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REVIEW

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Current perspectives in drug targeting intrinsically disordered proteins and biomolecular condensates

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Abstract

Intrinsically disordered proteins (IDPs) and biomolecular condensates are critical for cellular processes and physiological functions. Abnormal biomolecular condensates can cause diseases such as cancer and neurodegenerative disorders. IDPs, including intrinsically disordered regions (IDRs), were previously considered undruggable due to their lack of stable binding pockets. However, recent evidence indicates that targeting them can influence cellular processes. This review explores current strategies to target IDPs and biomolecular condensates, potential improvements, and the challenges and opportunities in this evolving field.

Keywords IDPs, Biomolecular condensates, Drug design

Biomolecular condensates and IDPs

Biomolecular condensates are membrane-less organelles or compartments within cells that undergo a process known as liquid–liquid phase separation (LLPS) [1, 2]. These condensates are dynamic and may comprise different subcellular components such as nucleic acids, proteins, and other biomolecules, thereby organizing the intracellular environment and compartmentalizing cellular processes without the need for membrane-bound structures [3]. Biomolecular condensates are responsible for coordinating complicated biochemical reactions in a spatial and temporal manner [4–6]. Dysfunction of phase separation, characterized by disruptions in the intracellular liquid–liquid phase separation process, encompasses several anomalies: the inability to execute LLPS, where biomacromolecules such as proteins and nucleic acids fail to spontaneously form high-concentration condensates via multivalent interactions [7, 8]; impediments in transitioning between dense and dilute phases, affecting biomolecule distribution and function due to either excessively rapid or slow phase transitions [9]; condensates aging into insoluble phases, leading to protein aggregation and fibrosis as observed in neurodegenerative diseases [10, 11]; compromised stability and dynamics of condensates, which are essential for accurate cellular signal response and effective participation in biochemical reactions [12]; and abnormal composition and regulation of condensates, indicating irregularities in regulatory mechanisms that alter condensate composition and size, thereby impacting their function [13].

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Biomolecular condensates consist of a large number of molecules that determine and contribute to the material properties, compatibility, and localization of the condensates. These molecules can be classified as scaffolds or clients [14], based on their function in the condensate [15]. Usually, scaffolds are recognized as the supports of phase separation, while clients contain binding elements that provide free access to the condensates (Fig. 1) [16]. In cells, scaffolds typically have high local concentrations with multiple valences that depend on intrinsically disordered proteins (IDPs) [17]. Scaffolds typically initiate condensation and are characterized by high partition coefficients [18]. The remaining molecules, which are classified as clients, are transferred into condensates through interactions with scaffolds [19]. Although clients typically exhibit lower concentrations and less pronounced interactions, the affinity between scaffolds and clients represents a crucial determinant in their recruitment to condensates [20, 21].

The concept of IDPs was first proposed many years ago [22]. Strictly defined, IDPs are proteins that are entirely disordered and do not fold into a single, stable globular shape [23]. And instead of the full-length protein, intrinsically disordered regions (IDRs) are partial regions of the protein that are disordered. IDRs that are longer than 30 residues account for approximately one-third of the proteomes of most eukaryotic organisms [5, 6, 16, 24, 25]. According to the SWISS-PROT database, unstructured regions are present in about 79% of proteins associated with human cancer [26]. In this review, we use the term IDP broadly to refer to proteins with extensive, though not necessarily complete, functional disorder. More detailed classifications of IDPs and IDRs have also been described in the literature [6]. IDPs are characterized by their flexibility and ability to adopt multiple conformations, unlike structurally elucidated proteins that have well-defined structures required for their function [27, 28]. The structural flexibility of IDPs enables them to be involved in many kinds of biological processes, like signaling transduction [29], transcriptional control [30], and DNA repair [31–33]. IDPs and IDRs play a crucial role in the formation and molecular properties of biomolecular condensate, and IDPs typically serving scaffolds in the condensates [16, 27, 34]. Due to their conformational variability, IDPs are recognized as challenging targets for drug design, but they are also considered to have high pharmacological potential due to their involvement in various diseases, typically cancers [35] and neurodegenerative diseases [36].

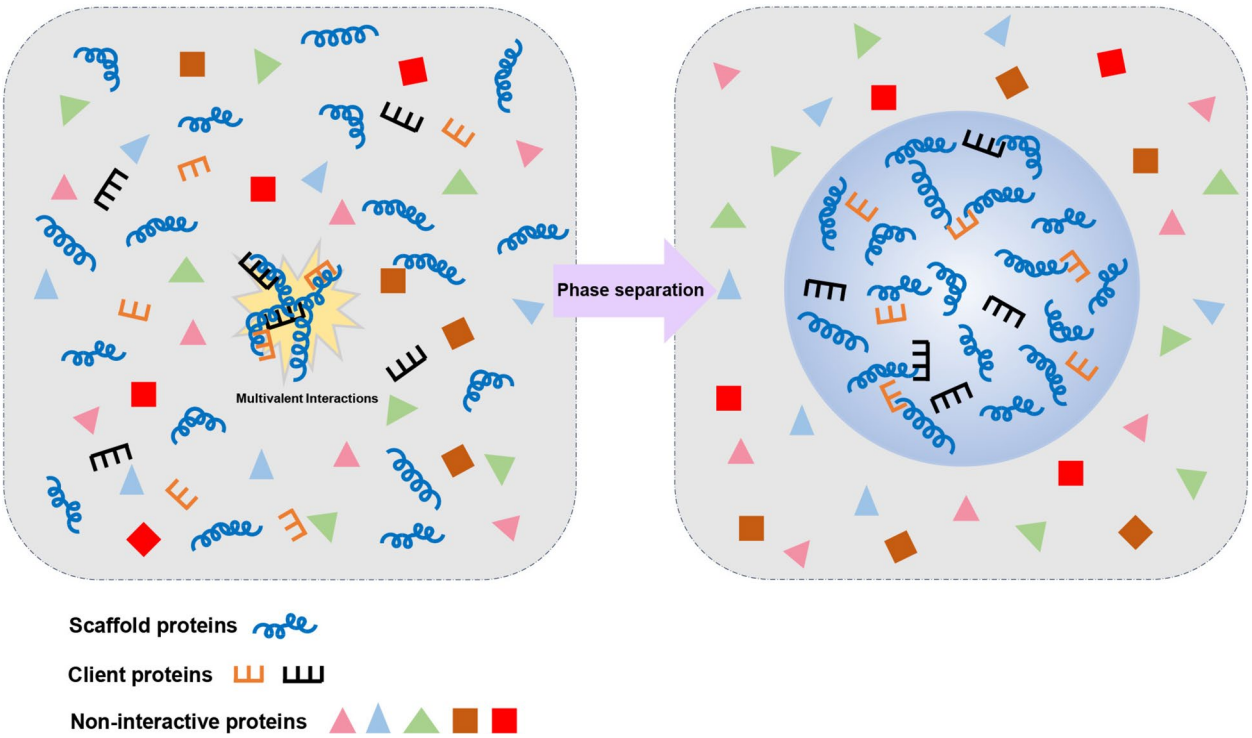

Fig. 1 The formation of biomolecular condensates. Though multivalent interactions, scaffolds and clients can engage in aggregative processes, thereby giving rise to biomolecular condensates

