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# Targeted Protein Degradation (TPD)

EU-IN Horizon Scanning Report

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# Abbreviations

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|---|---|
| ADME | Absorption, Distribution, Metabolism and Excretion |
| AI | Artificial Intelligence |
| AMR | Antimicrobial Resistance |
| ATTEC | Autophagosome-Tethering Compound |
| AUTAC | Autophagy-Targeting Chimera |
| BTK | Bruton's Tyrosine Kinase |
| CELMoD | Cereblon E3 Ligase Modulatory Drug |
| CHMP | Committee for Medicinal Products for Human Use |
| CMC | Chemistry, Manufacturing and Controls |
| CRBN | Cereblon |
| DAC | Degrader-Antibody Conjugate |
| DART | Developmental and Reproductive Toxicity |
| $DC_{50}$ | Degradation Concentration 50% |
| Dmax | Maximum Degradation |
| DMPK | Drug Metabolism and Pharmacokinetics |
| E3 | E3 Ubiquitin Ligase |
| EDR | Exposure-Degradation-Response |
| EMANS | European medicines agencies network strategy |
| ER | Oestrogen Receptor |
| FDA | Food and Drug Administration |
| HESI | Health and Environmental Sciences Institute |
| $IC_{50}$ | Half-Maximal Inhibitory Concentration |
| IKZF | Ikaros family zinc finger proteins |
| IMiD | Immunomodulatory Imide Drug |
| IQ | Innovation and Quality Consortium |
| ITF | Innovation Task Force |
| IVDR | In Vitro Diagnostic Medical Devices Regulation |
| LYTAC | Lysosome-Targeting Chimera |
| mCRPC | Metastatic castration-resistant prostate cancer |
| NAM | New Approach Methodology |
| NDA | New Drug Application |
| NSCLC | Non-small cell lung cancer |
| ODD | Orphan Drug Designation |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PFS | Progression-Free Survival |
| PK/PD | Pharmacokinetics / Pharmacodynamics |
| PRIME | PRIority MEdicines |
| PROTAC | PROteolysis-TArgeting Chimera |
| PTM | Portfolio and Technology Meeting |
| rPFS | Radiographic Progression-Free Survival |
| RIPTAC | Regulated Induced-Proximity Chimera |
| SA | Scientific Advice |
| SERD | Selective Oestrogen Receptor Degrader |
| TPD | Targeted Protein Degradation |
| VHL | Von Hippel–Lindau |

# Glossary

**Induced-proximity therapeutics:** Medicines designed to bring two proteins close together inside a cell so that one can modify, inactivate or eliminate the other.

**Event-driven pharmacology:** A mode of drug action in which the therapeutic effect results from triggering a biological event, rather than from continuous drug presence at the target.

**Ternary complex:** A temporary structure formed when a degrader molecule links a target protein to a cellular degradation enzyme, enabling the target to be marked for removal.

**Hook effect:** A reduction in drug effectiveness at high concentrations, caused by the drug binding proteins separately rather than forming the ternary complex needed for degradation.

**Degradome:** The full set of proteins that are removed from cells following treatment with a protein degrader, including intended targets and unintended proteins.

**Exposure-degradation-response:** The relationship between how much drug reaches the body or tissues, how much of the target protein is removed, and the resulting biological or clinical effect.

# Executive summary

Targeted Protein Degradation (TPD) is an emerging therapeutic modality that removes disease-causing proteins by harnessing endogenous cellular degradation pathways, rather than inhibiting protein function. By enabling elimination of targets previously considered "undruggable" (e.g. transcription factors, scaffolding proteins, and highly homologous targets), TPD represents a shift from occupancy-driven inhibition to event-driven protein removal. This approach may expand the therapeutically tractable target space and create opportunities in disease areas where conventional small molecules or biologics have had limited success.

The most mature TPD modalities are proteolysis-targeting chimeras (PROTACs) and molecular glue degraders, both of which induce selective degradation of target proteins. The first PROTAC has recently received FDA approval and more than 40 TPD candidates are currently in clinical development, predominantly in oncology. Beyond these, additional induced-proximity modalities are emerging and expanding the scope of TPD beyond intracellular proteins, although most remain at the preclinical stage. Regulatory engagement is also increasing, as reflected by growing scientific advice activity and the first TPD candidates entering the EMA PRIME and ODD pathways.

Besides presenting several opportunities, TPD also introduces important challenges. These include formulation and manufacturing complexity, degradome-wide off-target effects, tissue-specific E3 ligase biology, species-dependent toxicities, including the well-established developmental and reproductive toxicity (DART) of immunomodulatory drugs (IMiDs), as many PROTACs incorporate thalidomide analogues, and the clinical implications of event-driven pharmacology, including non-linear exposure–response relationships and dose and schedule optimisation.

This report highlights the need for enhanced EU regulatory preparedness through early regulatory engagement, development of scientific expertise, strengthened evidence generation, and improved visibility of the TPD landscape. Key areas for future attention include off-target safety assessment, DART considerations, biomarker-driven development, and exposure-degradation-response relationships. Coordinated action across the European Medicines Regulatory Network will be important to support consistent assessment and preparedness as TPD-based medicines progress towards broader clinical implementation.

# 1. Rational and objectives of the report

The following horizon scanning report on targeted protein degradation (TPD) supports the early identification of scientific and technological trends that may shape future regulatory and therapeutic landscapes in the European Union. It aims to inform early regulatory preparedness by summarising current scientific, clinical, and industrial developments, identify regulatory challenges and opportunities and address recommendations.

*What is TPD:* TPD represents a rapidly evolving modality that moves beyond classical target inhibition via small molecules to the controlled removal of disease-causing proteins.

*Why now:* The recent first approval of a protein degrader, together with a growing late-stage pipeline, signal increasing regulatory relevance. Clinical development remains predominantly US-led, with Europe contributing through collaborative research and innovation activities. The field is also characterised by strong pharmaceutical partnership activity, multi-billion-euro licensing and collaboration deals, and sustained venture-capital investment. Lastly, TPD has been recognized as a future-shaping technology by EMA in its 2022 horizon scanning report[1], and by the European Innovation Council in its 2024 Technology Report, which identified TPD among 34 emerging technologies with the potential to shape Europe's future competitiveness, reinforcing the strategic value of early regulatory attention in this area[2].

TPD is also beginning to align with a broader One Health agenda as applications extend beyond human therapeutics into agriculture and anti-infectives[3–6]. Early studies in crops, pests and pathogens suggest technical feasibility but raise regulatory questions around species selectivity, environmental fate, off-target ecological effects and cross-sector risk governance. In parallel, growing evidence shows that chemically induced degradation may disable essential microbial proteins and potentiate existing antibiotics, highlighting potential relevance for antimicrobial-resistance (AMR) policy.

Together, these developments signal that TPD may require cross-regulatory coordination across medicinal products, veterinary domains and environmental frameworks. Early monitoring of developments in this field would enable the European Medicines Regulatory Network (EMRN) to:

- identify current and anticipate emerging scientific/regulatory challenges,
- align guidance, and expertise with novel mechanisms of action,
- inform strategic research, funding, and policy priorities, and
- maintain Europe's competitiveness in biomedical innovation.

# 2. Introduction

Targeted protein degradation (TPD) is an emerging therapeutic approach that removes disease-causing proteins by exploiting the cell's own systems, rather than simply inhibiting their activity. This mechanism allows the elimination of targets previously considered "undruggable", such as proteins without a clear binding pocket or enzymatic active site, proteins involved in flat protein-protein interactions, highly homologous targets where selectivity is difficult to achieve, and intrinsically disordered or highly flexible proteins. Although the concept of induced protein degradation was introduced more than two decades ago[7], substantial progress has occurred only in recent years.

### *2.1. Mechanism of action and TPD modalities*

TPD approaches co-opt endogenous protein-degradation machinery to selectively eliminate target proteins. The most established strategies recruit the ubiquitin-proteasome system via E3 ubiquitin ligases, as outlined below (**Figure 1**):

1st *Ternary complex formation*. A degrader brings an E3 ubiquitin ligase into proximity with a protein of interest (POI; neo-substrate), either by physically bridging the POI and ligase or by reprogramming the ligase's substrate specificity.

2nd *Ubiquitination.* Productive geometry enables E2/E3 transfer of ubiquitin on the POI.

3rd *Proteasomal destruction.* The 26S proteasome recognises the ubiquitinated POI and degrades it. The degrader is not consumed, allowing it to turn over multiple POI molecules (event-driven pharmacology).

