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ILLUMINATING THE "DARK MATTER" OF PHARMACOLOGY: EMERGING STRATEGIES TO TARGET UNDRUGGABLE AND UNCHARACTERIZED BIOLOGICAL TARGETS

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ABSTRACT

Background: A large share of the proteins that matter most in human disease have never yielded to ordinary small-molecule chemistry. The reasons are structural rather than biological: some of these proteins simply have no deep cavity for a ligand to occupy, others flex between many shapes or remain partly unfolded, and a great many do their work through wide contact surfaces with partner proteins instead of through a single catalytic site. A further group has barely been characterised at all, so there is no clear picture of what a drug would need to do.[2] **Emerging modalities and advances.** It is more useful to read this collection of intractable proteins — the pharmacological "dark matter" — as unfinished business than as a fixed limit on what medicinal chemistry can reach. Over the past decade the toolkit has widened considerably: proteins can now be destroyed rather than merely blocked, glued to unintended partners, engaged covalently or from a distance through regulatory sites, probed with small fragments, silenced at the level of their transcripts, or intercepted with peptides and biologics. Structural biology and machine learning have accelerated all of these routes.[2] What unites them is that none depends on the classical recipe of a well-shaped orthosteric pocket; each instead makes use of something else the target offers — a fleeting cavity, an exposed surface, an interaction interface, a route into a degradation pathway, or the nucleic-acid sequence that encodes it.[2] **Clinical relevance**

and case examples. KRAS is the clearest demonstration that "undruggable" is a statement about available methods and not about the protein. Covalent chemistry aimed at a mutant cysteine, and later non-covalent recognition of a different mutant, converted a target that had frustrated the field for three decades into one with approved and advancing medicines.[8] Targeted degradation has made a parallel point from the opposite direction, clearing proteins from the cell that were never plausible candidates for occupancy-based inhibition.[3] **Conclusion and outlook.** This review draws together the principal strategies now being applied to hard targets, the classes of protein each strategy suits, what each buys and what it costs, and the steps still needed before poorly characterised biology can be turned into medicines.[2]

KEYWORDS: Undruggable targets; Dark proteome; Targeted protein degradation; PROTACs; Molecular glues; Allosteric inhibition; Protein–protein interactions; Covalent inhibitors; Artificial intelligence; Drug discovery.

1. INTRODUCTION

"Undruggable" is a label the field applies to proteins that clearly drive disease yet refuse to cooperate with standard drug design.[2] The obstacles recur in a small number of forms: no pocket worth binding, or one too shallow to hold a ligand; an active site so well conserved across a protein family that selectivity is unattainable; long stretches of sequence that never fold into a fixed shape; conformations that interconvert too quickly to be pinned down; and functional surfaces spread across broad protein–protein interaction (PPI) interfaces rather than concentrated at one site.[2] None of these amounts to a claim that the protein can never be manipulated. In practice the word says more about the modality being tried than about the biology, and it should be read as provisional.[2]

The change in thinking has been a change in what a drug is assumed to do. Classical discovery treated proteins as largely rigid objects with a single cavity, and success meant finding a molecule that sat in that cavity with high affinity. Genomic and proteomic surveys of the human proteome undercut this assumption by showing how many disease-linked proteins have no such cavity to begin with — transcription factors, scaffolding and adaptor proteins, and the hubs where several signalling pathways converge. Competitive inhibitors aimed at these proteins tend to fail in predictable ways: affinity stays weak, activity does not translate into a functional effect, or the compound cannot distinguish its target from close relatives and toxicity follows. The field has since moved towards models built on

conformational ensembles, on binding events that need not be orthosteric or even sustained, and on the cell's own machinery for disposing of unwanted protein.