Abnormal biomolecular condensates in disease

The presence of aberrant condensates has been linked to various diseases, including cancer and neurodegenerative diseases [37–43]. There are three main ways in which abnormal biomolecular condensates can lead to cancer and other diseases. Firstly, genetic mutations have the potential to alter the valence of either a scaffold or client proteins. Mutated residues in a scaffold protein could alter the biochemical interactions between molecules and thereby affect the properties of a condensate [40, 41]. For example, cancer related T-cell intracellular antigen 1 (TIA1) mutations significantly increases the propensity of TIA1 protein to undergo phase transition and promotes the assembly of non-dynamic stress granules (SGs) [42]. Amyotrophic lateral sclerosis (ALS)-related TDP43 mutations in its C-terminal can disrupt TDP-43 interactions, and lead to the formation of pathological aggregates [44, 45]. In Huntington's disease, the exon 1 fragment of the huntingtin protein, which contains an expanded polyglutamine tract, forms aggregates in the brains. Research has shown that this protein fragment can form liquid-like condensates, which can convert into solid-like fibrillar assemblies when the polyglutamine tract reaches disease-associated lengths [46]. Secondly, mutations of an upstream regulator of the condensate might lead to abnormal condensate and condensate properties. For example, dipeptide repeat polypeptides bind to the nucleolar protein Nucleophosmin 1 (NPM1), altering NPM1 phase separation, dispersing NPM1 from nucleoli, which might be a cause of ALS [43]. In Alzheimer disease (AD), tyrosine-protein kinase Fyn-mediated tau phosphorylation and interaction between Fyn and tau may change tau trafficking and cause synaptic impairment due to tau mis-sorting [47]. Thirdly, environmental perturbations can affect the general physicochemical conditions in the cell, resulting in abnormal ATP levels, salt concentrations, or pH value [48–50]. All these changes in the physiological environment could lead to aberrant condensate formation throughout the cell. For example, environmental stimuli can induce the formation of stress granules, which are believed to accelerate aging [51].

Biomolecular condensates are involved in many vital cellular activities (Fig. 2), including chromatin organization, signal transduction, DNA repair, and transcriptional regulation, which are critical functions often disrupted in cancer [52]. For example, mutations in cancer-related proteins can alter their phase behavior, leading to the formation of aberrant condensates that drive oncogenic processes [53, 54]. One such example is the LLPS of nuclear pore complex protein 98 (NUP98) with homeobox A9 (HOXA9), which contributes to the formation of a broad superenhancer (SE)-like binding pattern, thereby promoting transcriptional activation of leukemogenic genes [55]. Because of their structural flexibility or complex features, various oncoproteins are considered as undruggable targets in tumor targeted therapy. It is noteworthy that recent studies have indicated that a considerable number of these proteins are subject to regulation by phase separation. For example, the carcinogenic transcription factors cellular myelocytomatosis oncogene protein (c-Myc) and tumor protein 53 (p53) can regulate downstream gene expression by forming condensates that recruit (RNA Pol II) and positive-transcription elongation factor b (P-TEFb) [7, 56]. However, both c-Myc and p53 lack specific and defined binding pockets for small molecules to interact with, making it difficult to develop drugs that can specifically inhibit their activity [57, 58]. Targeting the c-Myc and p53 biomolecular condensates' formation or functions may be a better approach than direct targeting of c-Myc and p53 protein. Interfering with biomolecular condensates is a potential approach to targeting undruggable proteins and making these powerful proteins druggable targets.

IDPs lack stable three-dimensional structures under physiological conditions but play critical roles in various biological processes and are associated with many major human diseases. While some IDPs are known to form phase-separated condensates, others do not form such structures. For example, inhibitor of nuclear factor κB (IκB) is an IDP with a relatively loose structure and lacks a well-defined three-dimensional structure [59]. However, its amino acid sequence distribution does not support the formation of a structural basis for driving phase separation [59]. BMS- 345541 is a highly selective inhibitor of IκB kinase that binds at an allosteric site of the enzyme, blocking NF-κB-dependent transcription [60].

Drug design strategies target biomolecular condensates

A novel class of therapeutic agents, designated as "condensate modifying drugs (c-mods)," has emerged that exerts its effects either directly or indirectly on the structure and function of biomolecular condensates [61]. These agents are not confined to small molecules, peptides, and oligonucleotides [62, 63]. c-mods are developed to achieve specific objectives, including repairing or eliminating a condensate, removing a target from its original condensate, or disrupting the function of a normal condensate. Based on the phenotypic change of the condensate, c-mods can be classified into 4 categories: (1) dissolvers, (2) inducers, (3) localizers, and (4) morphers [63]. Dissolver c-mods can either dissolve or prevent the formation of a target condensate [64, 65]. A drug-like molecule called integrated stress response inhibitor (ISRIB) is a typical dissolver

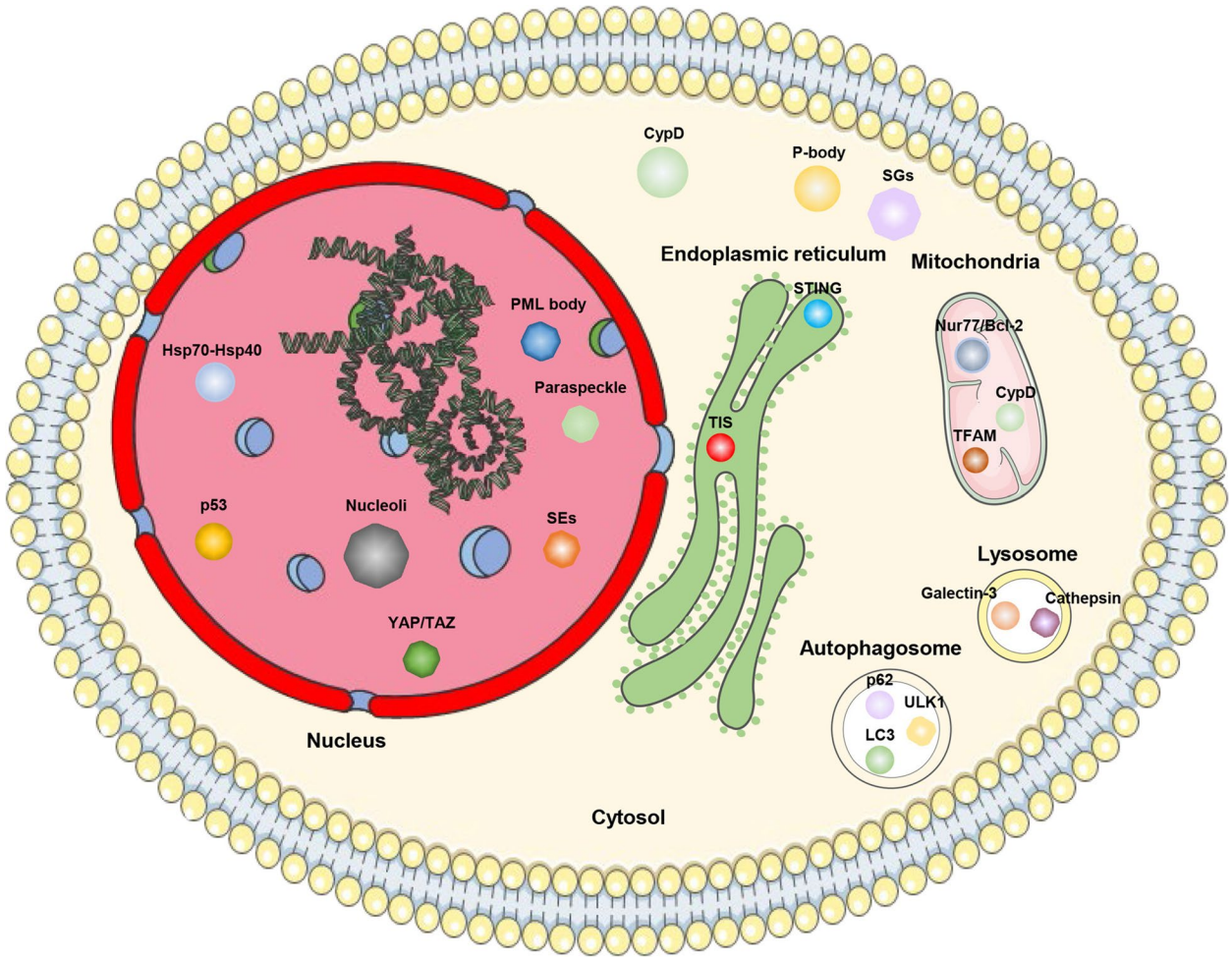

Fig. 2 Biomolecular condensates are important components of the cell. Biomolecular condensates are involved in many vital cellular activities, and are crucial to the functions of various organelles. The nucleus contains Hsp70-Hsp40 chaperone condensates for protein folding, SEs-related transcriptional condensates for gene regulation, YAP/TAZ and p53-related condensates for cell response to signals and DNA damage, paraspeckles for RNA retention, nucleoli for ribosome biogenesis, and PML bodies for gene regulation. Mitochondria have Nur77/Bcl- 2 condensates for apoptosis, TFAM for DNA maintenance, and CypD for permeability control. In the cytosol, SGs manage mRNA and protein sequestration during stress, fusion oncoprotein condensates drive oncogenic signaling, and P-bodies handle mRNA degradation. Lysosomes contain galectin- 3 and cathepsins condensates for immune response and protein degradation. Autophagosomes have ULK1, p62, and LC3 condensates for autophagy, while the endoplasmic reticulum houses STING for immune signaling and TIS granules for translation control. These condensates are critical for cellular homeostasis and are potential therapeutic targets in diseases like cancer and neurodegenerative disorders

c-mod which can reverse the eukaryotic Initiation Factor 2 alpha (eIF2α)-dependent stress granule formation and restores protein translation [66]. Inducer c-mods are capable of triggering the formation of condensate, thereby increasing biochemical reaction rates. Furthermore, inducer c-mods may be employed to accelerate or initiate biochemical reactions [67, 68]. For example, tankyrase inhibitors promote the formation of a post-translational modification (PTM)-derived degradation condensate that reduced beta-catenin levels [69]. Localizer c-mods can alter the sub-cellular localization of condensate community members [63]. For instance, NPM1, an abundant nucleolar protein, can form large oligomers and undergo liquid–liquid phase separation by binding to RNA or ribosomal proteins [70]. Localizer c-mods such as avrainvillamide can restore NPM1 in the nucleus and nucleolus and enhanced therapeutic efficacy against acute myeloid leukemia (AML) cells [71, 72]. Morpher C-mods are designed to target condensate functions by altering its morphology and material properties, including changes in condensate size, distribution, and shape. For instance, cyclopamine functions as a morphing c-mods, modifying the material properties of the respiratory syncytial virus (RSV)

condensate, thereby inactivating a transcription factor and inhibiting viral replication [73, 74].

Biomolecular condensates can be regulated by a variety of molecules [75]. Both scaffolds and clients could be effective targets for regulating biomolecular condensates. The majority of current research is concentrated on the development of drug targets for scaffolds, as it is believed that scaffolds represent the initial factor in the formation of biomolecular condensates [75, 76]. In light of the aforementioned considerations, we will now proceed to examine the strategy of drug-targeting IDPs and biomolecular condensates in greater detail (Fig. 3).

Modulating biomolecular condensates through scaffold proteins

During phase separation, the protein concentration of the target protein is of great consequence, and any alteration in this concentration will impact the formation and scale of biomolecular condensates [77]. However, many proteins that undergo phase separation have been reported to be overexpressed or under-expressed in cancers or other diseases, affecting their ability to undergo phase separation and leading to abnormal biological reactions [77, 78]. So, modulating the scaffold protein concentration may be an important and effective way to target biomolecular condensates. In the meantime, there are already established methodologies for regulating protein concentration, as described below.

Three types of protein degradation technologies are commonly used to down-regulate target proteins at the protein stage: proteolysis-targeting chimera (PROTAC), lysosome-targeting chimera (LYTAC) and autophagy-targeting chimera (AUTAC) [79]. PROTAC employs the ubiquitin–proteasome system (UPS) to degrade proteins [80]. The work of the PROTAC to degrade the protein relies on the UPS system, which binds the target protein through a ubiquitin ligase, resulting in Lys- 48-linked ubiquitination and further degradation of the target protein [81]. The LYTAC and AUTAC are both designed based on the lysosomal degradation system [82, 83]. Degradation of target substances occurs through the use of lysosomes in the lysosomal degradation system [84]. Two lysosomal degradation pathways are observed in eukaryotic cells: the endosome-lysosomal pathway and the autophagy pathway. The endosome–lysosomal pathway is responsible for the breakdown of target substances through membrane-based binding [85]. In the autophagy pathway, the target substance is engulfed by phagocytes

