Review Article

Journal of Biomedical and Pharmaceutical Insights (JBPI)
e-ISSN: Applied For
Volume 1 | Issue 1 | 2026 | Pages 91-106
DOI: To be assigned
https://jbpijournal.org

A Review on Liquid-Liquid Phase Separation (LLPS) as a Druggable Phenomenon: Small-Molecule Modulators of Oncogenic Biomolecular Condensates

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Abstract

Liquid-liquid phase separation is a key biological mechanism used to facilitate subcellular compartmentation leading to the formation of membrane-less compartments. Cancer cells, in malignant conditions, recruit this thermodynamic process to form “onco-condensates” – dense, multicomponent, macromolecular hubs that concentrate onco-genic transcription factors (e.g., c-Myc, EWS-FLI1, mutant ENL), sequester tumor suppressors (e.g., p53) and hyper-activate super-enhancer-driven transcriptional circuitry. