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Current Opinion in Structural Biology

Drug targeting of protein-nucleic acid interactions

Luca R. Genz[1,2,3], Sanjana Nair[1,3], Aaron Sweeney[1,3] and Maya Topf[1,3,4]

Protein–nucleic acid interactions are vital to gene regulation and disease, yet have long been considered "undruggable." Recent advances are reshaping this paradigm, enabling therapeutic targeting of DNA- and RNA-binding proteins. In this review, we highlight four major strategies: (1) direct disruption of protein-nucleic acid binding, (2) stabilization of specific complexes or conformations, (3) targeted degradation of interaction partners, and (4) allosteric modulation. We explore key examples across transcription factors, RNA-binding proteins, and DNA repair proteins, and emphasize emerging chemical, structural, and computational techniques that are accelerating discovery. Together, by intervening directly in the gene regulatory machinery, these approaches expand the druggable genome and open new avenues for treating cancer, genetic disorders, and viral infections.

Addresses
[1] Research Department of Integrative Virology, Leibniz-Institut für Virologie (LIV), Hamburg, Germany
[2] Department of Chemistry, Universität Hamburg, Hamburg, Germany
[3] Centre for Structural Systems Biology (CSSB), Hamburg, Germany
[4] Institute for Molecular Virology and Tumorvirology, Universitätsklinikum Hamburg Eppendorf (UKE), Hamburg, Germany

Corresponding author: Topf, Maya (maya.topf@cssb-hamburg.de)

Current Opinion in Structural Biology 2025, **95**:103165

This review comes from a themed issue on **Protein Nucleic Acid Interactions (2025)**

Edited by **Shandar Ahmad** and **Elodie Laine**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.sbi.2025.103165

Introduction

Protein–nucleic acid complexes are central to gene regulation and disease, yet many of the proteins that bind DNA or RNA (e.g., transcription factors and RNA-binding proteins) have traditionally been considered "undruggable" due to their lack of binding pockets for small molecules and dynamic binding modes [1,2]. However, recent advances are overcoming this barrier by developing inventive strategies to modulate protein–DNA and protein–RNA complexes. In this review, we examine four major drug discovery strategies for modulating protein–DNA and protein–RNA interactions: (1) direct disruption of binding, (2) stabilization of specific complexes or conformations, (3) targeted degradation of one of the interaction partners, and (4) indirect targeting through allosteric modulation. We highlight examples and elaborate on the techniques enabling these strategies.

