Targeted protein degraders

Hijacking cellular degradation pathways to address "undruggable" targets

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Clarivate

Targeted protein degraders

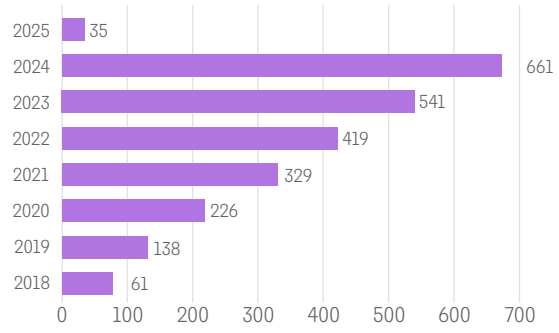
Big pharmaceutical companies are investing heavily in targeted protein degradation (TPD), enabling the elimination of disease-driving proteins previously deemed "undruggable" disease targets, expanding therapeutic possibilities, and generating blockbuster drugs. This emerging modality offers advantages over traditional inhibitors by completely removing harmful proteins rather than merely blocking their activity, enabling broader functional disruption and potential applications in cancer, neurodegenerative diseases, and more.

At the forefront of this innovation are two key E3 ligases: Cereblon (CRBN) and Von Hoppel-Lindau (VHL). These ligases serve as critical molecular tools for PROTACs (proteolysis-targeting chimeras) and molecular glue degraders, which catalytically hijack cellular degradation pathways to treat diseases like cancer, neurodegeneration, and autoimmune disorders.

Von Hoppel-Lindau (VHL) syndrome is a rare disease, affecting one in 36,000 people, characterized by cysts and benign tumors (which may progress to malignancy) and resulting from a mutation in the Von Hippel-Lindau tumor suppressor gene. Cereblon inhibitors, which include thalidomide and its analogues, have taken a winding path to utility as anticancer agents. Thalidomide was pulled from the market in 1961 after its use as an antiemetic in pregnant women revealed teratogenic effects, causing a wave of birth defects. However, it was subsequently found to have anti-angiogenic and anti-inflammatory properties, and was approved for use in multiple myeloma patients by the FDA in 1998.

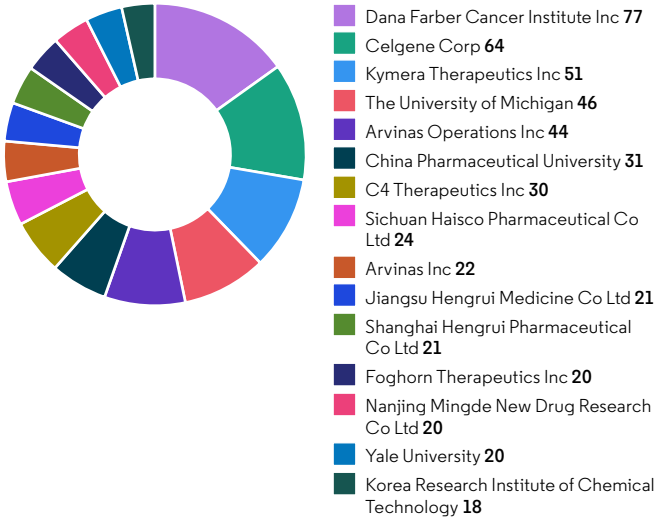
Celebron & VHL are the subject of an increasing number of patent filings