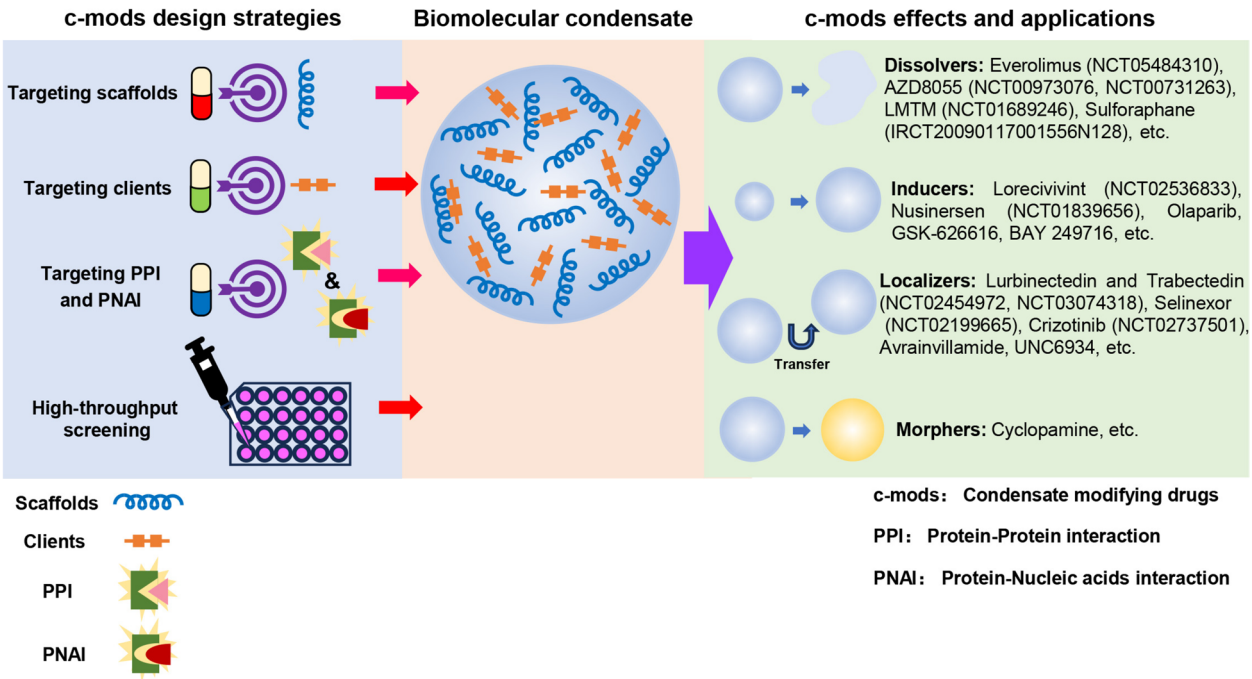

Fig. 3 c-mods Design Strategies and Applications. This figure illustrates the various approaches to designing c-mods that target biomolecular condensates and their effects on these condensates. The strategies are categorized into four main types: Dissolvers, which either dissolve or prevent the formation of target condensates; Inducers, capable of triggering condensate formation and increasing biochemical reaction rates; Localizers, which relocate biomolecular condensates to other positions without compromising the integrity of the condensate; and Morphers, designed to alter the morphology and material properties of condensates, including changes in size, distribution, and shape. The figure provides examples of c-mods, including those that are currently in clinical trials, which are indicated with their respective trial identifiers: Everolimus (NCT05484310), AZD8055 (NCT00973076, NCT00731263), LMTM (NCT01689246), Nusinersen (NCT01839656)

to form autophagosomes, which are subsequently degraded by lysosomes [86].

RNA interference (RNAi) has been demonstrated to modulate the synthesis of scaffold proteins at the RNA stage [87]. Two distinct types of RNAi are employed: small RNA and antisense oligonucleotides (ASOs) [88]. In the process of gene silencing, small RNAs interact with the RNA-induced silencing complexes (RISC), which are capable of recognizing complementary mRNA. This interaction results in the degradation of the mRNA [89]. ASOs are a series of single strands of deoxynucleotides that can interact with target RNA to form a DNA–RNA hybrid. This enables RNA to be cleaved by ribonuclease H1 (RNaseH1), which ultimately results in a decrease in target protein expression [90].

The process of DNA editing relies on the use of specific DNA recognition elements and endonucleases to introduce mutations into genes, thereby disrupting the synthesis of scaffold proteins at the DNA stage [91]. Due to the advantages of simple design, low cost, high efficiency, the most commonly used DNA editing system is clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR-Cas9), which was originally discovered in bacteria [92, 93]. The main components of CRISPR-Cas9 system are Cas9 endonuclease and single-guide RNA (sgRNA) [94]. These two components form a Cas9 ribonucleoprotein (RNP) that can bind and cleave the target DNA [95].

Many recent studies have shown that PTM is an important regulator of the phase separation and the properties of biomolecular condensates [96]. Given that PTM is capable of regulating the weak multivalent interaction that initiates phase separation, it has been regarded as a regulatory switch for the condensation process [97–99]. Regulating phase separation may be possible by controlling the activity of such enzymes. For example, LLPS of RNF168 is inhibited by small ubiquitin-like modification (SUMO)-specific peptidase 1 (SENP1), which specifically deSUMOylates RNF168 upon DNA double-strand breaks (DSB) [100]. Targeting SENP1 might be a better approach than direct target RNF168 phase separation. Further study experiments are necessary to prove its feasibility. However, identifying the right PTM targets and finding specific small molecule activators or inhibitors will be difficult because most diseases can involve the dysfunction of many biomolecular condensates [101].

Interfering with condensation-associated client molecules

The formation and maintenance of biomolecular condensates is also contingent upon the presence of client molecules within the condensate, including nucleic acids [102]. The chemical interactions that drive condensate formation are multifaceted and involve a variety of non-covalent interactions. For instance, electrostatic interactions between the negatively charged phosphate backbone of nucleic acids and the positively charged residues of proteins, such as arginine and lysine, are crucial for condensate assembly [103, 104]. Additionally, hydrophobic interactions and π-π stacking between aromatic amino acids and nucleobases contribute to the stability and dynamics of these condensates [105, 106].

Recent studies have demonstrated that RNA plays a role in facilitating phase separation and is involved in the formation of numerous biomolecular condensates, including stress granules [107, 108], processing bodies [109, 110], neuronal transport granules [111], nuclear paraspeckles [112], and germ granules [113]. Additionally, RNA can also inhibit the phase separation behavior of prion-like RNA-binding proteins (RBPs) [114, 115]. RNA's secondary and tertiary structures, such as hairpin loops, helical motifs, and G-quadruplexes, serve as building blocks that provide flexible binding sites for various molecules, thereby promoting the formation of biomolecular condensates. G-quadruplex structures can facilitate gel-like phase separation and act as scaffolds, enabling single RNA molecules to interact with multiple RNA molecules, thus resisting degradation by ribonucleases [116, 117].

Modifying biomolecule condensates by affecting RNA appears to be a viable approach, and certain regulatory elements are already present in cells. RNA modifications, such as N6-methyladenosine (m6 A), are crucial in regulating RNA's involvement in phase separation [118]. m6 A is the most abundant RNA modification in eukaryotes and can influence RNA structure, interaction networks, localization, and stability, thereby modulating RNA's participation in phase separation processes [118, 119]. m6 A modifications can alter the binding affinity of RNA, affecting its interactions with proteins and other molecules, and consequently impacting the assembly and function of condensates [120].

RNA helicases have been demonstrated to play a pivotal role in regulating phase-separated RNA–protein complexes [121]. RNA helicases utilize the energy from ATP hydrolysis to unwind RNA double strands or change the conformation of RNA–protein complexes [122]. They often contain IDRs that can facilitate condensate formation in the presence of ATP and RNA [123, 124]. For example, DEAD/H-box ATP-dependent RNA helicase 1 (Dhh1) is crucial for cytoplasmic mRNA metabolism and processing bodies (P-body) formation [125]. Dhh1's helicase activity can influence the secondary structure of mRNA and RNA–protein interactions, thereby regulating the assembly and function of P-bodies [126]. Mutations in Dhh1 can lead to abnormal P-body formation and dynamics, affecting cellular mRNA degradation and

storage processes [126, 127]. Similarly, mutations in other DEAD-box helicases like Ded1/Ddx3 have been shown to contribute to the formation of stress granules, likely by altering the stability and dynamics of RNA–protein complexes [128, 129].

