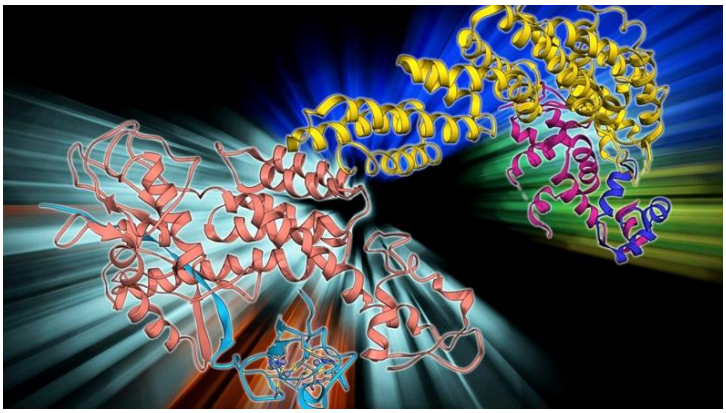
Drugging The Undruggable

28 Feb 2022 | **ANALYSIS**

by Alex Shimmings | @ScripAlexS | alex.shimmings@informa.com

Executive Summary

By hijacking a process that cells use to keep themselves shipshape, targeted protein degradation has become a hot new area of drug development. *Scrip* takes an in-depth look at the field ahead of a wave of data expected this year from early candidates that will give some insight into whether this strategy will truly open a new way to combat disease.



LIGASE ENZYME TAGS PROTEIN FOR DEGRADATION BY ATTACHING A UBIQUITIN MOLECULE

Source: Alamy

Targeted protein degradation, or TPD, has been steadily gaining attention in recent years as a highly promising new drug development strategy that has already attracted significant investment and big pharma attention.

With observers eagerly awaiting early clinical data for a range of novel TPD candidates, *Scrip* explains how these products work, looks at the various TPD strategies under investigation in the pipeline and surveys the major players and deals so far in the field.

What's The Deal With Targeted Protein Degradation?

The excitement with TPD lies in the fact that it is expected to open a new way to fight disease by targeting many disease-linked proteins that were previously thought of as "undruggable."

A protein target customarily considered suitable for pharmaceutical development was one that had a clear, deep hydrophobic pocket or active site – for example those seen on enzymes such as kinases – and much of traditional drug development has been based on this "occupancy-driven pharmacology" paradigm.

Targets deemed unamenable to drug development included those with no obvious pocket – the non-enzyme proteins that were just too smooth to provide a nook into which a drug can lock into and thereby modulate its function.

This need for an active site in the target protein has limited the scope of drug development. The human proteome is made up of around 20,000 different proteins, and about 600 play a role in cancer, a key area for TPD research, but of these, nearly 400 are non-enzyme proteins.

While injectable antibody-based products have been able to move in against non-enzyme protein drug targets found on the surface of cells, intracellular proteins have largely proved intractable to drug development. This is why there are so few drugs on the market that target scaffolding proteins, transcription factors and other non-enzymatic proteins found within the cell.

Other novel strategies such as RNA interference have been used successfully to create drugs that reduce the amount of an unwanted protein within the cell, and gene therapy and CRISPR/Cas9 technologies are being used to fix the gene for, or knock out production of, an aberrant protein, but these strategies are facing various challenges in development.

TPD, by contrast, aims to remove unwanted proteins, rather than inhibit them or stop their production, and it offers a whole new theatre for drug development – one that promises to take the positive qualities of oral, easily titratable small-molecule drugs to a new range of protein targets.

Researchers hope protein degraders may also avoid the resistance problems seen with small-molecule drugs when mutations in the active site render them less effective. And since protein degraders only need to bind transiently to their target to work, rather than having to remain sitting in an active site, one molecule can degrade many proteins, increasing their therapeutic window. Once a particular protein is degraded, the TPD drug is released, free to exert its effects once again on another. Mission accomplished, the protein degrader lives to fight another day.

Another potential benefit is that protein degrader drugs may be able to work in concert with inhibitor-based drug strategies, for example, to reduce feedback loops that are known to hamper the efficacy of some traditional drugs.

Where Did The Idea Come From?

Early attempts to capitalize on cells' housekeeping functions to treat disease focused on heat shock proteins but found little success. These drug candidates were too broadly targeted and suffered from poor *in vivo* pharmacological properties and severe hepatotoxicity.

TPD really started, like so much in the modern drug industry, with thalidomide, or rather its successor drugs, Celgene Corporation(now Bristol Myers Squibb Company)'s Thalomid (thalidomide), Revlimid (lenalidomide) and Pomylast (pomalidomide).

These immunomodulatory drugs (IMiDs) transformed treatment for multiple myeloma and erythema nodosum leprosum following their introduction in the 2000s, but back then no one really understood how they worked.

Not until 2014 – by which time Revlimid was notching up annual sales just shy of $5bn – was it discovered that thalidomide and its successors bind to a protein called cereblon, a ubiquitin ligase. (Cereblon loss in zebrafish causes fin defects reminiscent of the limb defects seen in children exposed to thalidomide *in utero*.)