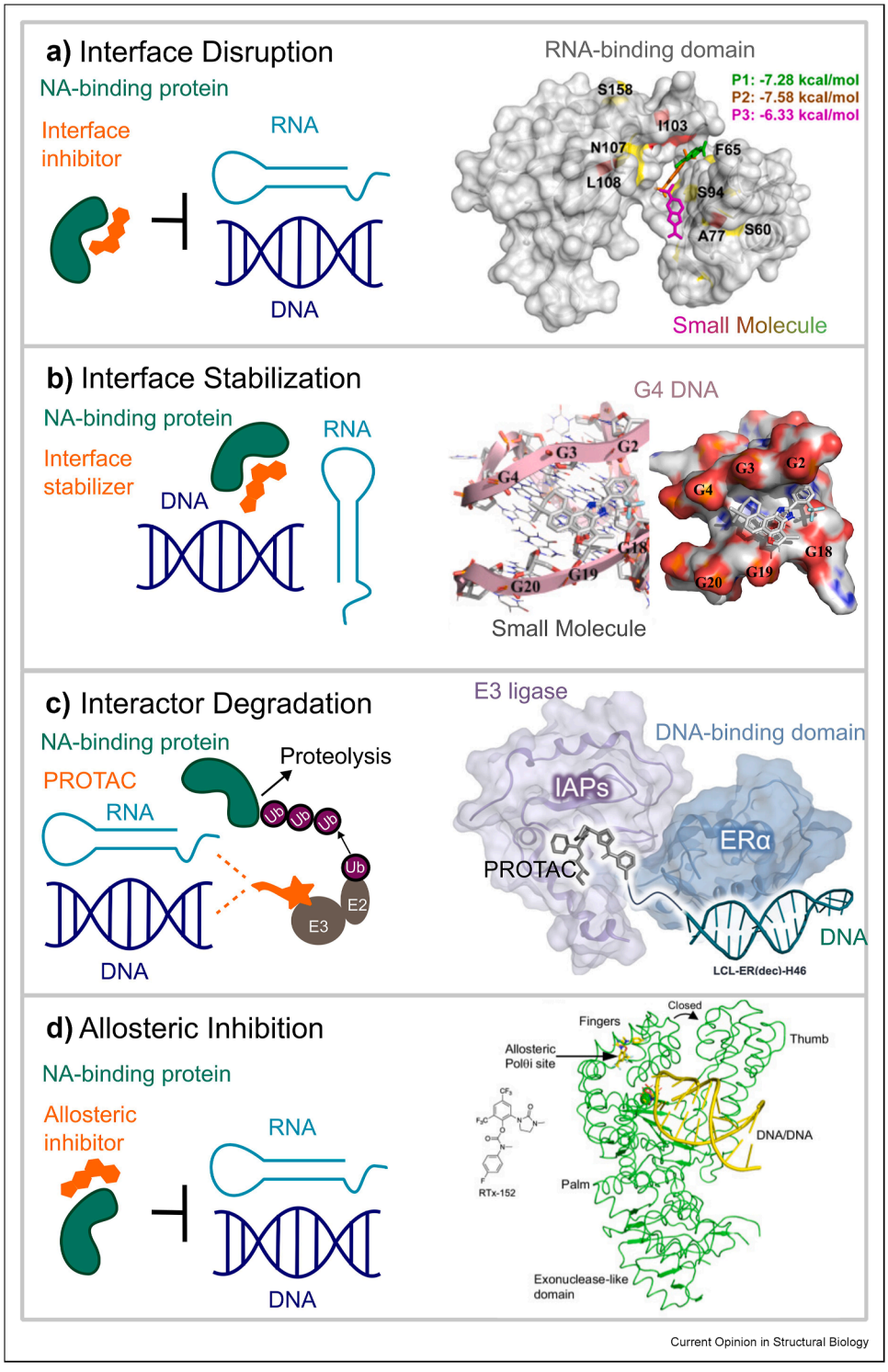
Disruption of protein–nucleic acid binding

One straightforward approach is to directly inhibit the protein-nucleic acid interaction, preventing the formation of a complex (Figure 1a). Many transcription factors (TFs) and RNA-binding proteins (RBPs) rely on defined nucleic-acid binding domains [3,4], and compounds that target these domains can inhibit their regulatory activity.

Several small molecules have recently been identified that disrupt DNA–protein interactions in transcription factors (TFs) and DNA repair proteins. For instance, Lin et al. (2023) showed that Eltrombopag inhibits the autophagy regulator TFEB by blocking its DNA binding and suppressing downstream gene expression [5]. Similarly, *in vitro* assays integrated with computational studies suggested that naphthoquinone analogs interfere with the TF TCF4, which disrupts its interaction with DNA, inhibits Wnt signaling, and promotes TCF4 degradation [6]. Radaeva et al. (2023) used ultra-large virtual screening to identify novel mode of action inhibitors that bind the androgen receptor (AR) DNA-binding domain, blocking its transcriptional activity [7].

Moreover, targeting oncogenic TF–DNA interactions has emerged as a promising therapeutic strategy. Using computer-aided drug design (CADD), Ton et al. (2022) identified the small molecule VPC-70619 that blocks the function of the TF N-Myc in prostate cancer [8]. Xu et al. (2025) expanded this strategy using arsenic trioxide, which interrupts the N-Myc–DNA interaction and developed a high-throughput cellular screen to identify similar inhibitors [9]. Additionally, Manguinhas et al. (2024) reported inhibitors of the endonuclease XPG, which target its DNA-binding domain to enhance cisplatin efficacy in lung cancer cells [10]. Bhat et al. (2023) identified a small molecule inhibitor of the DNA-repair protein RAD52, disrupting RAD52-ssDNA