Besides RNA, DNA is also an important client in some biomolecular condensates [130]. The behavior of single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) in complex with polycationic peptides differs significantly [131]. ssDNA is a shorter, more flexible, and hydrophobic polymer with a lower charge density, which strongly affects coacervation formation [132]. In contrast, long dsDNA has rarely been studied in peptide-based coacervation due to its stiff chain, hydrophilicity, and high charge density [132]. However, recent studies have shown that short dsDNA can form coacervates with poly-l-lysine (pLys), contributing to the exploration of prebiotic cell evolution [132, 133]. The coacervates of short dsDNA and poly-l-lysine exhibit liquid–liquid phase separation instead of precipitation, and the short dsDNA dominates the aggregation and packing process in coacervation [132–134].

In the event that disease-associated enzymes are the condensate's clients, it would be preferable to link a small-molecule inhibitor to a molecule that concentrates in the condensate. For instance, small molecule ISRIB can reverse the effects of eIF2α phosphorylation on translation and regulate the dynamics of stress granules, which may be significant for treating diseases associated with eIF2α phosphorylation, stress granule formation, and cognitive decline [134, 135].

Targeting protein–protein interaction or protein–nucleic acid interaction

A drug that could prevent the formation of protein–protein or protein-nucleic acid complexes is an option to disrupt biomolecular condensates [136]. In the case of protein–protein interactions, where one of the two partners exhibits a well-defined structure and the other displays a flexible structure, drug design can be utilized to target the structured partner. Subsequently, the interaction surface can be predicted utilizing the 3D structure and potential ligands can be developed based on this information [137]. For example, in the heat shock protein 90 (Hsp90)- cell division cycle 37 (Cdc37) interaction, a novel triazine derivative called DCZ3112 has been identified as a disruptor. Molecular docking studies have shown that DCZ3112 forms hydrogen bond interactions with key amino acid residues such as Arg32 A, Glu33 A, Ser36 A, Ser115 A, Gly118 A, Gln119 A, and Arg167B at the protein–protein interaction (PPI) interface, which are major contributors to protein–ligand interactions [138].

However, the challenges come when the interacting regions of both partners are disordered, because the interaction region among partners is ambiguous and it is difficult for small molecules to block the interaction [139]. In this context, the drug targeting strategy can be divided into two distinct steps. The initial step is to define the disordered regions that are involved in the interaction. The subsequent step is to identify a molecule that binds to one of these regions and inhibits the interaction. Although direct structural analysis of IDP-IDP complexes may be infeasible, several alternative approaches can still yield valuable insights. One way to evaluate the impact of sequence mutations is to follow a systematic approach, such as alanine scanning and deep mutational scanning [140, 141]. An alternative approach is to computationally predict potential complex structures through the use of techniques such as molecular dynamics simulation [142, 143] or machine learning-based structure prediction methods such as AlphaFold series [144–146]. For instance, AlphaFold 3 has shown the ability to predict structures from input polymer sequences, residue modifications, and ligand simplified molecular-input line-entry system (SMILES), and can generalize to a number of biologically important and therapeutically relevant modalities [146].

It has been demonstrated that disordered regions often contain relatively short disordered sequences that exhibit molecular recognition and binding abilities. These sequences are referred to as molecular recognition fragments (MoRFs) [147]. When MoRFs bind and initiate the protein–protein interaction, the IDRs transit from disorder to defined structure, they represent an ideal target for the drug design of biomolecular condensates [147]. Although there are multiple MoRF predictors online [148–150], designing protein–protein inhibitors remains a challenge. When a protein's inability to sustain liquid–liquid phase separation contributes to disease pathogenesis, pharmacological agents that promote phase separation of the protein may serve as an alternative therapeutic strategy. The objective is to utilize pharmacological agents to simulate the binding partner of the targeted disordered protein, thereby facilitating the transition to an ordered state [151]. For example, curcumin interacts with α-synuclein (α-Syn) during phase separation by binding to its hydrophobic regions, decreasing the fluidity of α-Syn inside the condensates and effectively delaying or inhibiting the transition to amyloid fibrils [138]. It can also destabilize preformed α-Syn amyloid aggregates in the condensates [138]. Another example is epigallocatechin gallate (EGCG), which directly binds to hydrophobic protein sequences through hydrophobic interactions and hydrogen bonding, modulating the phase separation

behavior of α-Syn and amyloid-β fibrils and maintaining them in a less aggregated, more soluble state [152–154].

Another important functional region within IDRs is short linear motifs (SLiMs). SLiMs are short sequences, typically 3 to 10 amino acids long, that mediate specific protein interactions. They are often flanked by disordered regions, which allow for conformational flexibility and the ability to engage multiple partners [155]. The recurrent interactions between SLiMs and well-structured domains suggest that SLiMs can affect phase-separated condensates, providing opportunities to manipulate these interactions to control biological activities [156, 157]. Targeting SLiMs within IDRs represents a new approach to achieving the targeting of IDRs [158]. For instance, targeting SLiMs in human double minute X (HDMX) can mediate its interaction with p53, thereby affecting the binding of p53 to DNA [159].

A novel approach has been devised to enhance the inhibitory capacity of a drug on protein–protein binding. This is achieved by chemically linking two monovalent structural domain inhibitors [160, 161]. This strategy has shown promise in improving the binding potential of the resulting compound by introducing novel interaction patterns while retaining key interactions. Additionally, some small molecules regulating protein phase separation have been identified through phenotypic screening, and they often share common characteristics such as strong hydrophobicity, high molecular weight, and the presence of multiple aromatic rings, long alkyl chains, or multiple functional groups that can provide a variety of chemical interactions [162–164]. However, whether these small molecules are selective in regulating condensates remains unclear. Rational drug design may be a good strategy if the LLPS mechanism of the target is well studied. For example, allosteric inhibitors of Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2) specifically bind to it to regulate its conformation and phase separation [165–167]. For disordered proteins, specific binding ligands can also be obtained through computer-aided drug design strategies or high-throughput screening [168–170].

High-throughput screening of phase-separation modulators

High-throughput screening (HTS) is the preferred method when the target is poorly characterized, as this approach precludes structure-based drug design [171, 172]. In addition, HTS can be utilized in conjunction with other strategies, such as fragment-based drug design (FBDD) and high-content imaging [173, 174]. Fragment discovery has been instrumental in the identification of novel targets that are challenging to engage with traditional chemical libraries, such as drug screening for IDPs. The most commonly used FBDD detection methods are nuclear magnetic resonance (NMR), mass spectrometry, and X-ray crystallography [175].

High-content imaging is the most commonly used and intuitive screening method for living cells. High-content imaging system can collect optical or fluorescent signals from living cells and these signals are further quantified and converted into numerical data [176]. PhaseScan is a droplet-based detection platform that enables rapid and high-resolution acquisition of multidimensional changes in biomolecular condensates [177]. This innovative technology facilitates high-throughput analysis of protein phase behavior, which is essential for elucidating the assembly mechanisms of biomolecular condensates [177]. The platform can quantitatively characterize the effects of small molecules on phase separation, providing insights into how these molecules modulate biomolecular condensates [177]. Furthermore, PhaseScan is versatile and can be applied to a wide range of condensate systems. It is capable of analyzing homo- and heterotypic phase separation of full-length proteins, as well as protein-RNA and protein–protein coacervates, and simple peptide systems [177].