Figure 1: Patent filings related to CRBN and VHL, by publication year



Source: Cortellis Drug Discovery Intelligence

Figure 2: Top patent applicants for drugs targeting CRBN and VHL

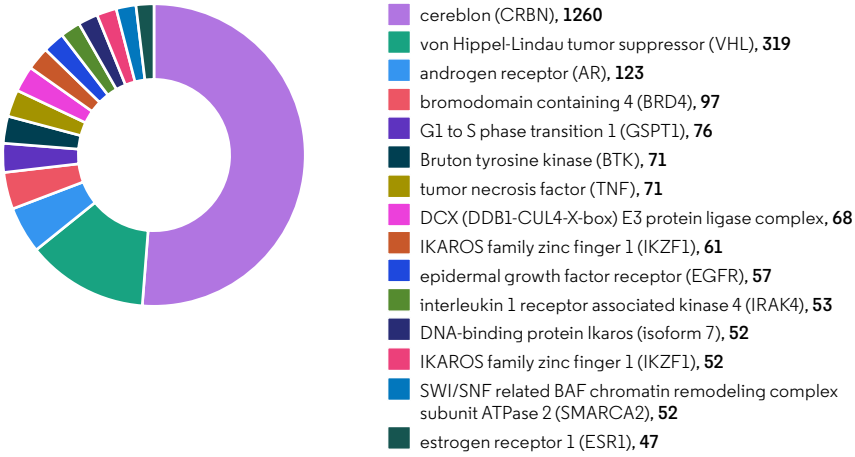


Source: Cortellis Drug Discovery Intelligence

Overcoming undruggable targets: Approximately 80% of human proteins lack binding sites for inhibition by conventional drugs. TPD agents bind to both the E3 ligase and the target, enabling degradation of these targets by recruiting cellular waste-disposal systems, bypassing the need for active-site inhibition.

Catalytic efficiency: Protein degraders like PROTACs act catalytically, meaning a single molecule can destroy multiple copies of a target protein. This allows efficacy at low concentrations, reducing off-target effects. CRBN and VHL are utilized in over 90% of clinical-stage PROTACs due to their strong binding affinities, structural characterization, and broad tissue expression.

Figure 3: Top drug targets relating to CRBN- and VHL-based protein degrader patents



Source: Cortellis Drug Discovery Intelligence

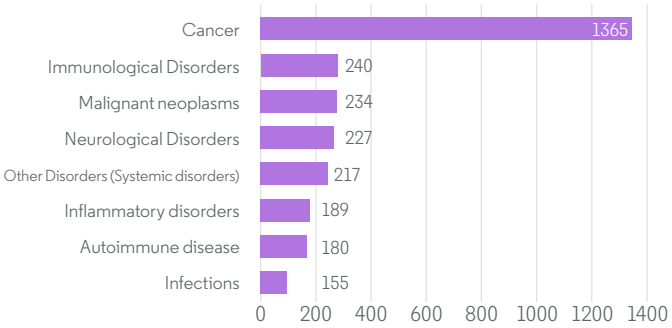
- Binding affinities: CRBN ligands (Kd = 0.5 nM), VHL ligands (VH032 Kd = 80 nM).
- Gene essentiality across cancer cell lines: CRBN non-essential in 1070 lines; VHL essential in 935 lines

Disease Breadth:

TPD's mechanism applies universally across diseases. Current pipelines focus on:

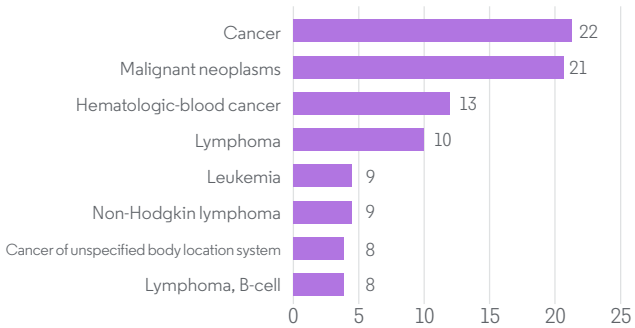
- **Oncology:** CRBN targets like IKZF1/3 and VHL targets like HIF-α drive therapeutic breakthroughs in hematologic malignancies and solid tumors (e.g., breast cancer, multiple myeloma)
- **Neurodegeneration:** CRBN-based degraders show promise against tau and α-synuclein aggregates (e.g., Alzheimer's, Parkinson's).
- **Drug Resistance:** Degradation circumvents resistance mechanisms seen with inhibitors by eliminating target proteins entirely.

Figure 4: Patent filings for drugs targeting CRBN and VHL, by condition



Source: Cortellis Drug Discovery Intelligence

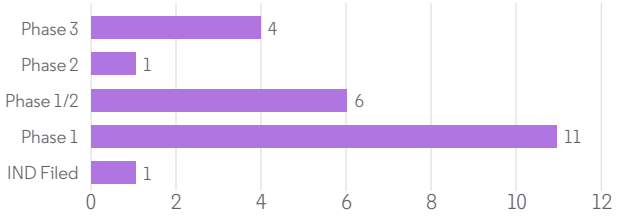
Figure 5: Top conditions for drugs targeting CRBN and VHL under active investigation



Source: Cortellis Drug Discovery Intelligence

Clinical validation:
CRBN-based therapies include FDA-approved IMiDs (e.g., lenalidomide) and advanced PROTACs like ARV-471 (breast cancer). VHL-based therapies include belzutifan, an HIF-2 alpha inhibitor for renal cell carcinoma, and emerging degraders targeting transcription factors like BRD4. Phase 2/3 trials for drugs like Arvinas ARV-471 (breast cancer) and early successes in PROTACs have bolstered confidence.