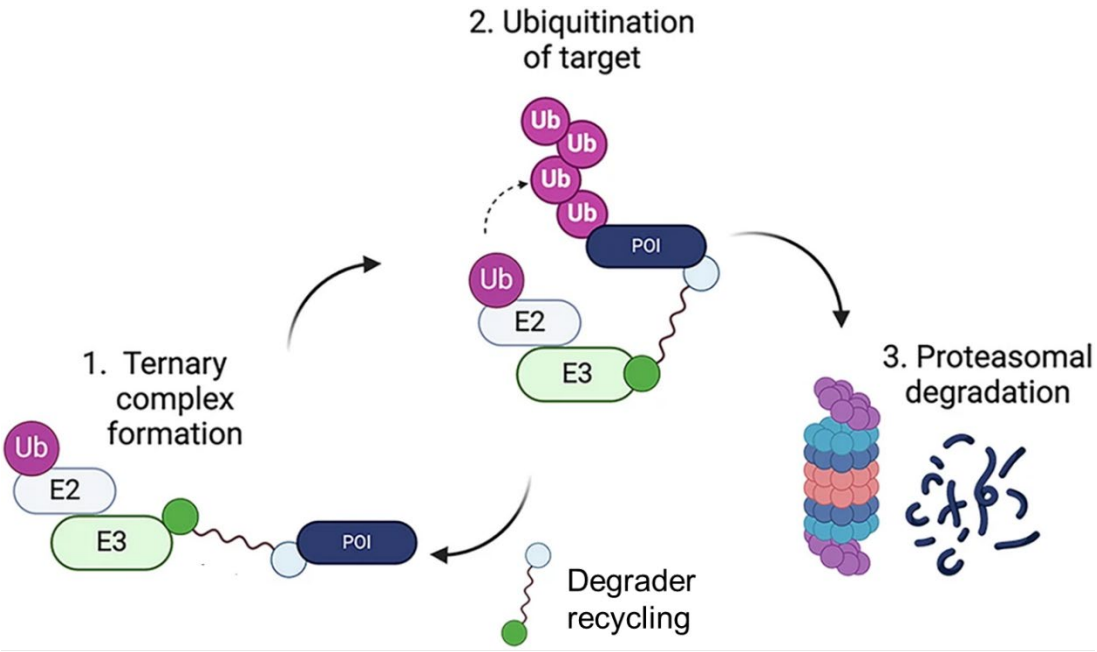


**Figure 1.** Schematic representation of TPDs mode of action. Adapted from [8].

The following paragraphs outline the major modalities of TPDs:

**Proteolysis-targeting chimeras (PROTACs)**

Proteolysis-targeting chimeras (PROTACs) are heterobifunctional small molecules comprising of (i) a binder/pharmacophore to the POI, (ii) a binder/pharmacophore to an E3 ligase, and (iii) a linker connecting them. By forming a ternary complex, PROTACs trigger the subsequent proteasomal degradation of the POI.

At low/moderate concentrations, ternary complex formation is favoured, however, at high concentrations PROTACs can preferentially form individual binary complexes with the target and the E3 ligase, reducing productive ternary complex formation and leading to the so called "hook effect". In addition, many PROTACs lie outside classical Lipinski "Rule of 5" space for orally bioavailable small molecules (e.g. >500 Da, multiple hydrogen bond donors/acceptors, high lipophilicity), underscoring the need to consider non-traditional physicochemical properties and delivery strategies when developing these agents.

**Molecular glue degraders**

Molecular glues, unlike PROTACs, are monovalent small molecules that induce or stabilise an interaction between a target protein and an E3 ligase, leading to ubiquitination and degradation. Key examples come from immunomodulatory imide drugs (IMiDs) such as thalidomide, lenalidomide, and pomalidomide, which bind cereblon and reprogramme its substrate profile to degrade transcription factors (e.g. IKZF1/3), a lethal event in multiple myeloma cells[9,10]. Thalidomide was, therefore, repurposed as a molecular glue degrader after its earlier identification as a teratogenic compound[11]. This observation validated the glue concept and led to next-generation CELMoDs (cereblon E3 ligase modulatory drugs) for cancer therapy.

**Emerging modalities – Induced proximity therapeutics**

Beyond PROTACs and molecular glues, TPD has broadened from proteasome-based strategies to a wider class of chemical and biologic induced-proximity therapeutics. On the small-molecule side, lysosome-targeting chimeras (LYTACs), autophagy-targeting chimeras (AUTACs), autophagosome-tethering compounds (ATTECs) and regulated induced-proximity chimeras (RIPTACs) direct extracellular, membrane and aggregated proteins to endocytic and autophagy-lysosome pathways for clearance[12]. In parallel, biologics-based degraders and degrader-antibody conjugates (DACs) use engineered antibodies and cleavable linkers to deliver degrader payloads with cell-type selectivity or to extracellular compartments. While these modalities remain largely preclinical or in early clinical testing, the broader TPD class is already advancing through multiple late-stage programmes and will bring specific regulatory and clinical challenges[13].

The TPD paradigm introduces new considerations, particularly exposure-degradation-response (EDR) relationships and the influence of E3 ligase biology and tissue distribution.

1. Degraders catalyse target removal via ternary complex formation and ubiquitination, so dose selection and benefit-risk hinge on parameters that extend beyond classical inhibitory concentration (IC) and effective concentration (EC) metrics:
    - $DC_{50}$ (Degradation Concentration 50%): Concentration producing 50% loss of the target protein under defined conditions. Unlike $IC_{50,}$ $DC_{50}$ reflects the dynamics of ternary complex assembly, ubiquitination efficiency, and cellular context.
    - $D_{max}$ (Maximum Degradation): Upper asymptote of target loss achievable in a given system. $D_{max}$ can be limited by E3 ligase abundance, target localisation/accessibility, proteasome capacity, and countervailing proteostasis.
    - $k_{(deg)}$ (Apparent Degradation/Recovery Rate): Composite kinetic descriptor capturing target depletion and resynthesis. $k_{(deg)}$ governs duration of effect relative to plasma exposure and is central to designing continuous vs intermittent regimens.
2. E3 ligases act as catalytic gateways for degradation and are highly context-dependent:
    - *Tissue expression gradients*. Ligase abundance differs across organs, influencing local $D_{max}$ and clinical translatability.
    - *Disease-state modulation.* Inflammation, tumour microenvironments, hypoxia, or differentiation states can up- or down-regulate ligases, altering degrader potency and selectivity in situ.

# 3. Current status and trends

The global field of TPD has progressed from early proof-of-concept to clinical validation. As of 2025, more than 40 TPD-based therapeutics are in human trials across oncology, immunology, and other therapeutic areas (**Tables 1**, **2** and **3, in Annex**). The period from 2019 to 2025 has also seen strong industrial and financial growth, with estimated partnership activity exceeding €30 billion and a further €2 billion raised through venture capital and public offerings[14]. Despite this global expansion, Europe currently accounts for a smaller proportion of clinical development and commercial investment compared either with the United States or China.

This section summarises the clinical development landscape, European investment ecosystem, regulatory interactions and innovation indicators including scientific output, patent activity, and European research funding programmes.

### *3.1. Scientific literature landscape*

The scientific publication output on TPD has expanded markedly in recent years. Across preprint servers such as *bioRxiv* and *medRxiv*, approximately 80,000 items under the search term "targeted protein degradation" are now indexed, including more than 10,000 posted in 2025 alone. The sustained surge since 2020 coincides with the first clinical proof-of-concept for PROTACs and molecular glues. The 2025 peak reflects iterative methodological publications, on screening workflows, assay standardisation, and AI-assisted ternary complex modelling, as well as reports of new E3 ligase ligands and a visible diversification of research beyond oncology into immunology and neurodegeneration.

Peer-reviewed literature shows a complementary trend using the search terms "targeted protein degradation", "PROTAC*", "molecular glue*", "CELMoD*". Since 2015, approximately 3,500 research articles, 1,000 reviews, and 1,000 conference abstracts have been indexed across PubMed and EMBASE. Reviews over this period consolidate best practices in degrader design, proteomics-based off-target profiling, and PK/PD principles for event-driven pharmacology, including management of the hook effect. Abstract analyses from EMBASE also indicate continued conference activity in assay development, E3-ligase diversification and formulation or ADME optimisation for beyond-Rule-of-5 chemotypes[15–18].