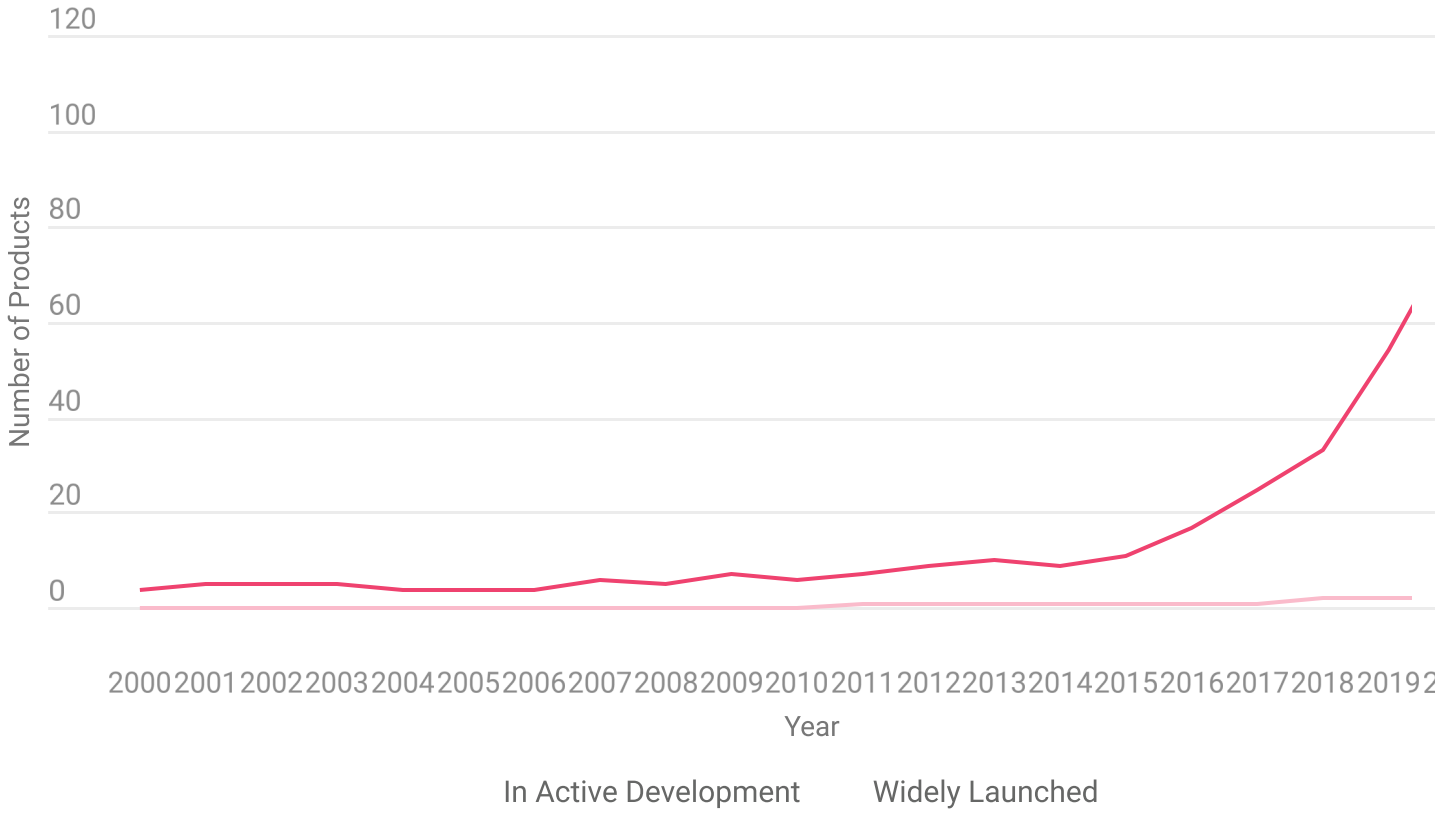
This drug binding activates the cereblon E3 ubiquitin ligase complex, which tags two transcription factors with ubiquitin, targeting them for destruction via proteolysis, with the knock-on effect of killing the diseased B-cells.

Another, older, marketed anticancer drug, fulvestrant (AstraZeneca PLC's Faslodex and generics), also acts by degrading a protein, this time the estrogen receptor. The selective estrogen receptor degrader, or SERD, does this by inducing a structural change to the estrogen receptor that makes it more hydrophobic, mimicking the unfolding which flags damaged proteins up for proteolysis – a process known as hydrophobic tagging.

In other words, TPD is already a clinically and commercially validated drug development strategy. In 2020, Revlimid hit sales of $12bn, making it the third best-selling drug worldwide that year.

With this kind of provenance and market potential, the race is on to capitalize on these discoveries and develop a new wave of drugs specifically designed to degrade proteins, not just to target cancers but also other diseases in neurology (including the famously difficult Alzheimer's) and the inflammatory/autoimmune area (see Pipeline 2000-2021 below).

Targeted Protein Degradation Pipeline 2000-2021



Source: Pharmaprojects, November 2021

Following a sharp increase in R&D activity in recent years, a wave of other protein degrader products for cancer and other indications is coming through the pipeline hoping to emulate these pioneers' market achievements: around 200 TPD products are now in development, with around 30 in the clinic, and it makes sense that the most advanced candidates are improvements on the injectable fulvestrant: the oral SERDs for breast cancer in Phase III development (see table).