Several lines of work opened simultaneously. Improved structural methods, fragment screening, chemoproteomic mapping of reactive sites, large phenotypic screens, oligonucleotide chemistry and computational molecular design have each exposed vulnerabilities that were invisible a generation ago.[2] Among these, targeted protein degradation deserves particular emphasis because it redefines the objective. Instead of asking a compound to keep an active site blocked for as long as the drug is present, degradation asks only that the compound bring the target and the disposal machinery together long enough for the cell to do the rest.[3] Two designs dominate: heterobifunctional PROTACs, which physically tether a protein of interest to an E3 ubiquitin ligase, and molecular glues, which coax a ligase and a target into an interface neither would form alone.[3] Work outside the ubiquitin–proteasome system extends the same logic to lysosomal and autophagic routes, reaching substrates the proteasome cannot handle. [6] Because these mechanisms are catalytic — one drug molecule can contribute to the removal of many copies of a target — they loosen the requirement for continuous high occupancy, which in turn permits lower exposures and narrows the window for off-target activity.

Running alongside this chemistry is a broader question about how much of the proteome we can even see. The "dark proteome" refers to regions and whole proteins that current methods describe poorly: disordered segments, short-lived conformations, and sequences with no assigned function.[12] Interaction sites that matter for signalling may sit precisely in these regions, which is why crystallography, optimised for ordered structure, has largely missed them.[12] Mass spectrometry, cryo-electron microscopy and machine-learning structure prediction are beginning to convert some of this territory from blank space into concrete, testable hypotheses.[11] The practical consequence is that the boundary of druggability is not fixed but keeps moving outward as biophysical and computational methods improve, and proteins written off as intractable are re-entering the pipeline.

2. Why Some Biological Targets Remain Difficult to Drug

A conventional small molecule needs somewhere to sit, and that site has to satisfy several conditions at once: an enclosed shape, a workable mix of hydrophobic and polar contacts, and enough stability for the ligand to remain bound long enough to matter.[2] A substantial part of the proteome offers nothing of the kind. Transcription factors, scaffolds and many regulatory

proteins carry out their function by presenting a surface, not by catalysing a reaction inside a cleft.[2] Where two proteins meet, the interface is often broad and comparatively featureless, so a small compound covers too little of it to compete; and where a protein is intrinsically disordered, there may be no single cavity in existence long enough to design against, since the chain samples many arrangements.[2]

Tractability should also be treated as a variable rather than a property.[2] The same protein may be undruggable in one state and druggable in another, because binding a partner, acquiring a mutation, or moving a domain can open a pocket that no static structure shows.[10] KRAS makes the point concretely. For years the protein was regarded as chemically inaccessible; recognition of the switch-II pocket provided a foothold for selective inhibitors of the G12C mutant, and later work showed that the G12D mutant could be engaged selectively without covalent chemistry at all.[9]

Table 1: Classes of target that have historically resisted conventional pharmacology.

Class of target	Where the difficulty lies	Examples	Route now being explored	Reference
Intrinsically disordered proteins	No persistent cavity; the chain samples many conformations	MYC, p53, Tau	Glue-induced interfaces, ligand-induced pockets, peptide ligands, degraders	Xie et al., 2023 ;[2] Sharma et al., 2025[12]
Protein–protein interaction surfaces	Contact area is wide and shallow, so small compounds cover too little of it	BCL-2 family members, transcriptional complexes	Fragment screening at hot spots, interface inhibitors, covalent fragments	Wang et al., 2023[7]
Small GTPases	Endogenous nucleotide binds too tightly to displace; surfaces are mobile	KRAS and other RAS-family proteins	Covalent and allosteric ligands; pockets that appear only transiently	Singhal et al., 2024[8]
Intracellular proteins with no ligandable site	Nothing for a conventional ligand to occupy	IKZF1/3, RBM39	Recruitment to E3 ligases via PROTACs or glue degraders	Zhang et al., 2024;[4] Wang et al., 2024 [5]
Poorly characterised and dark-proteome proteins	Structure and function largely unknown	Disordered and short-lived protein regions	Proteomic mapping, cryo-EM, predicted structures, empirical screening	Sharma et al., 2025;[12] Liu et al., 2025[11]

3. Targeted Protein Degradation: Turning a Binding Problem into a Disposal Problem

Of everything now applied to hard targets, degradation has had the widest reach.[2] The founding experiment showed that a single molecule with two ends — one recognising a target, the other an E3 ubiquitin ligase — could hold the two proteins close enough for the ligase to ubiquitinate the target and mark it for the proteasome.