Another noteworthy technology is phase-separated condensate-aided enrichment of biomolecular interactions in test tubes (CEBIT), which has been developed for the purpose of testing the effects of compounds on protein interactions [178, 179]. By inducing the formation of condensates, CEBIT enriches the local concentration of biomolecules within the test tube, significantly enhancing the likelihood of biomolecular interactions. This enrichment facilitates the detection and analysis of these interactions, which are often challenging to observe in bulk solutions [178]. CEBIT has broad applications in research areas such as protein–protein and protein-RNA interactions, drug screening, and the investigation of cellular processes involving condensates. Through the implementation of CEBIT, a novel inhibitor of the p53/human double minute 2 (HDM2) interaction, namely SUV39H1, was successfully identified from a compound library [178]. This technology represents a significant advancement in biomolecular research, offering a robust platform for exploring complex biological systems and developing novel therapeutic strategies.

Current experimental challenges in using and implementing c-mods

The development and implementation of c-mods face several challenges that need to be addressed. Target validation and specificity is a significant challenge. Identifying and validating specific condensates as therapeutic targets is complex due to their dynamic nature and involvement in multiple cellular processes. Multiomics

data, high-content imaging (HCI), and artificial intelligence (AI) technologies can be employed to predict condensate formation and validate their role in disease. For example, a novel approach combining the analysis of various therapeutic target-identifying parameters via the multiomic AI-powered PandaOmics platform and the assessment of protein PPS propensity using FuzDrop is presented to prioritize human diseases for proteins phase separation-based interventions [180, 181]. Functional validation in disease-relevant models is crucial to confirm the therapeutic potential of targeting specific condensates.

The elucidation of structure–activity relationships (SAR) within the context of c-mods presents a formidable challenge, attributable to the profound complexity of intermolecular interactions that occur within condensates. A substantial proportion of condensate constituents, such as IDRs, do not assume stable conformational structures, thereby complicating the application of structure-guided drug design paradigms. New techniques, such as DRPScore and AlphaFold 3, have the potential to predict potential binding sites and interactions with a high degree of accuracy, thereby providing a robust foundation for the design of more efficacious c-mods [146, 182].

Drug delivery and bioavailability constitute critical issues in the development of c-mods. Ensuring that c-mods effectively reach their target condensates within cellular environments represents a formidable challenge. The physicochemical attributes of c-mods, including solubility and permeability, necessitate optimization to enhance their overall bioavailability. The development of sophisticated drug delivery systems, such as nanoparticles or liposomes, holds promise in improving the cellular uptake and distribution of c-mods [183, 184]. Furthermore, the refinement of the chemical properties of c-mods through medicinal chemistry approaches can significantly augment their stability and bioavailability, thereby facilitating their therapeutic efficacy [62].

Off-target effects and toxicity constitute potential issues of concern in the context of c-mods. Given the extensive involvement of condensates in a myriad of cellular processes, c-mods may exert off-target effects, which in turn can precipitate unintended biological ramifications and toxicity. Thorough preclinical testing, encompassing both in vitro and in vivo studies, is indispensable for the assessment of the safety and efficacy profiles of c-mods. The utilization of disease-relevant models and patient-derived cells can aid in the identification of potential off-target effects and facilitate the optimization of the therapeutic window.

Clinical translation represents a formidable obstacle in the development of c-mods. The transition of c-mods from the laboratory setting to clinical application necessitates the surmounting of regulatory barriers and the unequivocal demonstration of clinical efficacy. The paucity of well-established biomarkers for condensate-related diseases poses a considerable challenge in quantifying the therapeutic response. Concerted collaborative endeavors among academia, industry, and regulatory agencies are imperative for the formulation of standardized protocols governing clinical trials. The identification and validation of biomarkers capable of monitoring the therapeutic response to c-mods will be of paramount importance for the successful clinical translation of these agents.

Conclusions

Understanding IDPs and biomolecular condensates provides an opportunity to design drugs with novel targeting strategies. Targeting LLPS offers a significant advantage in overcoming the limitations of traditional drug discovery. Proteins that are involved in biomolecular condensates, like IDPs, frequently lack distinct structures, making conventional targeting methods challenging [185].

By emphasizing the modulation of phase separation itself, rather than individual protein structures, a wider range of potential therapeutic targets can be identified, which can overcome the limitations of traditional approaches. Initial evidence suggests that some approved pharmaceuticals may concentrate into condensates [186]. Secondly, high-content cellular screening has demonstrated that certain drug-like molecules are capable of regulating condensate behaviors [187]. Thirdly, PTM enzymes represent the most promising drug targets, given that PTM exerts a pronounced regulatory influence on the formation and dissolution of condensates [188, 189]. A number of small molecules are currently undergoing clinical trials and have been demonstrated to target condensates (Table 1).

Nevertheless, further research is required to address several outstanding issues. First and foremost, we need to verify whether the relevant functions of the protein depend on its phase separation ability. Elucidating the molecular mechanisms underlying biomolecular condensates may facilitate the identification of novel therapeutic targets for clinical intervention. Moreover, biomolecular condensates represent a vast array of potential drug targets for a multitude of diseases. Specificity is a critical factor that must be taken into account. It remains unclear whether distinct condensates can be selectively targeted through the partitioning of a small molecule to a specific condensate. The druggability of these targets needs to be tested in future clinical trials. Degradation of scaffolds or IDPs can result in unexpected problems due to their involvement in many biological reactions.

Table 1 Drugs targeting IDPs or/and biomolecular condensates

Reltaed disease	Compound	Target	The Mechanistic Underlying Drug Action	Clinical trial number
Alzheimer disease (AD)	LMTM	Tau	LMTM interacts extensively with multiple structural domains of Tau proteins, inducing conformational extension and delays the formation of cytotoxic Tau amyloid fibers [190]	NCT01689246, TRx- 237–005
AD	Myricetin	Tau	The chelating activity of Myricetin prevent the conformational changes and subsequent aggregation [65]	-
AD	SEN1576	Amyloid-β (Aβ)	By binding to Aβ1–42, SEN1576 prevent the nucleation and elongation steps of Aβ aggregation, which are critical for the formation of amyloid plaques [191]	-
AML	Avrainvillamide	NPM1	Avrainvillamide targets NPM1 by directly binding to the C-terminal domain, specifically at Cys275 in certain mutants, and influences NPM1 localization and cellular functions [72, 192]	-
Anemia	GSK- 626616	DYRK3	GSK- 626616 binds to the ATP-binding site of DYRK3, preventing ATP from binding and inhibiting the kinase activity of DYRK3, which is essential for regulating the phase transitions of several types of membraneless organelles during mitosis [193, 194]	-
Amyotrophic lateral sclerosis (ALS)	Fasudil	α-Synuclein	Fasudil direct bind the tyrosine residues Y133 and Y136 in the C-terminal region of α-Synuclein, and affect its aggregation process [195, 196]	NCT03792490, NCT05218668
ALS	Curcumin	α-Synuclein	Curcumin interacts with α-Synuclein during phase separation by binding to its hydrophobic regions, decreasing the fluidity of α-Syn inside the condensates and effectively delaying or inhibiting the transition to amyloid fibrils [197]	
ALS	c9 ASO	C9ORF72	C9 ASOs are engineered to selectively silence the sense transcript of the C9ORF72 gene, which contains the hexanucleotide repeat expansion associated with ALS [198]	NCT04979369,
ALS	ION363	FUS	ION363 is engineered to selectively silence the sense transcript of the FUS gene, which contains mutations associated with ALS [199]	NCT04768972
ALS	Mitoxantrone	TDP- 43	Mitoxantrone promotes the dissociation of TDP- 43 from stress granules [200], However, the mechanism remains unclear	-