SERDs In Mid-To-Late-Stage Development

Drug	Company	Indication	Phase
camizestrant	AstraZeneca	Breast Cancer	Phase III Clinical Trial
giredestrant	Roche	Breast Cancer	Phase III Clinical Trial
amcenestrant	Sanofi	Breast Cancer	Phase III Clinical Trial
elacestrant	Radius Health/Eisai	Breast Cancer	Phase III Clinical Trial
imlunestrant	Eli Lilly (Loxo Oncology)	Breast Cancer	Phase III Clinical Trial
rintodestrant	G1 Therapeutics	Breast Cancer	Phase II Clinical Trial
ZB-716	Zenopharm	Breast Cancer	Phase II Clinical Trial
ZN-c5	Zentalis/ Zentera Therapeutics	Breast Cancer	Phase II Clinical Trial
AC-0682	Accutar Biotechnology	Breast Cancer	Phase I Clinical Trial
D-0502	InventisBio	Breast Cancer	Phase I Clinical Trial
SCO-120	Sun Pharma Advanced Research	Breast Cancer	Phase I Clinical Trial

Source: Pharmaprojects, January 2022

Taking Out The Rubbish – What Is TPD?

As briefly described previously, TPD works by removing unwanted proteins from the cell, and it does so by hijacking the system eukaryotic cells use to get rid of damaged proteins – the E3 ligase-directed ubiquitin-proteasome system.

By this means, an E3 ligase adds a flag, the small regulatory protein ubiquitin, to the unwanted proteins to signal to the proteasome that they need to be taken away and destroyed. The proteasome is a protein complex that keeps the cell in good order by breaking down unwanted or damaged proteins via proteolysis.

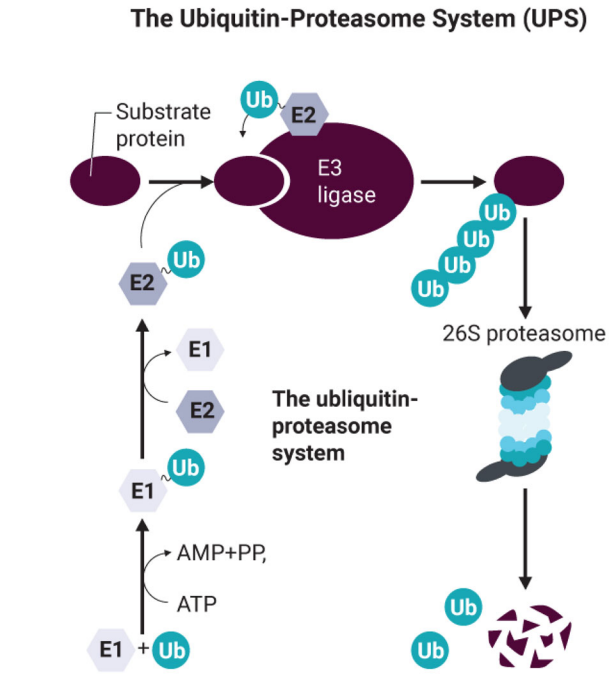
TPD drugs co-opt this process by bringing together the disease-associated protein target of interest and an E3 ligase so that it gets flagged with ubiquitin, alerting the proteasome that it needs removing (see diagram below).

There are many different E3 ligases – around 600. Some can ubiquitinate just a few target substrates, but others can target multiple proteins of interest, and this rich pool is waiting to be explored by researchers who are hopeful that they will be able to target specific oncoproteins for certain tissue and tumor types by recruiting an E3 ligase which is expressed only in that cell lineage.

Cereblon is by far the E3 ligase of choice for the products currently in development but others like von Hippel–Lindau, or VHL, protein, together with cellular inhibitor of apoptosis protein 1 (cIAP1), are also being looked at in the clinic.

Key to the efficacy of TPD drugs will be their ability to bring the E3 ligase and the protein of interest physically together to allow its ubiquitination and subsequent degradation by the proteasome.

TPDs can broadly be divided into two categories: molecular glues and heterobifunctional products such as PROTACs. Molecular glues are simpler in that these drugs just bind to the E3 ligase, altering its surface in a way

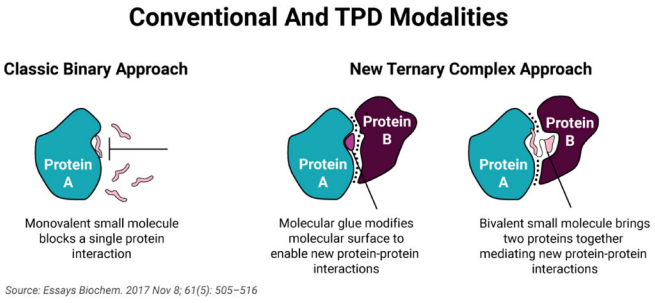


Source: Dale et al Nat Rev Cancer 2021

that lets it interact with the protein target, in effect sticking the two together, and sending that target protein off down the ubiquitination and degradation pathway.

Revlimid, Thalomid and Pomylast are all molecular glues. Specifically, they target the E3 ligase cereblon, and once bound, mark two B-cell transcription factors (Ikaros family zinc finger proteins 1 and 3 (IKZF1 and IKZF3 (Aiolos))) for proteasome destruction.