### *3.2. Patent landscape*

Patent activity in TPD has increased sharply over the past decade, illustrating the field’s shift from early academic proof-of-concept to broad industrial adoption. Analysis of Espacenet data using core TPD terms (e.g., PROTAC, molecular glue, protein degrader, proximity-induced degradation) show steady acceleration since 2015 (**Figure 2**): annual patent publications grew from 187 in 2015 to 429 in 2019, then more than doubled after 2023 (922 in 2024 and 1018 in 2025). Refer to the method section for more detailed information.

The majority of all Espacenet filings in our search remain chemistry-centric, reflecting early-stage composition and structure protection. Roughly a quarter cover mechanistic or translational uses (e.g., degradation assays, target claims), and about 15% address tooling, formulation, delivery, and next-generation strategies. The IP space is also fragmenting into well-defined layers: (i) composition of matter for PROTACs/glues, (ii) linker chemistry (Innovations in linker design that connect the target-binding moiety to the E3 ligase recruiter), (iii) E3-ligase binders (e.g., CRBN/VHL ligands), and (iv) methods governing ubiquitination and proteasomal routing.

While PROTACs and molecular glues remain the dominant focus, patent diversity has expanded rapidly toward non-proteasomal or alternative degradation routes and proximity-induced ligase platforms.

These newer approaches target extracellular, lysosomal, or aggregate-forming proteins (highlighted in 2.1.3), underscoring a widening therapeutic scope beyond oncology[19].

The United States alone accounts for almost half of all TPD patent publications (~46%), with China the second-largest source (~16%); together they comprise nearly two-thirds of filings (**Figure 2**), while Europe currently contributes mainly through cross-border partnerships and multinational licensing (analysed further in 3.4).

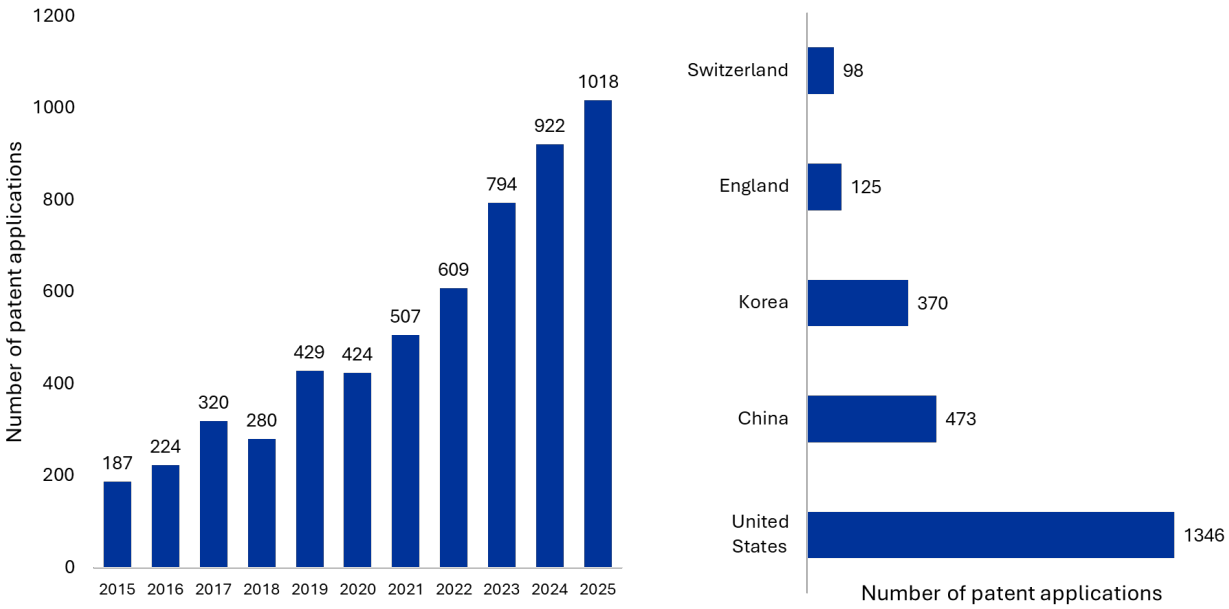


**Figure 2.** Number of TPD-related patent applications by year (left panel) and by applicant country (right panel; only top 5 applicants are shown). Refer to the method section for more detailed information.

### *3.3. Clinical landscape*

Historically, immunomodulatory imide drugs such as thalidomide and its analogues lenalidomide and pomalidomide were the first clinically approved examples of molecular glue degraders acting via the cereblon E3 ligase in haematological malignancies. More recently, the first PROTAC has been approved by the FDA and additional TPD candidates have entered clinical evaluation, with several programmes now in late-stage clinical trials (**Table 1, in Annex**). This expansion is reflected in the distribution of degrader programmes across clinical phases and tumour types, as shown in **Figure 3**.

The most advanced candidate, vepdegestrant, is being developed by Arvinas and Pfizer as an oestrogen-receptor degrader for breast cancer. The pivotal VERITAC-2 trial began in 2023 and received US FDA Fast Track designation in 2024. A new drug application (NDA) was accepted by the FDA in August 2025, with its subsequent approval followed in May 2026. Vepdegestrant represents the first PROTAC-based degrader for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer[20].

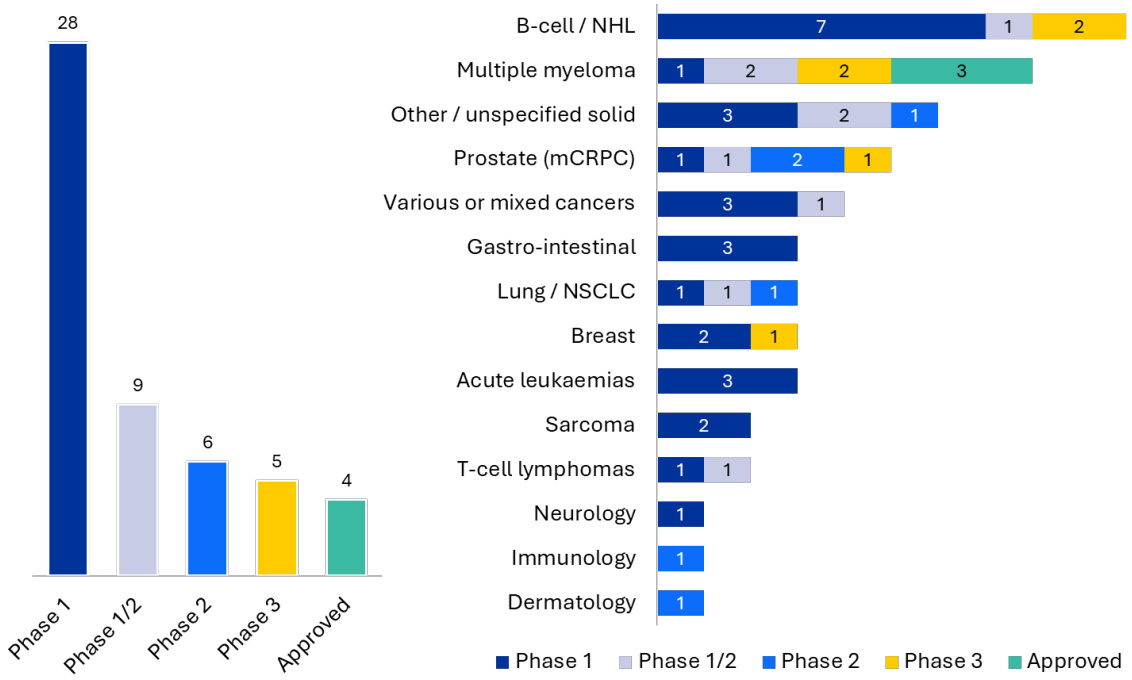


**Figure 3.** Number of degraders per clinical phase (left panel) and tumour type (right panel). The graph includes legacy approved molecular glues (thalidomide, lenalidomide, pomalidomide). Refer to the method section for more detailed information.

Several other late-stage degraders are advancing through Phase 3 development:

- Iberdomide and mezigdomide, both CELMoD molecular glues developed by Bristol Myers Squibb, are under evaluation in pivotal studies (EXCALIBER-RRMM and SUCCESSOR-2) for relapsed or refractory multiple myeloma.
- Catadegbrutinib, a BTK degrader from BeOne (formerly BeiGene), entered a global Phase 3 head-to-head study against pirtobrutinib (CaDAnCe-304) in 2025 for B-cell malignancies.
- Gridegalutamide, an androgen-receptor degrader, is in Phase 3 (rechARge) for metastatic castration-resistant prostate cancer.
- Golcadomide, another CELMoD compound, is in Phase 3 evaluation (GOLSEEK-1) for relapsed or refractory follicular lymphoma.