Table 1 (continued)

Reltaed disease	Compound	Target	The Mechanistic Underlying Drug Action	Clinical trial number
ALS	Lipoamide	SGs	Lipoamide specifically targets redox-sensitive stress granule proteins, such as SRSF1 and SFPQ. It dissolves stress granules by disrupting the phase separation process [201]	-
Breast cancer	Integrated Stress Response Inhibitor (ISRIB)	eIF2b	By binding the interface between the β and δ regulatory subunits of eIF2B, ISRIB restoring eIF2B activity and promoting translation, ISRIB can influence the assembly and disassembly of stress granules [202, 203]	-
Breast cancer	MYCMI- 6	MYC	As an IDP, MYC exists in a dynamic conformational ensemble[204]. MYCMI- 6 selectively binds to the basic helix-loop-helix leucine zipper (bHLHZip) domain of MYC [205, 206]	-
Cancer	Sulforaphane	nuclear β-catenin condensates	Sulforaphane can induce beta-catenin condensates in the nucleus, resulting in inhibition of the Wnt/β-catenin pathway, independent of beta-catenin degradation [207, 208]	NCT03517995, NCT01228084
Cancer	Trabectedin	EWS-FLI1	By disrupting the DBD's interaction with DNA, trabectedin inhibits the transcriptional activation of EWS-FLI1 target genes [209–211]	NCT00050427
Cancer	Cisplatin	MED1 and BRD4	Cisplatin has been shown to selectively partition into MED1 condensates. This partitioning is facilitated by interactions with aromatic residues in MED1 [186]. Prolonged treatment with cisplatin leads to the gradual and specific disruption of MED1 condensates [212]	
Cancer	ADH- 6	p53	ADH- 6 appears to disrupt the aggregation of mutant p53 by interfering with the interactions of the aggregation-nucleating subdomain of mutant p53 DBD [213]	-
Cancer	BAY 1892005	p53	BAY 1892005 affects the aggregation state of p53 without reactivating its function, providing a novel approach to targeting p53 in cancer cells [214]	-

Table 1 (continued)

Reltaed disease	Compound	Target	The Mechanistic Underlying Drug Action	Clinical trial number
Cancer	BAY 249716	p53	IBAY 249716 is described as a covalent binder, meaning it forms covalent bonds with p53, and induce the formation of condensates in p53 DNA-binding defective mutants [214]	-
Cancer	DCZ3112	Hsp90α-CDC37	DCZ3112 forms hydrogen bond interactions with key amino acid residues at the PPI interface, which leads to the degradation of HSP90 client proteins [138]	
Cancer	BI- 3802	BCL6	The binding of BI- 3802 to the BTB domain induces the aggregation of BCL6 into intracellular foci or"aggregates"[215, 216]	
Cancer	BMH21	RNA polymerase I	By binding to rDNA, BMH- 21 inhibits the transcription of ribosomal RNA (rRNA), which is the primary function of Pol I [217]	-
Cancer	Mitoxantrone, Etoposide	DNA topoisomerase II	Mitoxantrone and Etoposide intercalates into DNA and stabilizes the topoisomerase II-DNA cleavage complex. This prevents the re-ligation of the double-strand breaks made by topoisomerase II [218]	NCT00024492 NCT02043756 NCT00165451
Cancer	Leptomycin B	NUP98–HOXA9	By inhibiting CRM1, LMB prevents the nuclear export of NUP98-HOXA9. This results in the retention of NUP98-HOXA9 in the nucleus, where it forms nuclear aggregates [219]	-
Cancer	Polygonum cuspidatum	BRD4	PCG directly binds to the intrinsically disordered region of BRD4, specifically targeting proline-rich sequences [220]	NCT00768118
Cancer	Tamoxifen	MED1	The binding of tamoxifen to ER leads to the eviction of ER from MED1 condensates [186]	-
Cancer	ZZW- 115	NUPR1	By binding to Thr68, ZZW- 115 hinders the nuclear translocation of NUPR1. This is crucial because NUPR1's nuclear localization is necessary for its role in promoting cancer cell survival and proliferation [221]	-
Cancer	EN4	MYC	EN4 covalently binds to cysteine 171 in the intrinsically disordered region of MYC. This binding is crucial for disrupting MYC's function [222]	-

Table 1 (continued)

Reltaed disease	Compound	Target	The Mechanistic Underlying Drug Action	Clinical trial number
Cancer	GAP161	G3BP1	GAP161 is designed to bind to the NTF2-like domain of G3BP1. This domain is crucial for the formation of stress granules and the interaction with RasGAP [223]	-
Cancer	Allosteric	SHP2	SHP099 binds to a tunnel-like pocket in SHP2, stabilizing the auto-inhibited conformation[224, 225]	
Non-small-cell lung cancer	Crizotinib	EML4-ALK	Crizotinib binds to the ATP-binding site of the ALK kinase domain within the EML4-ALK fusion protein [226–228]	NCT02737501,
Pancreatic ductal adenocarcinoma	JQ1	BET family	JQ1 selectively binds to the bromodomains of BET proteins, which participate in the formation of transcriptional condensates [229]	-
Prostate cancer	EPI- 002 and EPI- 7170	Androgen Receptor	Both EPI- 002 and EPI- 7170 bind to the Tau-5 region of the AR NTD. This region is crucial for the transcriptional activity of the androgen receptor [230, 231]	NCT04421222
Prostate cancer	Oxaliplatin	Nucleolar and Cajal body	While oxaliplatin primarily targets the nucleolus, its effects on DNA damage can also influence Cajal bodies, which are involved in the modification of small nuclear RNAs and are crucial for proper splicing and RNA processing [232]	-
Fragile X-associated tremor/ataxia syndrome	ASO-CCG	FMR1	ASO-CCG binds to the expanded CGG repeats in the FMR1 mRNA with high affinity. This binding disrupts the formation of toxic RNA structures and interactions that contribute to FXTAS pathology [233]	-
Infectious disease	RK- 33	DDX3	RK- 33 binds to the ATPase domain of DDX3, prevents DDX3 from performing its functions in RNA metabolism, including translation initiation and viral RNA replication [234, 235]	-
Infectious disease	Cyclopamine	M2 - 1	Cyclopamine impairs the competition between the phosphoprotein (P) and RNA binding to M2 - 1. This disruption affects the dynamics of the M2 - 1-P interaction, which is crucial for the formation and function of viral inclusion bodies [74, 236]	-