[13]Present-day PROTACs retain that architecture: a target-binding warhead, a ligase-binding element, and a linker whose length and rigidity turn out to matter as much as either end.[3] The important consequence is kinetic. Since one drug molecule can help destroy many target molecules before it is cleared, the pharmacology no longer depends on keeping an active site saturated.[3]

Molecular glues arrive at removal by a different route and carry a different set of trade-offs.[3] These are single, generally drug-like compounds that do not tether anything; they insert themselves at the boundary between a ligase and a protein and make an interaction favourable that would otherwise not occur.[3] Effectively they rewrite the ligase's substrate preference, and because the target contributes only part of a composite surface, proteins with no ligandable pocket of their own become degradable.[3] The trade-off is discovery: glues have historically been found rather than designed, and predicting which pairs of proteins can be glued together remains largely empirical.[5]

Table 2: Degradation strategies applied to difficult targets.

Strategy	How it works	Principal advantage	Principal constraint	Where it is used	Reference
PROTACs	A bifunctional molecule tethers the target to an E3 ligase through a linker	Sub-stoichiometric, catalytic removal; modular and re-usable design	Molecules are large, with attendant permeability and pharmacokinetic penalties	Clearing intracellular proteins	Sakamoto et al., 2001 ;[13] Kannan & Sreeraman, 2023;[3]
Molecular glues	One small compound stabilises a new ligase–substrate interface	Retains conventional small-molecule properties; reaches proteins with no ligandable site	Hard to discover prospectively; selectivity must be mapped proteome-wide	IKZF1/3, RBM39 and other neo-substrates	Kannan & Sreeraman, 2023;[3] Zhang et al., 2024;[4]
LYTACs and other lysosome-directed	Route secreted or membrane proteins into lysosomal	Reaches the extracellular and membrane proteome, which	Depends on receptor expression; delivery and	Cell-surface and secreted proteins	Zhang et al., 2024;[4]

degraders	uptake	the proteasome cannot	exposure are limiting		
AUTACs and autophagy-directed designs	Recruit autophagic machinery to clear the target	Handles cargo unsuited to the proteasome	Mechanism incompletely defined; delivery unresolved	Large proteins, aggregates, organelle-associated targets	Kannan & Sreeraman, 2023;[3]
Degrader–antibody conjugates	An antibody delivers the degrader to a chosen cell population	Adds cell-type selectivity to a degradation payload	Manufacturing and intracellular release are demanding	Disease-driving proteins in defined cell types	Kannan & Sreeraman, 2023[3]

4. Cryptic Pockets, Allostery and Covalent Chemistry

Where an endogenous ligand binds too tightly to displace, one option is to stop competing with it. Allosteric ligands bind at a regulatory site some distance from the orthosteric one and act by shifting the protein's conformational preference.[2] Two benefits follow. Regulatory sites are typically less conserved than catalytic ones, so selectivity within a protein family becomes achievable; and because the ligand stabilises a particular state rather than simply blocking access, the pharmacology can be tuned rather than merely switched off.[2]

Cryptic pockets extend this idea to sites that are not present in the resting protein at all, appearing only when the structure moves.[10] They are attractive precisely because they are invisible to structure-based screening against a single static model — but not every transient opening is worth pursuing. Comparative analyses indicate that the pockets most likely to support real drug binding are those created by larger-scale loop and hinge movements, whereas openings that arise only from fast side-chain rearrangement tend to be too shallow and too short-lived to hold a ligand usefully.[10]

Covalent chemistry adds a third option, applicable whenever a reactive residue — most often a cysteine — sits inside a pocket that a ligand can reach.[8] Forming a bond converts weak, reversible recognition into durable engagement, which is what made the KRAS G12C programmes work: the mutation itself supplies the nucleophile, so the drug is selective for mutant over wild-type protein by chemistry rather than by shape alone.

[8]The G12D story shows that this is not the only path. There, selective recognition of the mutant surface was achieved non-covalently, which matters because most oncogenic mutations do not conveniently install a reactive cysteine.[9]

Table 3: Approaches that reveal or create new binding opportunities.