An analysis of the current TPD clinical landscape reveals a pronounced geographic concentration of development activity within the United States and China, which together account for approximately 75-80% of all identified sponsors. Europe's participation remains limited, primarily represented by early-stage or collaborative programmes rather than EU-originated late-stage development (**Table 2, in Annex**).

This under-representation of European sponsors is not specific to TPD but reflects a broader pattern of reduced regional leadership in emerging modalities, reinforcing the need for coordinated European strategies and incentives to strengthen innovation and competitiveness. The following section highlights EU- and UK-based organisations contributing to the field through discovery research, early-stage development, and partnership-driven innovation.

### *3.4. TPD developing companies in Europe and UK*

European involvement in the TPD clinical pipeline remains largely indirect, occurring mainly through cross-border collaborations, option and licence agreements, strategic equity investments, and asset acquisitions with US and Asia-Pacific developers, rather than through a large number of EU-originated clinical programmes. Within the European Union, a limited but expanding number of companies are advancing TPD research through combinations of public listings, private financing, and industry partnerships. Collectively, these activities reflect a developing but still early-stage ecosystem, characterised by partnership-driven innovation and public-private funding mechanisms (**Table 4** and **5, in Annex**). The examples are illustrative and non-exhaustive, and inclusion does not imply regulatory endorsement or assessment.

Captor Therapeutics (Poland/Switzerland) is currently the only EU-based company with a disclosed clinical-stage TPD programme. The company has raised approximately €40 million in private capital and has entered strategic collaborations with international partners and initiated a Phase 1 clinical trial of its lead candidate, CT-01, in hepatocellular carcinoma in Spain in 2025, following submission of an EU clinical trial application in 2024. This represents one of the first publicly reported degrader programmes initiated by an EU sponsor[21].

Several European entities contribute to TPD development primarily through preclinical discovery and optimisation platforms, often supported by strategic partnerships with global pharmaceutical companies, public funding instruments, and public-private collaborations (refer to section 3.5). In parallel, a number of emerging European developers are expanding the scientific base for next-generation degradation modalities, including approaches targeting extracellular or membrane-associated proteins, proximity-inducing biologics, and alternative degrader architectures (**Table 4, in Annex**). These early-stage efforts are mainly supported by European funding schemes (highlighted in more detail in 3.5).

The United Kingdom represents a distinct European hub for TPD innovation, hosting several biotechnology companies that have attracted substantial international investment and entered large-scale strategic alliances with global pharmaceutical partners. UK-based developers are advancing diverse degradation modalities, including bifunctional PROTACs, monovalent degraders and other induced proximity modalities, with most programmes currently in preclinical or early clinical development.

Overall, the European TPD ecosystem remains smaller and less clinically advanced than those in the United States and parts of Asia. It is characterised by strong scientific capabilities, extensive cross-border collaboration, and reliance on external financing to progress programmes toward clinical maturity. Continued monitoring of these developments is relevant for understanding future regulatory interactions, workload planning and innovation support needs within the European Medicines Regulatory Network.

### *3.5. EU Research funding landscape*

Between 2018 and 2030, Europe has built a broad TPD research base through ERC, Horizon Europe, IMI/IHI, and MSCA programmes, supporting both mechanistic discovery and translational development (**Table 5, in Annex**).

The initiative EUbOPEN, coordinated by Goethe University Frankfurt with a €63.5 million budget, is creating open-access degrader probes and chemogenomic resources[22]. Complementary efforts such as the EU-OPENSCREEN integrate screening infrastructure (although not solely focused to TPD) across nine countries, enabling precompetitive collaboration with industry and expanding access to chemical biology tools and datasets[23]. A network of academic-industrial TPD hubs has also emerged across

Europe, with early centres in Vienna, Dundee, and Basel and newer nodes in Barcelona, Frankfurt, and Lausanne[24]. Each site contributes distinct expertise, forming an interconnected ecosystem that advances proximity-inducing therapeutics. Although collaborations between these hubs have been productive, the next step lies in establishing large-scale, coordinated alliances to link expertise, share infrastructure, and accelerate innovation.

At the project level, ERC grants such as Glue2Degrade, PPI-Glue, PRIGLUE, SWEET DEGRADATION, and PROTAC-PDAC advance molecular glue and PROTAC design (typically €1-2.5 million each), while smaller MSCA and Horizon Europe actions, UBIMOTIF, TRIM-NET, NeoTraCs, support early-stage research and training networks (up to €4 million).

At the commercialization interface, Celeris Therapeutics (Austria) and Captor Therapeutics (Poland) have attracted €15 million and €45 million, respectively, through EIC Accelerator and national innovation programmes, underscoring Europe's growing capacity to translate TPD science into therapeutic impact.

# 4. Regulatory interactions

### *4.1. PRIority MEdicines (PRIME) and orphan designation*

Within the European regulatory framework, only two targeted protein degraders have so far entered formal support pathways such as the PRIority MEdicines (PRIME) scheme or received Orphan Drug Designation (ODD), an indication of both their clinical potential and the regulatory system's early engagement with this modality. The following analysis reflects exclusively public-domain data and does not disclose any confidential, proprietary, or otherwise restricted information.

Notably, catadegbrutinib, a Bruton tyrosine kinase (BTK) degrader and bexobrutideg, a BTK-targeting degrader, have been accepted into the EMA PRIME programme, reflecting their potential to address serious, unmet medical needs in B-cell malignancies. In addition, bexobrutideg has also been granted Orphan Drug Designation (ODD) in the European Union for the treatment of Waldenström's macroglobulinemia, underscoring its relevance for rare hematologic cancers. Lastly, clinical candidate BEA-17 used in glioblastoma is supported by FDA orphan drug designation and a first scientific advisory meeting with the Swedish Medical Products Agency[25].

These designations mark some of the first formal recognitions of TPD modalities within EU regulatory innovation tools, signalling that the modality is transitioning to early regulatory integration, based on details available from public sources.

### *4.2. Scientific advice*

The scientific advice (SA) procedures reflect a proactive effort to align development strategies with EMA standards, particularly in complex or innovative clinical contexts. A total of 23 SA procedures were identified in the Scientific Explorer database regarding TPD drugs, of which 21 were completed and 2 were withdrawn. The data cover the period of 2018 to 2025, showing a steady increase in activity across years. The dataset portrays a regulatory landscape where sponsors are primarily seeking scientific advice to optimise clinical trial designs, strengthen statistical methodologies, and ensure that efficacy and safety evidence will meet regulatory expectations (**Table 6, in Annex**). No confidential or commercially sensitive information is disclosed in this analysis.

### *4.3. Early EMA-developers interactions*

Innovation Task Force (ITF) briefing meetings provide an opportunity for developers to engage in early dialogue with EMA on innovative medicines, technologies and methodologies, through informal

discussions covering scientific, technical and regulatory topics[26]. Portfolio and Technology Meetings (PTMs) are informal meetings for pharmaceutical companies with large product portfolios and aim to identify issues affecting portfolio progress, support successful development and anticipate future scientific and regulatory expertise needs[27]. Between 2020 and 2026, during an ITF briefing meeting one selective oestrogen receptor degrader (SERD; **Box 1**) was discussed, while TPD-based therapeutics were discussed within the oncology portfolios of two large pharmaceutical companies at PTMs.

**Box 1. SERDs and PROTAC ER Degraders**

Selective oestrogen receptor degraders (SERDs) and PROTAC-based ER degraders both aim to suppress ERα signalling in ER+/HER2− breast cancer, particularly in tumours harbouring ESR1 mutations. While they differ mechanistically, SERDs are monofunctional ER antagonists that induce receptor destabilisation, whereas PROTACs are bifunctional molecules that actively recruit the ubiquitin–proteasome system, both are developed as small-molecule chemical medicinal products. Consequently, they are expected to follow largely similar regulatory pathways in the EU and US.

Both SERDs and PROTAC ER degraders are assessed under the centralised procedure in the EU. Approved SERDs and those with positive regulatory opinions could provide regulatory precedent for biomarker-enriched indications, trial design, and companion diagnostic strategies relevant to PROTAC ER degraders.