Figure 1



Strategies for modulating protein–nucleic acid interactions with small molecules. In schematic representations, proteins are shown in green, nucleic acids (DNA or RNA) in blue or cyan, and small molecules (including PROTACs and peptides) in orange. Representative structural models at right are adapted from primary literature sources as cited. **(a)** Interface disruption: Small molecules (and peptides, not shown in the figure) competitively inhibit nucleic acid–protein interactions by binding to the corresponding interfaces as demonstrated in the case of the RBP HuR [22] (Section Disruption of protein–nucleic acid binding). **(b)** Interface stabilization: Small molecules stabilize nucleic acid–protein complexes, e.g. by promoting interactions with structured DNA elements, such as G-quadruplexes [35]. **(c)** Interactor degradation: PROTACs direct nucleic acid-binding proteins for ubiquitin-mediated proteasomal degradation via recruitment of E3 ligases, as shown for ERα [40]. **(d)** Allosteric inhibition: Small molecules bind allosterically to either the protein (or DNA/RNA, not shown in the figure), altering conformation and reducing binding affinity as demonstrated for Polθ [56].

binding and inhibiting the cellular activities of the protein [11].

Synthetic DNA-binding agents have also shown promise in modulating transcription. Pyrrole-imidazole polyamides (PIPs) bind sequence-specifically to the minor groove of double-stranded DNA and have been used to target disease-relevant genes such as FXN, hepatocyte growth factor (HGF), and RUNX [12–15]. However, challenges related to off-target effects remain [16]. Meanwhile, "stapled peptides" have emerged as potent inhibitors that mimic α-helical domains to block protein–DNA interactions in TFs like NF-Y and AR-V7, along with DNA repair proteins and RBPs [17–20]. Covalent inhibitors provide another route by irreversibly altering key nucleophilic residues at the protein–DNA interface, as shown for TFs such as FOXA1 [21].

RNA–protein interactions are equally attractive targets, particularly in RNA-binding proteins (RBPs) that drive cancer progression [2]. For instance, the RBP HuR (Hu antigen R) has been identified as a potential target in multiple cancers. Wu et al. (2023) identified inhibitors of HuR that block its RNA-binding pocket and suppress tumor growth in breast cancer models (Figure 1a) [22]. They used a structure-guided approach combining molecular docking, molecular dynamics simulation, and a free energy decomposition method to find subpockets within the RNA-binding site of HuR. This suppression aligns with other studies showing that HuR inhibitors, such as KH-3 and CMLD-2, sensitize tumors to chemotherapy [23,24]. Qiu et al. (2025) showed that phenylpyrazoles inhibit another RBP, the m6A "reader" YTHDF2, by binding its YTH domain, leading to apoptosis and cell cycle arrest in cancer cells [25]. Similarly, Takayama et al. (2023) reported small molecules that block the splicing factor PSF from binding RNA, inhibiting tumor growth and AR expression [26]. Small molecules targeting RNA-binding interfaces have also been discovered using a high-throughput, fluorescence-based assay that detects disruption in hnRNPA2B1–RNA binding, reducing the vesicular enrichment of the pro-inflammatory microRNA [27].

Recent screening campaigns have further expanded this approach. Dunnett et al. used molecular dynamics (MD) and fragment-based crystallography to identify small molecules that bind the RNA-binding domain of the RBP hnRNPA1 [28]. A high-throughput fluorescence-polarization screen was used to identify an inhibitor of the RBP Igf2bp1, which significantly reduced KRAS mRNA levels in cancer cells [29]. Finally, Matias-Barrios et al. used CADD, in combination with quantitative biochemical and biological assays, to discover a small molecule that inhibits the binding of the RBP Lin28 to RNA and suppresses Lin28-driven cancer cell proliferation [30].

Stabilization of nucleic acid–protein complexes

In contrast to inhibition, some drugs stabilize protein-nucleic acid complexes (which are often referred to as "molecular glues") (Figure 1b). This strategy can either enhance or impair downstream biological outcomes depending on the functional role of the complex, offering an alternative therapeutic approach [31]. For example, Kathman et al. (2023) provided a strategy targeting NONO, an RBP that modulates AR expression at the RNA level. Their study revealed that electrophilic small molecules can stabilize NONO–RNA interactions, impair transcript processing, and selectively downregulate AR isoforms [32].

Another approach involves stabilizing non-canonical DNA structures. G-quadruplexes (G4s) are stable secondary DNA configurations found in telomeres and promoters of genes like hTERT and VEGF [33]. Small molecules that bind and stabilize G4s can block transcription and replication by hindering protein–DNA interactions. As a result, it induces replication stress, DNA damage, and cell fate outcomes such as apoptosis or ferroptosis. G4 ligands have shown therapeutic potential in cancers, such as triple-negative breast and liver cancer [34,35]. Huang et al. (2025) identified a selective inhibitor of liver cancer cells that binds and stabilizes VEGF G4 DNA structures via π-π stacking using molecular docking and molecular dynamics combined with *in vitro* and *in vivo* studies [35] (Figure 1b). It decreased VEGF release, inhibited angiogenesis, and induced apoptosis.