Figure 6: Pipeline drugs targeting CRBN and VHL, by development phase



Source: Cortellis Drug Discovery Intelligence

Figure 7: Adverse events in traditional inhibitors versus molecular degraders

Traditional inhibitors of cereblon and estrogen receptors tend to produce high toxicity and more adverse events; protein degraders such as vepdegestrant offer greater safety and tolerability

System Organ Class	SOC ID	Designated Medical Event	Cereblon Inhibitors	Cereblon Modulators	Estrogen receptor Modulators	Estrogen receptor Degraders	lenalidomide Launched 2005	vepdege-strant Phase 3
Blood and lymphatic system disorders	10005329	DME	595	63	255	47	414	3
Investigations	10022891		372	19	850	188	163	15
Respiratory, thoracic and mediastinal disorders	10038738	DME	267	17	290	42	158	
Congenital, familial and genetic disorders	10010331	DME	194		144	5	30	
Cardiac disorders	10007541	DME	190	8	233	48	104	2
Immune system disorders	10021428	DME	65	1	47	2	41	
Endocrine disorders	10014698		46	1	58	3	30	
Infections and infestations	10021881	DME	468	61	312	47	315	
Gastrointestinal disorders	10017947	DME	459	34	752	358	255	23
General disorders and administration site conditions	10018065	DME	356	36	523	133	194	10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10029104		251	8	487	3	216	
Metabolism and nutrition disorders	10027433		224	16	340	76	125	5
Musculoskeletal and connective tissue disorders	10028395	DME	167	9	447	113	92	8
Injury, poisoning and procedural complications	10022117		119	6	347	11	82	
Psychiatric disorders	10037175	DME	98		211	17	35	
Renal and urinary disorders	10038359	DME	73		97	6	43	
Hepatobiliary disorders	10019805	DME	60	3	238	16	40	1
Eye disorders	10015919	DME	46	1	271	43	16	2
Pregnancy, puerperium and perinatal conditions	10036585		34		79	5	10	
Ear and labyrinth disorders	10013993	DME	30		30		11	
Reproductive system and breast disorders	10038604		39	1	868	30	6	
Social circumstances	10041244				2			
Surgical and medical procedures	10042613				3			

Heat map based on OFF-X Target/Class Score: Very high, High, Medium, Low, Very low, Not associated

Heat map based on OFF-X Drug Score: Very high, High, Medium, Low, Not associated, Target/class evidence only, Combination evidence only

Lucrative Partnerships

Recent deals include:

Novartis

1.14B

deal with Dunad Therapeutics for oral degraders.

Pfizer

2B

partnership with Arvinas for ARV-471.

Bayer

1.3B

acquisition of Vividion Therapeutics.

Pharmaceutical companies have secured strategic deals to leverage CRBN or VHL E3 ligases for targeted protein degradation platforms.

Bristol Myers Squibb (BMS)

- **CRBN Focus:**
  - Inherited Celgene CRBN expertise through immunomodulatory drugs (IMiDs) like lenalidomide, which degrade IKZF1/3 in multiple myeloma[4,5].
  - Expanded collaboration with Evotec (2023) to develop molecular glue degraders using Evotec proteomics and AI platforms[7].

Merck & Co.

- **VHL Focus:**
  - Advanced belzutifan (Welireg), an FDA-approved HIF-2α inhibitor for VHL-associated tumors, validating VHL pathway targeting[2,3].
  - Developing VHL-based PROTACs leveraging high-affinity ligands like the tool compound VH032 for oncology targets (e.g., KRAS, STAT3)[8,10].

Novartis

- **CRBN Focus:**
  - Partnered with Monte Rosa Therapeutics to develop CRBN-based molecular glues, including MRT-6160 (VAV1 degrader for autoimmune diseases)[1,7].
  - Secured a €1.14B deal with Dunad Therapeutics (2023) for oral degraders targeting CRBN.

Pfizer

- **CRBN Focus:**
  - Partnered with Arvinas to co-develop ARV-471 (a CRBN-based PROTAC for ER+ breast cancer), with Phase III data showing tumor reduction[5,8].
  - Extended collaboration to include ARV-766 (PROTAC targeting androgen receptor in prostate cancer)[5].

Roche

- **CRBN/VHL Access:**
  - Entered a $135M partnership with Vividion Therapeutics (acquired by Bayer) to access its TPD platform, which includes E3 ligase recruitment strategies[9].