Approved and late-stage SERDs:

| Drug | Indication | Regulatory status |
|---|---|---|
| Elacestrant (Orserdu) | ER+/HER2− metastatic breast cancer with ESR1 mutation | EU centrally authorised (Sept 2023); US FDA approved (Jan 2023) |
| Imlunestrant (Inluriyo) | ER+/HER2− metastatic breast cancer with ESR1 mutation | EU CHMP positive opinion (Nov 2025) |
| Camizestrant | ER+/HER2− advanced breast cancer | Phase 3 |
| Giredestrant | ER+/HER2− advanced breast cancer | Phase 3 |
| Amcenestrant | ER+/HER2− breast cancer | Phase 3 (development discontinued due to efficacy issues) |

# 5. Challenges and opportunities

### *5.1. Quality and formulation*

CMC and formulation aspects of TPDs are primarily relevant where they affect clinical interpretability, labelling, and lifecycle management, rather than because of intrinsic chemical novelty.

PROTAC-based degraders are typically larger and more polar than molecular glues and frequently fall outside conventional small-molecule property space. Early candidates therefore showed limited oral exposure and, in some cases, required non-oral administration. Subsequent development has focused

on enabling formulations, scaffold optimisation, and prodrug strategies to achieve clinically meaningful exposure[28].

Low solubility and limited permeability are recurrent features of PROTACs and often necessitate fed-state dosing to increase exposure sufficiently to enable pharmacodynamic activity[29]. From a regulatory standpoint, such strategies raise questions about the consistency between clinical-trial conditions and the proposed conditions of use, and whether exposure achieved under controlled settings can be reproduced in routine clinical practice.

### *5.2. Nonclinical safety and off-target effects*

A key challenge for TPDs concerns mechanism-linked and class-effect toxicities arising from unintended protein degradation. Although TPDs explain a distinct mechanism of action for thalidomide and other IMiDs, many PROTACs continue to use thalidomide analogues as part of their molecular design. As a result, the known developmental and reproductive toxicity associated with thalidomide remains an important consideration for non-clinical safety assessment and risk management.

Because E3 ligases are not tissue-specific, degraders may induce loss of proteins in healthy tissues, resulting in clinically relevant toxicity. This issue is well recognised for cereblon-recruiting degraders derived from immunomodulatory scaffolds (e.g. thalidomide analogues), which can promote degradation of multiple off-target proteins and drive toxicity, including immunosuppression[30]. Clinical experience with mezigdomide illustrates the importance of linking non-clinical degradome findings with clinical risk management. In early studies, sustained degradation of Aiolos was associated with dose-limiting neutropenia under continuous dosing. Introducing an intermittent regimen enabled bone-marrow recovery while maintaining activity[31]. This experience highlights that the duration and reversibility of degradation may be as important as dose level when assessing safety.

A further issue is potential diversion of E3 ligases from physiological substrates. Prolonged engagement of an E3 on a neo-substrate could, in principle, stabilise native substrates and perturb proteostasis. This risk has been postulated for VHL- or IAP-recruiting agents, although definitive *in vivo* pathology remains limited, it warrants attention in hazard identification and biomarker planning.

Species translation represents a further challenge. Cereblon-binding agents have species-dependent teratogenicity[32], which needs to be considered in the selection of models for evaluation of potential embryo-fetal developmental toxicity based on ICH S5(R3). Given class history, enhanced teratogenicity precautions are common even in late-line oncology. Differences in target biology across species may further constrain interpretation, reinforcing the need for cautious extrapolation.

TPDs present specific evidence-generation challenges because their activity depends on a multi-step process, cellular uptake, target and E3 ligase engagement, ternary-complex formation, ubiquitination and subsequent proteasomal clearance. Each step may be rate-limiting and is not adequately characterised by single assay readouts. Non-linear features such as the hook effect further limit reliance on occupancy-based pharmacology. Consequently, development programmes should include orthogonal methods (e.g. biophysical assays, structural confirmation, proteomics and live-cell degradation kinetics) to demonstrate on-target ternary-complex formation, selective ubiquitination and sustained target loss. Emerging data also indicate that in-vitro degradation does not consistently predict in-vivo performance due to beyond-rule-of-5 ADME, high protein binding and linker or metabolite liabilities[33]. These factors highlight the need for comprehensive DMPK evaluation, metabolite profiling and integration of exposure-degradation-response assessments to support robust dose selection and risk evaluation (**Box 2**).

### *5.3. Clinical development*

For TPDs adequate systemic exposure is typically required to achieve sufficient tissue concentrations for effective degradation. Dose and schedule optimisation therefore often needs to consider target turnover and recovery kinetics in addition to plasma pharmacokinetics[31,34]. Clinical regimens may be therefore adapted to manage schedule-dependent toxicity while maintaining disease control.

There are challenges associated with endpoints and biomarkers for patient selection and/or pharmacodynamic confirmation. Where biomarkers inform treatment decisions or efficacy interpretation, their analytical robustness and clinical integration become central considerations; in the EU, readiness of any required IVD (including under IVDR) can represent a development risk.

Selection of clinically meaningful primary endpoints is closely linked to these considerations. Surrogate endpoints such as progression-free survival (PFS), radiographic PFS (rPFS) or objective response rate (ORR) require appropriate contextualisation, particularly where overall survival (OS) remains a key outcome in the proposed setting. Open-label designs, limited blinding (including in all-oral regimens), and heterogeneity from broad inclusion criteria or multiple prior-therapy settings can further affect the interpretability of efficacy.

Similarly, the alignment between trial population and intended indication becomes particularly relevant for TPDs, given their mechanism-dependent effects and frequent development in molecularly defined subpopulations. While enrichment strategies can strengthen biological plausibility, they may limit generalisability; consistency of effects across clinically relevant subgroups is therefore an important consideration.

Lastly, across scientific advice interactions, comparator selection is a recurrent challenge. For TPDs, this is amplified by rapidly evolving standards of care and increasing molecular stratification. The use of outdated or suboptimal comparators may limit interpretability of clinical benefit and complicate benefit–risk assessment.

### *5.4. Regulatory frameworks, classification and guidance gaps*

Currently, TPDs are regulated in the EU as chemical medicinal products, and no modality-specific framework exists. Emerging hybrid approaches, such as degrader-antibody conjugates, may challenge existing assessment paradigms and are likely to require cross-disciplinary review analogous to antibody-drug conjugates. As of 2025, clinical experience with such hybrids remains limited, and none has progressed beyond Phase 1 development[35,36]. Emerging hybrid or purely biologic TPD modalities may raise additional classification and assessment questions in the future.

Platform-technology elements are increasingly referenced by applicants (e.g. shared E3 ligase binders, linker chemistries, or delivery approaches). Whether such approaches can be considered a regulatory platform remains unclear. Any platform-based reasoning would need to demonstrate predictable quality, safety, and performance across assets, supported by appropriate bridging data.

Finally, there is no dedicated EU-wide mechanism to identify and track TPD clinical trials as a modality class. Improved tracking could support horizon scanning, promote consistency in scientific advice, and strengthen regulatory preparedness as the field matures.

**Box 2. Ongoing efforts to harmonise safety assessment for targeted protein degraders (TPDs)**

Several multi-stakeholder initiatives are underway to harmonise the evaluation and safety assessment of targeted protein degraders. These collaborative efforts aim to establish shared scientific principles for non-clinical study design, chemistry-manufacturing-control (CMC) characterisation, and translational safety evaluation across industry, academia, and regulatory stakeholders[37].

- Health and Environmental Sciences Institute (HESI) (2022–2024). Community statement and workshops advocating standardised toolkits, endpoints, and comparative datasets (DART, degradome profiling, PK/PD translation)[38].
- IQ Consortium Protein Degrader Working Group (2023). Industry perspective on modality-specific toxicology (event- vs occupancy-driven pharmacology, degradome characterisation) and adaptations to study design/decision trees[39].
- Professional societies (Society of Toxicology/American College of Toxicology, 2024). Sessions on substrate selectivity, degradome mapping, and biomarkers of target loss to benchmark internal risk registers[40].
- IQ Consortium (DruSafe/Translational & ADME): "Points to Consider" for CRBN-engaging degraders (2025). Practical recommendations to mitigate teratogenicity risk (e.g. SALL4-focused assays), off-target screening, and documentation of risk controls in submissions[41].
- PROXIDRUGS (EU) white paper (2025). Discussion of CMC and delivery evolution for degrader-antibody conjugates (DACs); promotes shared development standards (non-regulatory but informative for EU stakeholders)[42].

These initiatives collectively support the development of common scientific standards for non-clinical safety evaluation of TPDs. Their outputs can inform regulatory strategy, guide dossier preparation, and enhance alignment between innovators and assessors as the modality progresses toward routine clinical application.