Therapeutic modulation of RNA splicing has also benefited from stabilization-based strategies. White et al. demonstrated that the small molecule Branaplam selectively stabilizes the U1 snRNP-5′ splice site complex, exemplifying precise targeting of an RNA–protein interface [36].

Collectively, these studies reveal how stabilizing protein-nucleic acid interactions can reshape regulatory pathways and enable therapeutic outcomes that are difficult to achieve through inhibition alone.

Targeted degradation of interaction partners

Because many nucleic acid–binding proteins lack pockets considered classically druggable, induced-proximity degradation strategies have emerged as powerful alternatives (Figure 1c) [37]. Application of PROteolysis-TArgeting Chimeras (PROTACs) has

proven to be an attractive method of targeting DNA and RNA-binding proteins by taking advantage of the ubiquitin—proteasome pathway in order to drive selective protein degradation [38]. PROTACs are two-part molecules that bring a disease-causing protein and the cell's degradation machinery together, causing the unwanted protein to be tagged and proteolyzed.

Some examples are PROTACs against the Androgen Receptor (AR), the Estrogen Receptor α DNA-binding domain (ERα-DBD), and BRD4 [39—41]. Naganuma et al. used a structure-based approach to develop decoy oligonucleotide PROTACs targeting ERα, incorporating a phosphorothioate backbone and a T4 hairpin loop to enhance structural stability, nuclease resistance, and ERα degradation activity in breast cancer cells [40] (Figure 1c). Notably, the selective PROTAC degrader Vepdegestrant (ARV-471) of ERα is currently in clinical trials, showing superior degradation of both wild-type and mutant ER and improved tumor growth inhibition compared to standard endocrine therapies [42].

Most recently, a recognition-based covalent PROTAC was developed that uses a DNA aptamer to selectively degrade the Z-DNA binding protein 1 (ZBP1) as a potential therapy for infection-induced inflammation [43]. Kashkush et al. (2024) demonstrated the selective degradation of Lin28, a repressor of the tumor suppressor microRNA let-7, using PROTACs and small molecule molecular glues [44]. Similarly, Lin28A-miRNA-based PROTACs were developed to degrade Lin28A selectively, restoring tumor-suppressive let-7 miRNA levels. This approach inhibited cancer cell proliferation and migration, enhanced chemotherapy sensitivity, and reduced tumor growth [45]. Wang et al. (2023) designed a methylated cytosine-containing oligonucleotide conjugate (methyl-PROTAC) to degrade the DNA methylation reader MeCP2. The compound induced apoptosis and selectively eliminated MeCP2-overexpressing cancer cells, illustrating a novel epigenetic degradation strategy [46].

Further demonstrating the versatility of nucleotide-guided degradation, Li et al. (2023) developed a PROTAC using a threose nucleic acid (TNA) and a DNA aptamer targeting and degrading the TF c-Myc in breast cancer [47]. Another study by Wang et al. (2023) introduced prototype telomere-targeting chimeras (TeloTACs) that degrade the telomeric repeat-binding factors 1 and 2 (TRF1/2). TeloTACs induce telomere shortening and proliferation inhibition in cancer cells [48]. Notably, the splicing factor RBM39 is being targeted in a completed phase II clinical trial using the sulfonamide E7820 for degradation in Leukemia patients [49], demonstrating the clinical translation of degradation strategies for RNA-binding proteins.

Computational structural modeling of the PROTACs has also led to insights for their optimization and rational design, for example, by integrating protein—protein docking, structural alignment, and atomistic MD simulations [50,51]. Resources like PROTAC-DB 2.0, which now includes predicted ternary complex structures for degraders with high efficacy, are accelerating structure-guided development of next-generation PROTACs [52]. Recently, PRODE, a novel *in silico* framework for PROTACs, has been developed to model ternary complexes, predict binding thermodynamics, assess complex stability, and design degraders for challenging targets [53].

Together, these advances underscore how induced-proximity degradation is reshaping the landscape of therapeutic targeting, enabling the pharmacological elimination of nucleic acid—binding proteins that lack classical ligandable pockets.