Products in the second category, the heterobifunctional degraders, are larger and more complex. As their name suggests, these have two separate binding domains, joined by a linker that bind to the protein target and the E3 ligase, like a chain dragging the two together. With heterobifunctional degraders, factors like the length and chemical properties of the linker are important in orientating the two parties together in such a way that they form a stable ternary complex and allows ubiquitination. It was actually first shown back in the early 2000s that a PROTAC (proteolysis-targeting chimeras) could successfully lead to ubiquitination and subsequent protein destruction by the proteasome. However, these first products used a peptide as the E3 ligase ligand making them too unwieldy and unstable to make good drugs. It was not until 2015 that the first small-molecule PROTACs were designed that showed drug-like potential.



Source: Essays Biochem. 2017 Nov 8; 61(5): 505–516

The jury is still out on which approach will prove most successful, and the two types each have their pluses and minuses. Molecular glues already enjoy clinical and market validation but finding targets for novel therapies is expected to be more difficult, while the heterobifunctional degraders may be easier to target but their large size makes them more cumbersome and may cause problems for their delivery.

Who Is Leading The Field?

The potential of TPD is such that there is barely a major pharma company without a program under development, both internal and via partnerships. Bristol Myers Squibb, Pfizer Inc., Sanofi and Novartis AG are most visible in this regard.

Analysts at SVBLeerink note that the wide variety of protein degradation targets and potential indications means that there is plenty of scope for all sorts of players in the area. “Many of the public companies do not have significantly overlapping lead/key opportunities, which we believe continues to facilitate a ‘rising tide’ sentiment,” they said in a 14 October research note.

Analysts at Bernstein add that while the barrier to entry in the field is low ("anyone can link an IMiD to a kinase inhibitor and create an effective degrader"), the complex medicinal chemistry needed to create an effective bifunctional TPD is no trivial matter. "Success with one TPD does not provide high odds of success against other targets, and one would expect differentiation between molecules targeting the same molecule," they said in an 18 February research note. "This is a clear difference between TPD and technologies like mRNA when success of the core technology predicts success against multiple targets; or monoclonal antibodies, where activity is often similar across drugs with the same target."

Almost all of the 30 or so products in the clinic are for cancer indications and, with the exception of the SERDs previously noted, most are still at the early phases (see table below). Various firms may be developing a range of proprietary TPD platform technologies, but there is little, so far, in the way of clinical validation for any of these, and few details are available on those under development by private companies.

Owing mainly to its acquisition of Celgene with its IMiD history, BMS currently takes the most commanding position of all the major firms over the pipeline, with a raft of next-generation IMiDs called CELMoDs (cereblon E3 ligase modulation drugs) in development to target blood cancers, including myeloma as well as immune-mediated diseases.

Of the specialist TPD biotechs, Connecticut-based Arvinas, Inc., founded by one of the inventors of the technology, Craig Crews, is seen as the leader. It is developing proprietary PROTAC protein degraders using its PROTAC Discovery Engine, and has three clinical candidates.

This firm has probably the most clinically validated technology. Its lead product, ARV-471, an estrogen receptor degrader aimed at breast cancer and the subject of a major licensing deal with Pfizer last year, is expected to enter two Phase III clinical trials in 2022, and early data presented at the San Antonio Breast Cancer Conference in December show that it is bidding fair to be a serious contender against the SERDs already in Phase III studies.

Arvinas also has two androgen receptor degraders in the clinic for metastatic castration-resistant prostate cancer (mCRPC): ARV-110 in Phase II and ARV-766 in Phase I.

Further back in the research stage, Arvinas is looking at both cancer, targeting KRAS and myc and hematopoietic progenitor kinase 1 (HPK1), and neuroscience indications, targeting tau for Alzheimer's, alpha-synuclein for Parkinson's and mutant huntingtin for Huntington's disease.

But a number of other TPD specialist firms have entered the clinic, surveyed briefly below:

C4 Therapeutics

Massachusetts-based C4 Therapeutics, Inc. is using its proprietary **TORPEDO** (Target Oriented Protein Degrader Optimizer) platform to develop both molecular glues (what it terms MonoDACs, or monofunctional degradation activating compounds) and heterobifunctional BiDACs (bifunctional degradation activating compounds) for various cancers including solid tumors. It has also signed early-stage collaborations with companies that include Roche Holding AG (cancer) and Biogen, Inc. (neurological).

C4 has one product in the clinic, CFT7455, in Phase I for multiple myeloma and lymphoma targeting IKZF1/3. Initial data from this are expected in the first half of 2022.

Its next most-advanced compound, CFT8634, a degrader targeting BRD9, is on track to start a Phase I study in synovial sarcoma and SMARCB1-null solid tumors also in the first half, while CFT1946, a BRAF V600X degrader, is due to enter Phase I in the second half for BRAF V600X-driven cancers including melanoma, colorectal and non-small cell lung cancers.

Nurix Therapeutics

Nurix Therapeutics, Inc.'s **DELigase** platform allows it to identify small molecules that can not only degrade proteins but also potentially prevent degradation, in a process the California firm calls "targeted protein modulation." Its lead candidate, NX-2127, is in Phase I for B-cell malignancies and degrades BTK and Ikaros family zinc finger 3 inhibitor (Aiolos).