# 6. Recommendations

Guidance:

- Promote early and proactive regulatory engagement, particularly through Innovation Task Force (ITF), Portfolio and Technology Meetings (PTM), and Scientific Advice, to support early-stage developers and align development strategies with regulatory expectations[43].
- Develop scientific and regulatory considerations for TPD assessment, covering exposure-degradation-response, off-target degradation, biomarkers, endpoints and comparator selection.

Evidence generation:

- Strengthen non-clinical risk assessment approaches, including systematic proteomic profiling to characterise off-target effects and early use of New Approach Methodologies (NAMs), such as human-relevant in vitro models, to identify toxicology risks.
- Focus on DART considerations, particularly for cereblon-recruiting degraders, and encourage appropriate species selection and precautionary measures.

Training:

- Provide training opportunities within the EU Network Training Centre for assessors at NCAs on TPD specific non-clinical and clinical safety and efficacy endpoints not readily measurable with available standard tests.
- Use the European Platform for Regulatory Science Research to identify evidence gaps and promote EU research addressing regulatory needs.
- Use recurring issues from ITF/PTM/SA interactions to inform training.

Stakeholder engagement:

- Support integration of TPD into the EU regulatory ecosystem, to strengthen innovation capacity and competitiveness.
    - Enable active engagement with European biotech hubs and technology transfer offices.

Data infrastructure:

- Improve EU-level tracking and visibility of TPD clinical trials to support horizon scanning, consistency in scientific advice, and regulatory preparedness as the field evolves.

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# 8. Methods

Espacenet patent search: We queried Espacenet to identify patent publications related to TPD using the following query: ta=( PROTAC* OR "proteolysis targeting chimera*" OR "proteolysis-targeting chimera*" OR "targeted protein degrad*" OR "protein degrad*" OR "molecular glue*" OR "molecular gluer*" OR ("induced proximity" OR "proximity induced" OR "proximity-induc*") OR (degrad* prox/distance<3 (protein OR target* OR ubiquitin)) OR "E3 ligase recruit*" OR "E3 ligase binding" OR "E3 recruitment" OR "ternary complex" OR "ternary complex formation" OR LYTAC* OR DUBTAC* OR AUTAC* OR ATTEC* OR AbTAC* OR KineTAC* OR PHOTAC* OR PROTAB* OR "bioPROTAC*" OR "bio-PROTAC*" OR bioTPD OR TRIM21 OR "TRIM21-based" OR VIPERTAC* OR CELMoD* OR AceTAC* OR PhosTAC* ). A publication-date filter was then applied (2015-01-01 to 2025-12-31). Result counts were taken directly from Espacenet and exported at publication level. The search yielded 2,903 records

in total (as of 22 January 2026); annual counts were 2015, 187; 2016, 224; 2017, 320; 2018, 280; 2019, 429; 2020, 424; 2021, 507; 2022, 609; 2023, 794; 2024, 922; 2025, 1018. By applicant country, top contributors were United States 1,346; China 473; Korea 370; England 125; Switzerland 98.

Scientific advice search: Scientific advice and protocol assistance records were retrieved from the EMA internal database using Scientific Explorer. The search was restricted to records containing an entry for active substance other names (synonyms/alternative identifiers): ABBV-787, AC176, AC676, AC682, AC699, AR-LDD, ARV-102, ARV-110, ARV-393, ARV-471, ARV-766, ASP3082, ASP4396, Avadomide, Bavdegalutamide, BAY-2666605, BEA-17, BGB-16673, BMS-986348, BMS-986365, BMS-986497, BTX-1188, bexobrutideg, BTR-701, Catadegbrutinib, CC-122, CC-220, CC-90009, CC-92480, CC-94676, CC-99282, CFT-1946, CFT-7446, CFT-7455, CFT-8634, CFT-X114, CG00149, CT-01, DKY-709, DT2216, E7070, E7820, FD-001, FHD-609, GLB-002, golcadomide, Gridegalutamide, GT-919, GT20029, HP518, HSK29116, Iberdomide, ICP-490, Indisulam, KT-253, KT-333, KT-413, KT-474, KT-621, Lenalidomide, Luxdegalutamide, mezigdomide, MRT-2359, NST-628, NVP-DKY709, NX-2127, NX-2128, NX-2323, NX-5948, ORM-5029, ORM-6151, PF-07850327, PLX-4545, Pomalidomide, PRT3789, RMC-6291, RNK05047, SP-3164, Thalidomide, vepdegestrant, Zelebrudomide. For each record, descriptive variables were extracted where available. Results were summarised, without any confidential content from individual advice dossiers being disclosed.

ClinicalTrials.gov search: We queried ClinicalTrials.gov to identify clinical studies of TPD agents using a pre-specified panel of active substances. Recruitment statuses included: Recruiting, Active, not recruiting, Enrolling by invitation, Not yet recruiting, Completed, No longer recruiting; excluded: Terminated, Withdrawn, Suspended, Unknown status (Query 1). An EU subset was generated by filtering for study locations in EU/EEA/UK countries (Austria-United Kingdom; Query 2). The search yielded (as of 22 January 2026) 1,224 studies globally of which 335 listed European sites. Query 1**:** (Thalidomide OR Thalomid OR Lenalidomide OR Revlimid OR Pomalidomide OR Pomalyst OR Vepdegestrant OR "ARV-471" OR "PF-07850327" OR Iberdomide OR "CC-220" OR Mezigdomide OR "CC-92480" OR Golcadomide OR "CC-99282" OR Catadegbrutinib OR "BGB-16673" OR Gridegalutamide OR "CC-94676" OR "AR-LDD" OR Bavdegalutamide OR "ARV-110" OR Luxdegalutamide OR "ARV-766" OR "KT-474" OR E7820 OR Indisulam OR E7070 OR "GT-20029" OR "PRT3789" OR DT2216 OR HP518 OR "RMC-6291" OR "ICP-490" OR "CFT-7455" OR "MRT-2359" OR CG00149 OR RNK05047 OR Avadomide OR "CC-122" OR Zelebrudomide OR "NX-2127" OR "DKY-709" OR "ARV-102" OR bexobrutideg OR "NX-5948" OR "NX-2128" OR "CFT-1946" OR "CFT-8634" OR "NST-628" OR "ORM-6151" OR "BMS-986497" OR "FHD-609" OR "FD-001" OR "GLB-002" OR "ORM-5029" OR HSK29116 OR "KT-413" OR "KT-333" OR AC699 OR AC682 OR AC176 OR AC676 OR ASP3082 OR ASP4396 OR "KT-253" OR "GT-919" OR "BTX-1188" OR "PLX-4545" OR "ARV-393" OR "SP-3164" OR "CT-01" OR "CC-90009" OR "NX-2323" OR "BTR-701" OR "KT-621" OR "CFT-7446" OR "CFT-X114" OR "ABBV-787" OR "BEA-17" OR "BMS-986365" OR "NVP-DKY709" OR "BAY-2666605" OR "BMS-986348") AND ("Recruiting" OR "Active, not recruiting" OR "Enrolling by invitation" OR "Not yet recruiting" OR "Completed" OR "No longer recruiting") AND NOT ("Terminated" OR "Withdrawn" OR "Suspended" OR "Unknown status"). Query 2: (Thalidomide OR Thalomid OR Lenalidomide OR Revlimid OR Pomalidomide OR Pomalyst OR Vepdegestrant OR "ARV-471" OR "PF-07850327" OR Iberdomide OR "CC-220" OR Mezigdomide OR "CC-92480" OR Golcadomide OR "CC-99282" OR Catadegbrutinib OR "BGB-16673" OR Gridegalutamide OR "CC-94676" OR "AR-LDD" OR Bavdegalutamide OR "ARV-110" OR Luxdegalutamide OR "ARV-766" OR "KT-474" OR E7820 OR Indisulam OR E7070 OR "GT-20029" OR "PRT3789" OR DT2216 OR HP518 OR "RMC-6291" OR "ICP-490" OR "CFT-7455" OR "MRT-2359" OR CG00149 OR RNK05047 OR Avadomide OR "CC-122" OR Zelebrudomide OR "NX-2127" OR "DKY-709" OR "ARV-102" OR bexobrutideg OR "NX-5948" OR "NX-2128" OR "CFT-1946" OR "CFT-8634" OR "NST-628" OR "ORM-6151" OR "BMS-986497" OR "FHD-609" OR "FD-001" OR "GLB-002" OR "ORM-5029" OR HSK29116 OR "KT-413" OR "KT-333" OR AC699 OR AC682 OR AC176 OR AC676 OR ASP3082 OR