Allosteric modulation of interactions

A related strategy is allosteric modulation, where small molecules bind to a site on the protein or on the RNA/DNA separate from the protein-nucleic acid interface and trigger a conformational change that affects binding affinity (Figure 1d) [54]. In some instances, this involves binding to a nearby region of the DNA or RNA to alter its structure.

Allosteric strategies have emerged as effective means to modulate DNA-binding enzymes by stabilizing inactive conformations, bypassing direct active-site competition. For example, the covalent inhibitor VVD-133214 targets C727 in the WRN helicase, inducing a compact conformation that blocks DNA unwinding and selectively kills MSI-H cancer cells through DNA damage [55]. Fried et al. (2024) identified a nanomolar allosteric inhibitor that traps the DNA damage response protein DNA Polymerase θ (Polθ) on B-form DNA via an induced-fit mechanism (Figure 1d) [56]. Using X-ray crystallography and biochemical assays, they showed that the inhibitor stabilizes Polθ in a closed conformation, selectively blocking its activity and overcoming PARP inhibitor resistance in breast cancer cells. The TF STAT3, a well-established oncotarget, has also been subjected to allosteric modulation. While most efforts have focused on its SH2 domain, Szalai et al. (2025) identified a previously underexplored pocket at the junction of the coiled-coil and DNA-binding domains. They identified covalent ligands with virtual screening, representing a promising scaffold for targeting this allosteric site in future studies [57].

Notably, targeting the nucleic acids is another way to achieve allosteric modulation. Recent studies on DNA-binding heterocyclic diamidines demonstrated that binding to one region of DNA can redistribute

transcription factor occupancy elsewhere, exerting an indirect yet potent influence on gene regulation [58].

Together, these diverse examples highlight the versatility of allosteric strategies in expanding the druggable space for protein—nucleic acid interactions.

Advances in structural and computational techniques

Technological breakthroughs in structural biology and computational modeling have significantly expanded the landscape for targeting protein—nucleic acid interactions. Recent AI-based approaches, such as AlphaFold3 and RoseTTAFoldNA, enable modeling of protein—protein (or peptide), DNA—protein, and RNA—protein complexes with increasing accuracy, supporting rational drug design for previously intractable targets [59,60]. Similarly, DOCKGROUND provides a resource for the development and benchmarking of structure-based modeling of protein-RNA interactions [61]. However, despite the success of structure prediction softwares, they still fall short of their protein-level accuracy with RNA structures, as observed in the last two structure prediction competitions, CASP15 and CASP16 [62].

Over the last decade, cryoEM has significantly expanded the structural landscape of RNA/DNA-protein interactions. Softwares like TEMPy-ReFF/RIBFIND2 [63] in combination with ERRASER2, a yet to be published successor to ERRASER [64], can be used for improving model refinement of complexes involving nucleic acid structures [65]. This has been demonstrated on many CASP15 targets, highlighting the value of integrating computational methods with experimental techniques to aid protein-nucleotide drug discovery. Such advances will allow more accurate identification of druggable pockets on traditionally challenging RNA/DNA-protein targets.

A comprehensive design cycle might use the prediction of a protein-RNA/DNA structure, or protein-stapled peptide structure, to identify a binding site, dock the small molecule (or peptide) to the target protein/RNA or DNA using docking algorithms for evaluating small-molecule interaction (e.g. NPDock [66], HADDOCK [67] and SwissDock 2024 [68]), and then run MD simulations (e.g. with GROMACS [69]). Other computation methods have been developed for the evaluation of small molecules/peptides [70]. For example, recently, StaPep has enabled detailed characterization of stapled peptide interactions by analyzing their structure and molecular features, improving rational design strategies [71].

For RNA-focused discovery, several structure-based and deep-learning methods have emerged. DRLiPS, a structure-based SVM (Support Vector Machine) framework, predicts druggable RNA-ligand binding pockets with improved accuracy over prior models like DrugPred_RNA [72,73]. Recent attention has also focused on molecular docking scores developed specifically for RNA, with RLaffinity being introduced in 2024 as one of the first deep-learning methods for predicting RNA-ligand affinity [74]. FingeRNAt utilizes a machine learning model encoding covalent interactions as structural interaction fingerprints to predict key interactions driving ligand binding to RNA [75]. Recently, RNAmigos2 introduced a deep learning pipeline that allows the representation of RNA binding sites as 2.5D graphs. The model leveraged synthetic data to overcome the limited number of RNA-ligand structures, achieving a high speed up, which enables ultra-high throughput docking [76]. In parallel, DRPScore, a deep learning model using 4D-CNN architecture, significantly improves the identification of native-like protein—RNA complexes from docking decoys, outperforming existing methods. However, its modest success rate on unbound—unbound cases underscores the ongoing challenges in accurate RNA—protein structural prediction [77].