Kymera Therapeutics

Kymera Therapeutics, Inc. has used its **Pegasus** platform to identify the expression profile of nearly 600 E3 ligases across different tissues, and is using this information to match a target protein with the appropriate E3 ligase based on expression, distribution, intracellular localization and biology.

It combines this with biochemical, biophysical, and computational characterization of ternary complexes to prospectively design selective and potent degraders for its targets.

Kymera's initial programs are focused on IRAK4, IRAKIMiD and STAT3, which are each centered on a single critical signaling node within the IL-1R/TLR or JAK/STAT pathways to treat a broad range of immune-inflammatory diseases, hematologic malignancies, and solid tumors. Its lead product, KT-474, targeting IRAK4, is in Phase I for immuno-inflammatory diseases has been licensed to Sanofi in a wider deal (see later). Analysts at Cowen believe the product could provide the Massachusetts-based firm with peak revenues of $1.2bn for atopic dermatitis and hidradenitis suppurativa (in a 24 September 2021 research note).

Dialectic Therapeutics

In October 2021, Texas-based Dialectic Therapeutics, Inc. started a Phase I trial with DT2216, the first-generation compound built using its proprietary Antiapoptotic Protein Targeted Degradation (**APTaD**) technology, in patients with relapsed or refractory solid tumor and hematologic malignancies. It targets BCL-XL, the most commonly over-expressed antiapoptotic protein in cancer.

Six Greater China-based firms have also entered the clinic with TPD products:

Shanghai-based Kangpu Biopharmaceuticals, Ltd. has two molecular glue products in early trials: KPG-818 for a range of blood cancers and KPG-121 for CRPC. Its earlier-stage pipeline is mostly aimed at cancer indications but also has some candidates for auto-immune diseases and inflammatory disorders;

BeiGene, Ltd.is looking at blood cancers including Bruton tyrosine kinase targeting agent for B-cell lymphoma with BGB-16673;

Sino Biopharmaceutical Limited is aiming at non-Hodgkin's lymphoma/myeloma with the IKAROS family zinc finger 2 and 3 degrader TQB-3820;

Haisco Pharmaceutical Group Co., Ltd.'s PROTAC HSK29116 is targeted at BTK kinase to block the B-cell receptor signalling pathway in B-cell lymphoma;

Inventis Bio's D-0502 is a SERD in Phase I for breast cancer; and

Hong Kong-based Kintor Pharmaceutical Ltd.has an AR-PROTAC compound in Phase I.

Targeted Protein Degrader Clinical Pipeline

Drug Name	Company/ Partner	Company Type	Disease	Phase	Target	Type
ARV-110	Arvinas	Public	Prostate Cancer	II	Androgen receptor	Heterobif
ARV-471	Arvinas/Pfizer	Public	Breast Cancer	II	Estrogen receptor 1	Heterobif
iberdomide	Bristol Myers Squibb (Celgene)	Public	Hematological Cancers	II	IKAROS family zinc finger 1 IKAROS family zinc finger 3	Molecula
avadomide (CC-122)	Bristol Myers Squibb (Celgene) BeiGene	Public	Hematological Cancers	II	IKAROS family zinc finger 1 IKAROS family zinc finger 3	Molecula
CC-92480	Bristol-Myers Squibb (Celgene)	Public	Hematological Cancers	II	IKAROS family zinc finger 1 IKAROS family zinc finger 3	Moleucul
CFT-7455	C4 Therapeutics	Public	Non-Hodgkin's Lymphoma/Myeloma	II	IKAROS family zinc finger 1 IKAROS family zinc finger 3	Molecula
KPG-818	Kangpu Biopharmaceuticals	Private	Hematological Cancers	II	Cereblon	-
ARV-766	Arvinas	Public	Prostate Cancer	I	Androgen receptor	Heterobif
BGB-16673	BeiGene	Public	B-Cell Lymphoma	I	Bruton tyrosine kinase	-
AR-LDD targeting therapy, CC-94676	Bristol Myers Squibb	Public	Prostate Cancer	I	Androgen receptor	Heterobif
cK1 alfa degrader	Bristol Myers Squibb	Public	Hematological malignancies	I	CK1a	Molecula
CC-90009	Bristol Myers Squibb (Celgene)	Public	Acute Myelogenous Leukemia/ Myelodysplastic Syndrome	I	G1 to S phase transition 1	Molecula
CC-99282	Bristol Myers Squibb (Celgene)	Public	Chronic Lymphocytic Leukemia / B-Cell Lymphoma/ Non-Hodgkin's Lymphoma	I	IKAROS family zinc finger 1 IKAROS family zinc finger 3	Molecula
DT-2216	Dialectic Therapeutics	Private	Unspecified Solid Cancer	I	BCL2 like 1	Heterobif

Preclinical Companies

Further back in the preclinical pipeline, other specialist TPD companies include Monte Rosa Therapeutics, Inc. (Boston, MA), which is developing a portfolio of novel molecular glue degrader precision medicines via its proprietary protein degradation platform, called **QuEEN** (Quantitative and Engineered Elimination of Neosubstrates). This enables it to rapidly identify protein targets and highly selective molecular glue degrader product candidates. Its lead product is a molecular glue degrader that targets GSPT1, a translational termination factor and degron-containing protein, for the treatment of cancers overexpressing one of the Myc family genes. The Myc transcription factors are some of the most frequently mutated, translocated and overexpressed oncogenes in human cancers.