ASP4396 OR "KT-253" OR "GT-919" OR "BTX-1188" OR "PLX-4545" OR "ARV-393" OR "SP-3164" OR "CT-01" OR "CC-90009" OR "NX-2323" OR "BTR-701" OR "KT-621" OR "CFT-7446" OR "CFT-X114" OR "ABBV-787" OR "BEA-17" OR "BMS-986365" OR "NVP-DKY709" OR "BAY-2666605" OR "BMS-986348") AND ("Recruiting" OR "Active, not recruiting" OR "Enrolling by invitation" OR "Not yet recruiting" OR "Completed" OR "No longer recruiting") AND NOT ("Terminated" OR "Withdrawn" OR "Suspended" OR "Unknown status" ) AND ("Austria" OR "Belgium" OR "Bulgaria" OR "Croatia" OR "Cyprus" OR "Czechia" OR "Czech Republic" OR "Denmark" OR "Estonia" OR "Finland" OR "France" OR "Germany" OR "Greece" OR "Hungary" OR "Iceland" OR "Ireland" OR "Italy" OR "Latvia" OR "Liechtenstein" OR "Lithuania" OR "Luxembourg" OR "Malta" OR "Netherlands" OR "Norway" OR "Poland" OR "Portugal" OR "Romania" OR "Slovakia" OR "Slovenia" OR "Spain" OR "Sweden" OR "Switzerland" OR "United Kingdom" OR "UK" OR "England" OR "Scotland" OR "Wales" OR "Northern Ireland").

# 9. Annex

**Table 1.** Clinical landscape of TPD modalities including sponsor, country and indication/therapeutic area (non-exhaustive list).

| Drug | Sponsor (Country) | Lead Indication / Therapeutic Area | Phase |
|---|---|---|---|
| Thalidomide (Thalomid) | Bristol Myers Squibb / Celgene (USA) | Multiple myeloma | Approved (1998) |
| Lenalidomide (Revlimid) | Bristol Myers Squibb / Celgene (USA) | Multiple myeloma | Approved (2005) |
| Pomalidomide (Pomalyst) | Bristol Myers Squibb / Celgene (USA) | Multiple myeloma | Approved (2013) |
| Vepdegestrant (ARV-471) | Arvinas / Pfizer (USA) | Breast cancer | Approved (FDA, 2026) |
| Iberdomide (CC-220) | Bristol Myers Squibb / Celgene (USA) | Multiple myeloma / solid tumours | Phase 3 |
| Mezigdomide (CC-92480) | Bristol Myers Squibb / Celgene (USA) | Multiple myeloma | Phase 3 |
| Golcadomide (CC-99282) | Bristol Myers Squibb / Celgene (USA) | Lymphoma | Phase 3 |
| Catadegbrutinib (BGB-16673) | BeiGene (China) | Relapsed/refractory CLL/SLL | Phase 3 |
| Gridegalutamide (CC-94676, BMS-986365) | Bristol Myers Squibb (USA) | mCRPC (Prostate cancer) | Phase 3 |
| Bavdegalutamide (ARV-110) | Arvinas / Pfizer (USA) | mCRPC (Prostate cancer) | Phase 2 |
| Luxdegalutamide (ARV-766) | Arvinas / Novartis (USA / Switzerland) | mCRPC (Prostate cancer) | Phase 2 |

| Drug | Sponsor (Country) | Lead Indication / Therapeutic Area | Phase |
|---|---|---|---|
| KT-474 | Kymera Therapeutics / Sanofi (USA / France) | Immune-inflammatory (HS, AD) | Phase 2 |
| E7820 | Eisai, Inc. (Japan / USA) | Solid tumours / myeloid malignancies | Phase 2 |
| GT-20029 | Kintor Pharmaceuticals (China) | Acne vulgaris, androgenetic alopecia | Phase 2 |
| PRT3789 | Prelude Therapeutics (USA) | SMARCA4-del NSCLC | Phase 2 |
| DT2216 | Dialectic Therapeutics / Univ. of Florida (USA) | R/R PTCL and CTCL | Phase 1/2 |
| HP518 | Hinova Pharmaceuticals (China) | mCRPC (Prostate cancer) | Phase 1/2 |
| RMC-6291 | Revolution Medicines (USA) | Solid tumours (KRAS G12C) | Phase 1/2 |
| ICP-490 | InnoCare Pharma (China) | Multiple myeloma | Phase 1/2 |
| CFT-7455 | C4 Therapeutics (USA) | Multiple myeloma, NHL | Phase 1/2 |
| MRT-2359 | Monte Rosa Therapeutics (USA / CH) | Lung and other MYC-driven solid tumours | Phase 1/2 |
| CG00149 | Cullgen (USA / China) | Solid tumours | Phase 1/2 |
| RNK05047 | Ranok Therapeutics (USA / China) | DLBCL | Phase 1/2 |
| Avadomide (CC-122) | Bristol Myers Squibb / Celgene (USA) | Various cancers (DLBCL, solid tumours, etc.) | Phase 1/2 |
| Zelebrudomide (NX-2127) | Nurix Therapeutics (USA) | B-cell malignancies | Phase 1a/1b |
| DKY-709 | Novartis (Switzerland) | Solid tumours | Phase 1/1b |
| ARV-102 | Arvinas (USA) | Neurological (Parkinson’s disease, PSP) | Phase 1/1b |
| Bexobrutideg (NX-5948) | Nurix Therapeutics (USA) | B-cell malignancies | Phase 1 |
| CFT-1946 | C4 Therapeutics (USA) | NSCLC, colorectal cancer, melanoma | Phase 1 |
| CFT-8634 | C4 Therapeutics (USA) | Synovial sarcoma, SMARCB1-null tumours | Phase 1 |
| NST-628 | Nested Therapeutics (USA) | Solid tumours (RAF–MEK pathway) | Phase 1 |

| Drug | Sponsor (Country) | Lead Indication / Therapeutic Area | Phase |
|---|---|---|---|
| ORM-6151 | Orum Therapeutics (USA / Korea) | Acute myeloid leukaemia | Phase 1 |
| FHD-609 | Foghorn Therapeutics (USA) | Synovial sarcoma, SMARCB1-loss tumours | Phase 1 |
| FD-001 | Chengdu Fendi Pharmaceutical (China) | AML, NHL, MM | Phase 1 |
| GLB-002 | GluBio Therapeutics (China) | R/R non-Hodgkin lymphoma | Phase 1 |
| ORM-5029 | Orum Therapeutics (USA / Korea) | HER2+ solid tumours | Phase 1 |
| HSK29116 | Haisco Pharmaceutical (China) | B-cell lymphoma / neoplasm | Phase 1 |
| KT-413 | Kymera Therapeutics (USA) | MYD88-mutant B-cell lymphomas | Phase 1 |
| KT-333 | Kymera Therapeutics (USA) | CTCL, NHL, PTCL | Phase 1 |
| AC699 | Accutar Biotech (USA / China) | Breast cancer | Phase 1 |
| AC682 | Accutar Biotech (USA / China) | ER+ breast cancer | Phase 1 |
| AC176 | Accutar Biotech (USA / China) | mCRPC (Prostate cancer) | Phase 1 |
| AC676 | Accutar Biotech (USA / China) | Hematology & oncology | Phase 1 |
| ASP3082 | Astellas (Japan) | Pancreatic, colorectal, lung (KRAS G12D) | Phase 1 |
| ASP4396 | Astellas (Japan) | Colorectal and pancreatic cancer | Phase 1 |
| KT-253 | Kymera Therapeutics (USA) | ALL, AML, solid tumours | Phase 1 |
| GT-919 | Gluetacs Therapeutics (USA) | Multiple myeloma | Phase 1 |
| BTX-1188 | Biotheryx (USA) | Hematologic & solid malignancies | Phase 1 |
| PLX-4545 | Plexium (USA) | Various cancers | Phase 1 |
| ARV-393 | Arvinas (USA) | NHL, AITL | Phase 1 |

| Drug | Sponsor (Country) | Lead Indication / Therapeutic Area | Phase |
|---|---|---|---|
| SP-3164 | Salarius Pharmaceuticals (USA) | Non-Hodgkin lymphoma | Phase 1 |
| CT-01 | Captor Therapeutics (Poland) | Hepatocellular carcinoma | Phase 1 |

**Table 2**. Count of degraders per clinical phase.

| Phase | Count |
|---|---|
| Approved | 4 |
| Phase 3 | 5 |
| Phase 2 | 6 |
| Phase 1/2 | 9 |
| Phase 1 | 28 |

Note: "Phase 1" total includes entries labelled Phase 1, Phase 1a/1b (n=1) and Phase 1/1b (n=2).