Bayer

- **VHL/CRBN Expansion:**
  - Acquired Vividion Therapeutics (2021), inheriting its Roche collaboration and TPD platform focused on undruggable targets via E3 ligases like VHL[9].

Evotec

- **CRBN Expertise:**
  - Collaborates with BMS to systematically discover molecular glue degraders using CRBN, combining proteomics and AI-driven platforms[7].

[1] https://www.certara.com/services/quantitative-systems-pharmacology

[2] https://www.delveinsight.com/blog/von-hippel-lindau-market

[3] https://www.merck.com/news/fda-approves-mercks-hypoxia-inducible-factor-2-alpha-hif-2%CE%B1-inhibitor-welireg-belzutifan-for-the-treatment-of-patients-with-certain-types-of-von-hippel-lindau-vhl-disease

[4] https://www.alacrita.com/blog/targeted-protein-degradation-a-new-pharmacology-paradigm

[5] https://discovery.dundee.ac.uk/files/72865835/2472555220965528.pdf

[7] https://www.evotec.com/partnership-spotlight/pharma

[8] https://pmc.ncbi.nlm.nih.gov/articles/PMC8013866

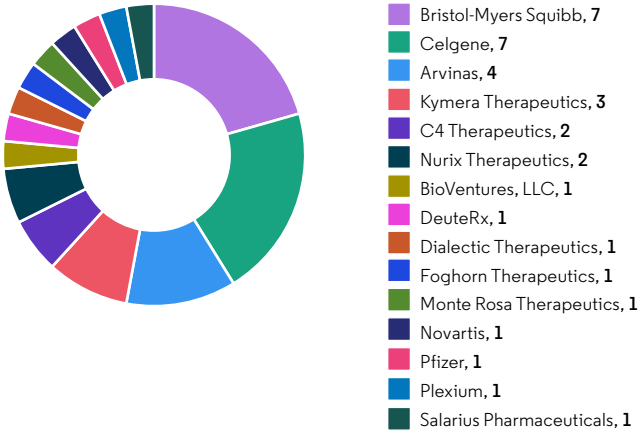
[9] https://njbio.com/targeted-protein-degraders

[10] https://pmc.ncbi.nlm.nih.gov/articles/PMC7614256

Strategic Implications

- **CRBN dominance:** BMS and Pfizer lead in CRBN-based degraders, capitalizing on catalytic efficiency and clinical validation from IMiDs.
- **VHL innovation:** Merck and academic partners (e.g., Ciulli Lab) pioneer VHL ligands for PROTACs targeting hypoxia-related pathways.

Figure 7: Top organization



Source: Cortellis Drug Discovery Intelligence

Table 1: Most active biotech companies in protein degradation

Arvinas	**Focus**: PROTAC-based degraders for oncology and neuroscience. **Pipeline**: ARV-471 (Phase 3 for ER+/HER2- breast cancer) and ARV-766 (Phase 1/2 for prostate cancer). Partnered with Pfizer and Novartis.
C4 Therapeutics	**Focus**: Degraders for cancer via its TORPEDO platform. **Pipeline**: CFT7455 (Phase 1 for multiple myeloma) and collaborations with Merck KGaA and Roche.
Dunad Therapeutics	**Focus**: Oral small-molecule degraders. **Recent Deal:** €1.14B partnership with Novartis for four undisclosed targets.
Booster Therapeutics	**Innovation:** Proteasome activators to broadly degrade misfolded proteins (e.g., in Alzheimer's). **Backing:** €15M seed round led by Novo Holdings.
Monte Rosa Therapeutics	**Focus:** Molecular glues for autoimmune diseases. **Milestone:** Partnered with Novartis on VAV1 degrader MRT-6160[7].
Bristol Myers Squibb	**Strategy:** Extended collaboration with Evotec on degraders for oncology and immunology. **Emerging Trends** **Molecular Glues:** Companies like Neomorph and Degron Therapeutics are advancing small molecules that induce protein-protein interactions for degradation, attracting deals with Biogen and Takeda[7]. **Non-PROTAC Approaches:** LYTACs (lysosome-targeting) and AUTACs (autophagy-targeting) are gaining traction for extracellular and intracellular targets, respectively[6].

With over 15 TPD candidates expected in clinical trials by 2025, this field represents a strategic priority for big pharma seeking first-molecule advantages in high-need therapeutic areas.

[6] https://njbio.com/targeted-protein-degraders

[7] https://www.evotec.com/partnership-spotlight/pharma

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