San Francisco, CA-based Lycia Therapeutics, Inc.'s **LYTAC** (lysosomal targeting chimera) protein degraders are slightly different in that they harness the cell's lysosomal trafficking and degradation pathway to target both soluble and membrane-bound extracellular proteins. It hopes that the technology will target challenging membrane proteins, clear pathogenic immune complexes in circulation and deplete antibodies to specific antigens of interest.

The private Chinese and American firm Ranok Therapeutics Co. Ltd. claims to have developed an innovative, next-generation approach to TPD. Its chaperone-mediated protein degradation/degrader (**CHAMP**) technology takes advantage of different underlying biological processes from other TPD approaches, and has a few unique advantages, including improved safety due to the selective targeting of tumors, the firm says. Ranok's pipeline includes both well-validated and novel drug targets implicated in cancer and other diseases with significant unmet medical needs.

Private San Diego, CA-based Cullgen Inc. is developing a proprietary technology platform, **uSMITE**, that it says is based on recent advances in the science of protein degradation. Cullgen's initial focus is on oncology and immune diseases.

The leading European TPD company is Scotland, UK-based Amphista Therapeutics which is developing several novel mechanisms to remove disease-causing proteins that it says have the potential to overcome many of the limitations seen with current TPD approaches. Its therapeutics, known as **Amphistas**, are being aimed at several hard-to-treat tumor types, but the company claims its approach is also well suited to a wide range of non-oncology indications such as neurological and neurodegenerative conditions, as well as immunology.

What Is The Financial Interest In TPD?

The promise of TPD is evidenced in part by the way it has brought both investors and big pharma to the deal table, resulting in significant investment and number of potential $2bn+ licensing deals.

Some $1.8bn has been plowed into TPD companies by private and public investors over the past two years (see table). Nurix in 2020 and Monte Rosa in 2021 both achieved IPOs priced at more than $200m and follow-on public offerings for Kymera and Arvinas and Kymera topped $250m in 2020 and $430m in 2021, respectively. More is expected to follow.

Targeted Protein Degradation Company Financings 2020-22

Selected company financings from 2020-22, red text links to *Scrip*'s coverage.

Deal Date	Company	Financing Type	Value $m
23 Feb 2022	Plexium	Series B	102
18 Nov 21	Avilar Therapeutics	**Seed**	60
9 Sep 21	Lycia Therapeutics	Series B	70
18 Aug 21	Ranok Therapeutics	**Series B**	40
28 Jun 21	Kymera Therapeutics	**Follow-On Public Offering**	257
23 Jun 21	Monte Rosa	**Initial Public Offering**	222
20 May 21	BioTheryX Announces	**Series E**	92
23 Mar 21	Dunad Therapeutics	**Seed**	5
25 Feb 21	Cullgen	**Series B**	50
22 Dec 20	Neomorph, Inc	Series A	109
14 Dec 20	Arvinas	**Follow-On Public Offering**	432
20 Aug 20	Kymera Therapeutics	**Initial Public Offering**	186
28 Jul 20	BioTheryX	**Series D**	35
23 Jul 20	Nurix	**Initial Public Offering**	209
26 May 20	Monte Rosa	**Series A**	33

Source: Biomedtracker 18 January 2021; Scrip

There has also been some notable licensing deal activity.

Bernstein analysts said that the imperative for big pharma to acquire specialist TPD companies is reduced given that the design of TPDs was not generalizable. Indeed, partnerships with pharma on specific classes has been the general strategy so far. Major players like Pfizer, Eli Lilly, Novartis and Sanofi, have been using their financial firepower to maneuver into a better TPD position via large partnering deals with specialist firms over the last two years or so (see table).

Back in July 2020, Sanofi joined forces with Kymera, agreeing to pay $150m up front for rights to develop and commercialize first-in-class protein degrader therapies targeting interleukin-1 receptor associated kinase 4 (IRAK4) in patients with immune-inflammatory diseases and a second earlier-stage program. Sanofi also agreed to pay more than $2bn in potential development, regulatory and sales milestone fees as well as royalties on sales. (Kymera entered a drug discovery collaboration with GlaxoSmithKline in 2018.)

Sanofi had earlier teamed up with Nurix in January 2020 to develop protein degradation therapies for three specified targets. That deal could be worth more than $2.5bn in all.

But in terms of upfront payments, the largest TPD deal reported to date came in mid-2021 - between Arvinas and Pfizer for the former's Phase II asset, the estrogen receptor targeting PROTAC ARV-471, for $650m cash plus a $350m equity investment.

While it lags the other oral SERDs, the companies insisted that Arvinas's PROTAC approach could make for a best-in-class drug. With Pfizer on board, Arvinas can accelerate the product into Phase III, while Pfizer gains a promising SERD contender that would complement its multi-blockbuster CDK4/6 inhibitor breast cancer therapy, Ibrance (palbociclib). Development will prioritize later lines of HER2-negative/ER-positive breast cancer but could move to early treatment settings as well, including the adjuvant and neoadjuvant settings.

Pfizer also announced a deal last November with Ranok Therapeutics for its CHAMP technology for an unnamed cancer target, though no financial details were disclosed.