**Table 3**. Count of degraders per tumour type and therapeutic area.

| Tumour type | Therapeutic area | Count |
|---|---|---|
| Hematologic malignancies | Multiple myeloma | 8 |
| | B-cell / non-Hodgkin lymphomas | 10 |
| | T-cell lymphomas | 2 |
| | Acute leukaemias | 3 |
| Solid tumours | Prostate | 5 |
| | Breast | 3 |
| | Lung | 3 |
| | Gastro-intestinal | 3 |
| | Sarcoma | 2 |
| | Other / unspecified solid | 6 |
| Mixed tumours | Various or mixed cancers | 4 |
| Non-oncology | Dermatology | 1 |
| | Immunology | 1 |
| | Neurology | 1 |

**Table 4.** TPD companies based in EU or UK and key collaborations (non-exhaustive list).

| Company | Country | Key Collaborations | Stage |
|---|---|---|---|
| Captor Therapeutics | Poland / Switzerland | Sosei Heptares (2020; now Nxera Pharma)<br>Ono Pharma (2022) | Phase 1 (CT-01) |
| Proxygen | Austria | Boehringer Ingelheim (2020)<br>Merck KGaA (2022)<br>Merck & Co (2023) | Preclinical |
| Evotec SE | Germany | BMS (2023)<br>BMS (2024) | Discovery |
| Draupnir Bio | Denmark | Seed funding (2024) | Preclinical |
| Laigo Bio | Netherlands | Seed funding (2025) | Preclinical |
| Orionis Biosciences | Belgium / US | Genentech (2023)<br>Genentech (2025) | Preclinical |
| Celeris Therapeutics | Austria | Boehringer Ingelheim (2022) | Preclinical |
| Merck KGaA | Germany | C4 Therapeutics (2024) | Discovery |
| Amphista Therapeutics | U.K. | BMS (2022)<br>Merck KGaA (2022)<br>Merck KGaA (2025) | Preclinical |
| TRIMTECH Therapeutics | U.K. | Seed funding (2025) | Preclinical |
| Dunad Therapeutics | U.K. | Novartis (2021) | Discovery |

**Table 5.** European Consortia funding landscape (>€100M from 2018-2030; not an exhaustive list).

| Project Acronym/ Program | Duration (approx) | Coordinated by | Short description | Source |
|---|---|---|---|---|
| EUbOPEN (IMI2 IHI) | 2020-2025 | Goethe University Frankfurt (Germany) | Pan-EU consortium generating open-access chemical probes, assays, and data to enable difficult targets, including TPD-relevant biology. | CORDIS |
| Glue2Degrade (ERC Starting) | 2019-2025 | CEMM Institute (Austria) | Fundamental research to discover and characterize molecular glues that reprogram E3 ligases for targeted protein degradation. | CORDIS |

| Project Acronym/ Program | Duration (approx) | Coordinated by | Short description | Source |
|---|---|---|---|---|
| PPI-Glue (ERC Consolidator) | 2023-2028 | Eindhoven University of Technology (Netherlands) | Methods to induce or stabilize protein–protein interactions with glue chemotypes to drive selective degradation. | CORDIS |
| PRIGLUE (ERC Advanced) | 2023-2028 | University of Münster (Germany) | Advanced chemical biology and medicinal chemistry to design next-generation molecular glues and define their mechanisms. | CORDIS |
| Sweet Degradation (ERC Starting) | 2025-2030 | Leiden University (Netherlands) | Exploration of glyco/chemical strategies for directing proteins to cellular disposal pathways for selective degradation. | CORDIS |
| RECOBIN-PROTACs (H2020 MSCA-IF) | 2020-2022 | University of Cambridge (United Kingdom) | MSCA fellowship advancing design and evaluation of PROTAC degraders and enabling methodologies. | CORDIS |
| SBPD In-Silico (H2020 MSCA-IF) | 2020-2022 | University of Dundee (United Kingdom) | Computational and in-silico approaches to guide degrader discovery and structure–activity relationships. | CORDIS |
| PROTACs (Research and innovation action) | 2021-2023 | CEU San Pablo University (Spain) | RIA project developing tool compounds and workflows for PROTAC synthesis, profiling, and target validation. | CORDIS |
| PROTAG-8 (Research and innovation action) | 2024-2026 | University of Ljubljana (Slovenia) | RIA effort to prototype novel degrader modalities and screening platforms for priority disease targets. | CORDIS |
| DELETER (Research and innovation action) | 2021-2023 | University of Dundee (United Kingdom) | Development of degradation-enabling assays and chemistries to accelerate TPD translation. | CORDIS |
| NeoTraCs (Research and innovation action) | 2025-2030 | AITHYRA Institute (Austria) | Multi-year program to create next-generation tracers, chemistries, and workflows for degrader discovery. | CORDIS |
| UBIMOTIF (MSCA-ITN) | 2019-2024 | University of Copenhagen (Denmark) | Doctoral training network on ubiquitin signaling, ligases, and turnover assays underpinning TPD. | CORDIS |
| TRIM-NET (MSCA-ITN) | 2019-2023 | University of Trieste (Italy) | Training network focused on TRIM E3 ligases and their exploitation for targeted degradation. | CORDIS |

| Project Acronym/ Program | Duration (approx) | Coordinated by | Short description | Source |
|---|---|---|---|---|
| PROTAC-PDAC (ERC Consolidator) | 2023-2028 | Kiel University (Germany) | ERC program applying PROTAC strategies to pancreatic ductal adenocarcinoma and related oncogenic drivers. | CORDIS |
| NextTPD (Proof of Concept) | 2026-2027 | Bar-Ilan University (Israel) | PoC project translating academic TPD findings toward application and feasibility studies. | CORDIS |
| DEGRON (Proof of Concept) | 2025-2027 | Kiel University (Germany) | PoC project to validate degron-based targeting concepts for therapeutic degradation. | CORDIS |
| TrickE3 (ERC Advanced) | 2022-2027 | IRB Barcelona (Spain) | ERC program engineering and redirecting E3 ligases to expand the degradable proteome. | CORDIS |
| ProAPP (Proof of Concept) | 2022-2024 | Max Planck Society (Germany) | PoC study leveraging protein homeostasis and proximity-based strategies to enable degradation applications. | CORDIS |
| DETRIMODE (MSCA-ITN) | 2018-2020 | Nerviano Medical Sciences Srl (Italy) | Training network on degrader modalities, screening, and translational workflows for drug discovery. | CORDIS |
| EIC Accelerator | 2022- | Celeris Therapeutics (Austria) | EU translational funding (grant + equity) supporting AI-guided degrader design and early pipelines. | News Outlet |
| EIC Accelerator | 2025 | Captor Therapeutics (Poland) | EU SME instrument funding to progress targeted protein degradation assets toward clinic. | Captor Therapeutics |
| Horizon Europe / National (Poland, ERDF/NCBR/MRA) | 2018-2025 | Captor Therapeutics (Poland) | National/EU co-funding program building TPD platform capacity and advancing lead candidates. | Captor Therapeutics |

**Table 6.** Analysis of Scientific Advice data, summarized using scientific explorer. No confidential or commercially sensitive information is disclosed in this analysis. All content has been generalized and aggregated, and no proprietary details or internal communications are included.

| Scientific Advice Analysis | |
|---|---|
| Temporal distribution | Scientific advice activity expanded over time, suggesting a growing engagement from applicants or increased regulatory interactions. The distribution by year was as follows: |

| Scientific Advice Analysis | |
|---|---|
| | 2018-2021: 3 cases, 2022: 4 cases, 2023: 4 cases, 2024: 4 cases, 2025: 6 cases. |
| Application area of advice | Most requests focused on clinical trial aspects. Across all rounds, the most frequent trial scope elements were:<br><br>clinical: 21 cases, non-clinical: 6 cases, quality: 6 cases, significant benefit: 1 case. |
| Trial design-related questions | The main themes of design-related queries were:<br><br>Study population definition: 17 cases, primary and secondary endpoint selection: 16 and 13 cases respectively, use of active comparators: 16 cases, primary statistical analysis: 15 cases, target indication: 15 cases, interim analysis: 12 cases, safety issues: 9 cases. |