Table 1 (continued)

Reltaed disease	Compound	Target	The Mechanistic Underlying Drug Action	Clinical trial number
Infectious disease	NIP-V	SARS2-NP	NIP-V targets the dimerization domain of SARS2-NP, which is crucial for its LLPS. By binding to this domain, NIP-V disrupts the protein–protein interactions that drive phase separation [64]	-
Inflammatory bowel disease	Rho-rock inhibitors (Y27632, Y39983)	INAVA	ROCK inhibitors, including Y27632, can modulate the formation of cytosolic condensates [237]	-
Lymphoma	YK- 4–279 and TK- 216	ETS family members	YK- 4–279 and TK- 216 are designed to disrupt the interactions between ETS family transcription factors and RNA helicases such as DDX5 and DHX9. This disruption is crucial for the function of ETS factors in gene regulation [238]	NCT03752138
Melanoma	PJ34	PARP	PJ34 acts as a competitive inhibitor by binding to the active site of PARP. This binding prevents PARP from catalyzing the transfer of ADP-ribose units from NAD + to target proteins, thereby inhibiting the formation of poly-PAR polymers [239, 240]	-
Myeloma	UNC6934	NSD2	UNC6934 targets NSD2 by binding to its PWWP domain and disrupting its chromatin interactions, leading to altered localization and function [241]	-
Myeloma	SI- 2	SRC3/NSD2	SI- 2 disrupts the interaction between SRC3 and NSD2, leading to the dissolution of SRC3 condensates and sensitization of multiple myeloma cells to bortezomib treatment [242]	-
Spinal muscular atrophy	Nusinersen	Cajal body	SMN is a key component of Cajal bodies, which are involved in the biogenesis of snRNPs. Nusinersen indirectly restores the function of Cajal bodies by increasing the availability of full-length SMN [243, 244]	NCT01839656

The patho-mechanism of condensates is unclear in many neurodegenerative diseases and cancers, it is necessary to clarify whether the abnormality of protein phase separation is a pathological consequence or a causative factor of the disease. Conducting further fundamental investigations into disease pathomechanisms is essential to designing drugs that target IDPs and biomolecular condensates.

Abbreviations

LLPS	Liquid-Liquid Phase Separation
IDPs	Intrinsically Disordered Proteins
IDRs	Intrinsically Disordered Regions
TIA1	T-cell intracellular antigen 1
SGs	Stress granules
NPM1	Nucleophosmin 1
ALS	Amyotrophic lateral sclerosis
NUP98	Nuclear pore complex protein 98
HOXA9	Homeobox A9
SE	Superenhancer
c-Myc	Cellular myelocytomatosis oncogene protein
p53	Tumor protein 53
RNA Pol II	RNA polymerase II
P-TEFb	Positive-transcription elongation factor b
IκB	Inhibitor of nuclear factor κB
c-mods	Condensate modifying drugs
ISRIB	Integrated stress response inhibitor
eIF2α	Eukaryotic Initiation Factor 2 alpha
PTM	Post-translational modification
AML	Acute myeloid leukemia
RSV	Respiratory syncytial virus
PROTAC	Proteolysis-targeting chimera
LYTAC	Lysosome-targeting chimeria
AUTAC	Autophagy-targeting chimera
UPS	Ubiquitin-proteasome system
RNAi	RNA interference
ASOs	Antisense oligonucleotides
RISC	RNA-induced silencing complexes
RNaseH1	Ribonuclease H1
CRISPR-Cas9	Clustered regularly interspaced short palindromic repeats-associated protein 9
sgRNA	Single-guide RNA
RNP	Ribonucleoprotein
SUMO	Small ubiquitin-like modification
DSB	DNA double-strand breaks
RBPs	RNA-binding proteins
m6 A	N6-methyladenosine (m6A)
ssDNA	Single-stranded DNA
dsDNA	Double-stranded DNA
pLys	Poly-l-lysine
Hsp90	Heat shock protein 90
Cdc37	Cell division cycle 37
PPI	Protein-Protein Interaction
SMILES	Simplified molecular-input line-entry system
MoRFs	Molecular recognition features
α-Syn	α-Synuclein
EGCG	Epigallocatechin gallate
SLiMs	Short linear motifs
HDMX	Human double minute X
SHP2	Src homology 2 domain-containing protein tyrosine phosphatase 2
HTS	High-throughput screening
FBDD	Fragment-based drug design
NMR	Nuclear magnetic resonance
CEBIT	Condensate-aided enrichment of biomolecular interactions in test tubes
HDM2	Human double minute 2
HCI	High-content imaging
AI	Artificial intelligence
SAR	Structure-activity relationships
TAZ	Tafazzin
PML body	Promyelocytic leukemia nuclear body
Nur77	Nuclear Hormone Receptor NUR/77
TFAM	Transcription factor A, mitochondrial
CypD	Cyclophilin D
ULK1	Unc-51 Like Autophagy Activating Kinase 1
p62	Sequestosome 1
LC3	Microtubule-Associated Protein 1 Light Chain 3
STING	Stimulator of interferon genes
TIS	Translation initiation stimulatory
PNAI	Protein-nucleic acids interaction
AD	Alzheimer disease
ALS	Amyotrophic lateral sclerosis
Aβ	Amyloid-β
DTRK3	Dual specificity tyrosine phosphorylation regulated kinase 3
ISRIB	Integrated Stress Response Inhibitor
C9ORF72	Chromosome 9 open reading frame 72
FUS	Fused in sarcoma
TDP- 43	TAR DNA-binding protein 43
EWS	Ewing sarcoma breakpoint region 1
FLI	Friend leukemia integration 1
MED1	Mediator complex subunit 1
BRD4	Bromodomain-containing protein 4
bHLHZip	Helix-loop-helix leucine zipper
CDC37	Cell division cycle 37
BCL6	B-cell lymphoma 6
NUPR1	Nuclear protein 1
G3BP1	Ras-GTPase-activating protein-binding protein 1
EML4	Echinoderm microtubule-associated protein-like 4
ALK	Anaplastic lymphoma kinase
NAD +	Nicotinamide Adenine Dinucleotide
BET	Bromodomain and extra-terminal domain
FMR1	Fragile X Mental Retardation 1
DDX3	DEAD-box RNA helicase 3
M2 - 1	Respiratory syncytial virus M2-1 protein
SARS2-NP	Severe acute respiratory syndrome coronavirus 2-nucleocapsid protein
INAVA	Innate immunity activator
ETS	Erythroblast transformation specific
PARP	Poly ADP-ribose polymerase
NSD2	Nuclear receptor-binding SET domain protein 2
SRC3	Steroid receptor coactivator protein 3

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Authors' contributions
C.Q. and Y.L.W. drafted the manuscript, and should be regarded as joint first authors. J.Z. provided a wealth of information for the study. X.B.W. and X.J.F. reviewed and edited the manuscript. X.B.W. and X.J.F. are the joint corresponding authors of this paper. All authors read and approved the final manuscript.

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Declarations

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