Lilly, meanwhile, stumped up $300m cash up front along with an $80m equity investment in Foghorn Therapeutics Inc. in December 2021 for a potentially wide-ranging collaboration, including TPD, that could expand its precision cancer therapy pipeline born out of its Loxo Oncology acquisition. That deal came a few months after it paid Lycia $35m to use its LYTAC protein degradation technology which targets the extracellular proteome, including cell surface receptors and secreted proteins. These deals followed a tie-up with Seed Therapeutics, Inc. in November 2020.

Novartis inked a deal with Cambridge, UK-based Dunad Therapeutics, Ltd. in November 2021 just a few months after the firm emerged from stealth mode. The collaboration is for up to four targets across a variety of therapeutic areas and will use Dunad's plug-and-play mono-valent degrader platform to develop next-generation TPD products. In return, the biotech received $24m in upfront and equity investments and could also enjoy up to $1.3bn in milestones and royalties.

It remains to be seen how the growing number of big pharma firms in the space will shape its future, but analysts reckon further deals are in the offing. Other big pharma firms have signaled interest such as Bayer AG, AstraZeneca and Amgen, Inc.. Last summer, for example, Bayer acquired Vividion Therapeutics, Inc. for $1.5bn up front to get its hands on a pipeline of precision therapeutics targeting traditionally undruggable targets in oncology and immunology that included TPD products, and Amgen signed a $500m+ deal with Plexium, Inc. just last month. (Also see "The Inside Story On How Bayer Swooped On NASDAQ-Bound Vividion" - Scrip, 5 Aug, 2021.)

Targeted Protein Degradation Deals

A summary of company deals from the past 18 months involving targeted protein degradation. Red t
to *Scrip* coverage.

Search

Deal Date	Deal Title	Deal Summary	Potential Deal Value $m	Up Tot
3 Feb 2022	Amgen and Plexium Inc.	**To identify novel targeted protein degradation therapeutics**	$500m+	Un
25 Jan 2022	Monte Rosa Therapeutics and Yeda Research and Development Company	To accelerate the discovery and development of novel covalent molecular glue degraders leveraging CoLDR (covalent ligand-directed release) technology	Undisclosed	Un
18 Jan 2022	Almirall and IRB Barcelona (the Institute for Research in Biomedicine)	A research collaboration to identify new oral treatments for immune-inflammatory skin diseases with remaining high unmet medical needs using molecular glue degraders	Undisclosed	Un
12 Jan 2022	Salarius Pharmaceuticals and DeuteRx	**For an oral, small molecule targeted protein degradation portfolio including the cereblon-binding molecular glue SP-3164 (formerly DRX-164), and the opportunity to develop additional undisclosed targeted protein degradation cancer assets**	358	1.5 sha
10 Jan 2022	Cullinan Oncology with Mount Sinai	A collaboration to develop novel small molecule immune modulators focused on the optimization and development of oral protein degraders targeting hematopoietic progenitor kinase 1 (HPK1)	Undisclosed	Un
13 Dec 2021	Lilly and Foghorn Therapeutics	**A collaboration to create novel oncology medicines by applying Foghorn's proprietary Gene Traffic Control platform, including TPD**	1,680	380
29 Nov 2021	Ranok Therapeutics with Pfizer	**Ranok Therapeutics (Hangzhou) Co. Ltd., to apply and evaluate Ranok's CHAMP (Chaperone-mediated Protein Degradation) platform technology on an undisclosed cancer target**	Undisclosed	Un
2 Nov 2021	Dunad Therapeutics with Novartis	**A collaboration and license agreement with Novartis to generate orally bioavailable covalent and protein degrading small-molecule drugs.**	1,324	24
17 Jun 2020 (updated 26 Oct 2021)	Celgene and Ubiquigent and Celgene; Bristol-Myers Squibb Later Extends Collaboration	Ubiquigent is continuing a previously undisclosed drug discovery collaboration with Bristol Myers Squibb that was originally between Ubiquigent and Celgene, for Ubiquigent's deubiquitylase (DUB) enzyme inhibitor drug discovery platform	Undisclosed	Un
25 Aug 2021	Eli Lilly and Lycia Therapeutics	**A collaboration and licensing agreement focused on the discovery, development, and commercialization of novel targeted therapeutics using Lycia's proprietary lysosomal targeting chimera (LYTAC) protein degradation technology**	1,635	35
		To develop and commercialize products containing ARV-471		

What are the potential problems with TPD?

Despite the promise, questions remain over the technology that need to be answered before it can be deemed likely to reach its potential. Like all drugs, there are some potential downsides to the TPD therapeutic strategy. TPDs are relatively complex drugs, making their design and development potentially trickier.

Despite the hope that protein degraders will prove less susceptible to resistance than more traditional drugs, resistance mechanisms have come into play with Revlimid and other thalidomide analogs. Given the lack of data so far with the newer tranche of candidates, these suggest that problems such as mutations in the E3 ligase or reductions in E3 ligase expression may raise their heads in future.

Another potential issue is their uncertain safety profile and the potential for off- or on-target adverse events – so much is still unknown about the very many E3 ligases that exist, for example.