A recent study reported an experimental technique for large-scale analysis of RNA-small molecule interactions [78,79]. This approach adapted the FOREST platform, which was originally developed for RNA—protein interaction profiling, for high-throughput mapping of RNA—small molecule interactions by combining barcoded RNA libraries with bead-based pull-down and microarray readout.

Lastly, TRIBE-ID (Targets of RBPs Identified by Editing induced through Dimerization) offers transcriptome-wide *in vivo* mapping of RNA—protein interactions using chemically induced A-to-I editing by fusing an RNA-editing enzyme to an RBP. It can quantify drug-induced changes in binding, as shown with the RBP G3BP1 under oxidative stress [80].

Collectively, these advances are transforming our ability to identify, predict, and manipulate protein-nucleic acid interactions with precision.

Conclusion and outlook

Targeting protein-DNA and protein-RNA interactions for drug discovery has made great progress in recent years. For example, disrupting such interfaces with small molecules has shown promise for inhibiting oncoproteins like the transcription factor N-Myc or the RBP HuR. Conversely, stabilizing protein-nucleic acid complexes demonstrates how enhancing instead of inhibiting these interactions can reprogram regulatory pathways and achieve therapeutic effects that traditional inhibition strategies often cannot. Additionally, targeted degradation strategies like PROTACs have

successfully eliminated "undruggable" transcription factors and RBPs. Finally, allosteric approaches are also emerging, providing new ways to influence binding. These diverse strategies demonstrate that there is no one-size-fits-all solution, but rather a toolkit of approaches to tackle different facets of these complex targets.

Despite these advances, challenges remain. Specificity is critical, as many DNA- or RNA-binding proteins have similar motifs, and minimizing off-target DNA and RNA interactions remains an essential goal. Designing ligands that can distinguish between closely related binding sites without affecting homologous proteins is particularly difficult and requires high-resolution structural data and careful optimization. Equally important is optimizing pharmacokinetic properties, including cell permeability, metabolic stability, and bioavailability, particularly for emerging therapeutic modalities such as PROTACs and stapled peptides. In addition, a deeper understanding of potential resistance mechanisms and the broader systemic consequences of perturbing fundamental cellular processes is necessary to ensure both efficacy and safety.

In the future, integrating structural biology, multi-omics-based approaches, and high-throughput screening will likely uncover new chemotypes for targeting protein–nucleic acid complexes. The ability to degrade, stabilize, or allosterically modulate these interactions opens exciting opportunities to treat cancers, as well as genetic and viral diseases by directly intervening with the gene regulators. However, realizing the full clinical potential of these approaches will require addressing challenges related to scalability, drug stability, and regulatory pathways. Alongside these, advances in computational methods are expected to accelerate this progress by improving the prediction of protein–nucleic acid interactions and guiding the design of selective ligands. Machine learning can identify key interaction patterns and optimize molecules faster than traditional approaches. While generative AI models offer novel compound design beyond existing chemical space, they are currently restricted due to the limited availability of structural data. Explainable AI, which makes the behavior of AI systems understandable to humans, will enhance mechanistic insights, helping to reduce off-target effects and resistance. Together, these advances promise to amplify the therapeutic toolkit for targeting protein–nucleic acid interactions and are rapidly changing what was once considered "undruggable".

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT-4 to edit the text and shorten the manuscript to the issue's specification of 2000 words. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement and Funding

We thank the Topf group for discussions and valuable feedback. This work was supported by the Leibniz ScienceCampus InterACt (funded by the BWFGB Hamburg and the Leibniz Association), the BMBF Computational Life Sciences project (ASPIRE, 031L028), the Landesforschungsförderung Hamburg (HamburgX), and DFG CRC1648.

Data availability

No data was used for the research described in the article.

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* of special interest
** of outstanding interest

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