Approach	What it adds	Illustrative target	Why it helps	What limits it	Reference
Allosteric inhibition	Uses a regulatory site instead of the conserved catalytic one	KRAS, SHP2	Family-level selectivity; effect cannot be reversed by substrate accumulation	Identifying sites that are genuinely coupled to function	Xie et al., 2023[2]
Cryptic-pocket targeting	Exploits cavities that open only when the protein moves	KRAS and other conformationally mobile proteins	Reaches sites no static structure displays	Pocket may be too transient or too shallow to bind a ligand well	Lazou et al., 2024[10]
Covalent inhibition	Converts transient binding into a permanent bond at a reachable residue	KRAS G12C	Deep, long-lasting engagement at modest exposure	Off-target reactivity; resistance through loss of the residue	Singhal et al., 2024[8]
Fragment-based discovery	Detects weak binders at interaction hot spots and cryptic sites	PPI interfaces	Samples chemical space efficiently with small libraries	Starting affinities are very low; substantial elaboration required	Wang et al., 2023[7]
Conformation-selective inhibition	Locks the protein in a state relevant to disease	KRAS and other signalling proteins	Turns conformational dynamics into a selectivity handle	The relevant states are hard to predict and harder to trap	Zhang et al., 2024[4]

5. Nucleic-Acid, Peptide and Biologic Strategies

If a protein cannot be bound, the instructions that produce it can often be intercepted instead.[2] Antisense oligonucleotides and RNA interference both lower the amount of protein made, and neither requires a pocket — only a sequence, which makes them applicable in principle to targets that offer chemistry no purchase at all.[2] CRISPR-based editing acts one level further upstream, altering a gene or its regulatory elements outright; the appeal is

permanence and the concern is the same, since delivery, off-target editing and irreversibility all have to be resolved before the approach is broadly acceptable.[2]

At the other end of the size range, peptides, macrocycles and biologics succeed for the reason small molecules fail: they present enough surface to cover a wide interface, which makes them a natural fit for protein–protein interactions.[2] What they gain in contact area they give back in drug-like behaviour — proteolytic stability, movement across membranes, immunogenicity, penetration into tissue and cost of manufacture are all harder than for a conventional small molecule.[2] Modality selection therefore turns less on elegance than on circumstance: where the target sits in the cell or body, how long its activity must be suppressed, and whether the tissue involved can be reached.[2]

Table 4: Non-traditional modalities for difficult targets.

Modality	Level at which it acts	Typical application	Main advantage	Main limitation	Ref.
Antisense oligonucleotides (ASOs)	RNA	Lower the abundance of proteins that resist inhibition	Designed from sequence alone; no pocket needed	Restricted tissue distribution and uptake	[2]
siRNA and RNA interference	mRNA	Silence disease-associated transcripts	Deep, dose-dependent knockdown	Escape from endosomes; duration of effect	[2]
CRISPR-based editing	DNA (and RNA)	Disrupt or re-regulate a gene	Programmable and potentially one-time	Delivery, unintended edits, permanence	[2]
Peptides and macrocycles	Protein surfaces and PPIs	Disrupt or stabilise an interaction	Large enough to cover a broad interface	Metabolic stability and cell entry	[2], [7]
Antibodies and other biologics	Extracellular and membrane proteins	Neutralisation, receptor modulation, payload delivery	Exceptional specificity	Little or no access to the cytosol	[4]

6. Artificial Intelligence, Structural Biology and the Dark Proteome

Computational methods now contribute at several points in a discovery programme: predicting a fold, flagging where a ligand might bind, ranking compounds before synthesis, and proposing new chemical matter outright.

[2]Their value is greatest exactly where experiment is weakest. When the pocket of interest is

transient, allosteric, or simply absent from the one structure that happens to have been solved, a single crystallographic snapshot is the wrong evidence to design against, and modelling can supply the conformational range that snapshot omits.[2] This does not displace experiment. Predictions narrow the field of possibilities; whether a predicted pocket exists, binds anything, and produces a functional consequence is still settled at the bench through biochemical, cellular and structural work.[2]

The dark proteome is where these methods are likely to matter most, because it is defined by absence of information — disordered stretches, transient states and proteins with no annotated function, many of them plausible participants in signalling and disease.[12] Deep proteomic profiling, cryo-EM of heterogeneous complexes and predicted structural models are together starting to give these regions shape, and with shape comes the possibility of identifying an interaction surface or a ligandable state.[12] The productive combination is not any single technique but the chain of them: a predicted structure that suggests a site, fragment screening that tests whether the site binds, chemoproteomics that confirms engagement in cells, and functional genomics that establishes whether engagement matters — which is how an uncharacterised protein becomes a target hypothesis worth funding.[2]

Table 5: Technologies contributing to the discovery of new pharmacological targets.