Also, as analyst Zhiqiand Shu at Berenberg pointed out in a report in April 2021, PROTACs have potential limitations in that they are limited to degrading intracellular proteins only (although LYTACs are being aimed at extracellular and membrane proteins). Plus, they are relatively large and unwieldy which may affect their pharmacokinetics/dynamics leading to potential problems for absorption, metabolism and toxicity.

Then there is the potential for the so-called hook effect – because PROTACs involve the formation of a ternary systems, problems could appear if the concentration of the PROTAC gets too high. When there is too much of one component, the formation of the ternary complexes decreases in favor of binary complexes, reducing the amount of target protein that can be degraded. Whether the doses of PROTACs used in the clinic will be high enough to prompt this scenario is uncertain, however. Molecular glues have an advantage in this regard but are likely to suffer from having a limited number of targets.

Overall, this means that a lot will rest on the early data due to come out this year for a number of the early products.

What Are The Future Catalysts?

At present, TPD as a whole is enjoying the glow of positive sentiment surrounding the field. 2022, however, should see data coming through that will start to differentiate the various technologies, providing an early indicator of which avenues are most promising.

As the Leerink analysts pointed out, “While there are approved protein degraders on the market, many were discovered and approved prior to the understanding of the mechanism of action. Therefore, this validation may be needed for current protein degraders that are developed purposefully with these novel development processes and platforms.”

The biotech with, so far, the most validated technology, Arvinas, plans this year to present data from its ongoing Phase Ib combination study with Ibrance (palbociclib) and from its ongoing Phase II monotherapy dose expansion study of ARV-471, now licensed to Pfizer. It is gearing up to start Phase III trials this year on the back of the Pfizer deal.

A key inflection point identified by Bernstein is the upcoming results of Kymera/Sanofi’s KT-474, targeting IRAK4, against which standard inhibitors struggled. “We would also look for large pharma-partnered assets moving into the clinic, as this would imply an external party being convinced [it had] achieved its target profile. Several of those would suggest broader applicability of the technology” (see table below for other expected catalysts).

Upcoming TPD Data And Pipeline Catalysts

Company	Drug	Data Due In 2022	Trial Starts Planned in 2022
Arvinas	**ARV-471**	Data from the ongoing Phase Ib combination study with Ibrance and from a Phase II monotherapy dose expansion study	Phase III studies across lines of ther metastatic breast cancer, as both monotherapy and in combination
		Present data from the VERITAC Phase II expansion trial (200 and 500mg)	A Phase Ib combination trial with ev in 2L/3L metastatic breast cancer
		-	A Phase II neoadjuvant trial in early l cancer
	ARV-110	Present completed Phase I dose escalation data at ASCO Genitourinary Cancers Symposium (February 2022)	-
		Present interim data from the ARDENT Phase 2 dose expansion (420 mg) at ASCO Genitourinary Cancers Symposium (February 2022)	-
	ARV-110	Announce Phase I dose-escalation data in mCRPC	Initiate Phase II expansion trial in m(
C4 Therapeutics	**CFT7455**	Present initial clinical data from Cohort A of the ongoing Phase I/II trial in relapsed or refractory MM and NHL at a medical meeting in 1H 2022	Progress the CFT7455 Phase I/II tria identifying a recommended Phase II MM and NHL
	CFT8634	-	A Phase I trial in synovial sarcoma a SMARCB1-null solid tumors in 1H
	CFT1946	-	A Phase I trial in BRAF V600X-driven including melanoma, colorectal and 2H
Kymera Therapeutics	**KT-474**	Completes dose escalation in healthy volunteer portion of Phase I trial, plans patient cohort and proof of biology data	-
	KT-253	-	Planned IND filing for the MDM2 deg program in 2H
Nurix	**NX-2127**	Present additional data from Phase Ia in 2H	Initiate the Phase Ib expansion phas ongoing Phase Ia/Ib clinical trial in a relapsed or refractory B-cell maligna mid-year
	NX-5948	Report initial safety and PK/PD data from the Phase Ia portion of a Phase I study in 2H	Expects to begin dosing at multiple c centers in the UK in the ongoing Pha in 1H
Foghorn Therapeutics	**FHD-609**	Expects to have initial Phase I data in synovial sarcoma in 1H	-
Kangpu Pharmaceuticals	**KPG-818**	Data from a Phase Ib/IIa study in SLE due in 2H	-

Where Might The Technology Go Next?

These early data for the new wave of TPD products should set the stage for further innovation, based on the large amount of academic interest in the field, and Berenberg analyst Shu highlighted a few areas he expects to advance into the clinic in the coming years.

These include trivalent PROTACs that can degrade two protein targets, with the added benefit of improved ternary complex stability, and light-activated PROTACs that include photo-removable blocking groups to enable more targeted action.

Another future possibility is improving the target tissue specificity of PROTACs by using them as payloads in antibody-PROTAC conjugates in a manner similar to antibody-drug conjugates. “We view PROTACs as ideal payloads given the low quantity requirement of PROTACs for its catalytic activity in the cell,” Shu said.

It may also be possible to use oligonucleotide-based PROTACs to degrade DNA/RNA binding proteins – targets currently considered undruggable. Many diseases are the result of defects in these binding proteins, but they too have proven intractable to traditional drug development, providing yet more scope for TPD to effect a major change in drug development over the coming years.