Technology	Contribution	Output	Strength	Present limitation	Ref.
Machine-learning structure prediction	Models folds and proposes candidate pockets	Structural models, pocket hypotheses, docked poses	Operates at proteome scale and at speed	Confidence varies; experimental confirmation still required	[11]
Generative models	Propose and refine candidate ligands	New chemical scaffolds and optimised analogues	Explores regions of chemical space no library covers	Predicted activity, synthesisability and safety all need testing	[11]
Cryo-electron microscopy	Resolves large assemblies and coexisting conformations	Complex structures; populations of states	Tolerates heterogeneity that crystallography cannot	Resolution and sample behaviour remain limiting	[12]
Chemoproteomics	Maps reactive, ligandable residues	Ligandable-site inventories;	Uncovers binding sites nobody	Technically demanding; data	[2]

	across the proteome	direct evidence of engagement	predicted	interpretation is non-trivial	
Integrated multi-omics	Links genetic, transcriptional and protein-level evidence	Ranked, disease-anchored target hypotheses	Prioritises targets in a systems context	Harmonising datasets; separating correlation from cause	[2]

7. CHALLENGES AND FUTURE PERSPECTIVES

A widening definition of druggability should not be mistaken for a promise that every hard target will yield a medicine.[2] The list of things that still go wrong is long and mostly familiar: targets that turn out not to be causal once engaged; drugs that reach the wrong tissues; exposure that cannot be sustained safely; resistance; off-target activity; dependence on cellular machinery that varies between tissues; biomarkers that fail to identify responders; and biochemical potency that never becomes clinical benefit.[2]

Each modality also brings its own failure modes. Degradation, for instance, only works where the required ligase is expressed at useful levels, where a productive ternary complex actually forms rather than merely being possible on paper, and where target and ligase occupy the same subcellular compartment — so the same degrader can be highly active in one cell type and inert in another.[3] Cryptic-pocket and computationally driven programmes carry the opposite risk, that of a confident prediction with no physical counterpart, which is why structural, biochemical and cellular confirmation should precede significant chemistry investment.[10] For oligonucleotides and biologics, delivery remains the dominant variable and often decides whether an otherwise sound mechanism is developable at all.[2]

The reasonable expectation, then, is that hard targets will be approached with several methods in combination rather than with whichever one a group happens to favour.[2] A programme that works usually looks the same in outline: genetic evidence establishes that the target matters, structural and computational work suggests where to bind, chemoproteomics and fragment screening test that suggestion empirically, design is guided computationally, and functional pharmacology decides whether the effect is the intended one.[2] Framed this way, “undruggable” is best understood as a description of the current state of a project rather than a property of a protein.[2] KRAS is the proof: a target that resisted the field for decades became clinically validated once the right pocket and the right chemistry were found.[8] Whether comparable progress follows for uncharacterised proteins depends largely on how

quickly the dark proteome becomes experimentally accessible.[12]

8. CONCLUSION

What counts as a difficult target is being redefined by the methods now available to approach it.[2] Degraders and molecular glues remove proteins instead of blocking them; allosteric and covalent ligands bind where conservation and competition are less punishing; fragment-based work chips away at interaction surfaces; oligonucleotides act before the protein is made; biologics cover surfaces small molecules cannot; and computational design shortens the search at every stage. Each addresses a different failure of the classical occupancy model, which is why they are complements rather than rivals.[2] Combined with structural biology and functional genomics, they offer a credible route from an undruggable or uncharacterised protein to a genuine therapeutic target.[2] Which of them ultimately produces durable medicines will be decided by the unglamorous parts of the problem — selectivity, delivery, resistance, safety, and target validation rigorous enough to be believed. [2]

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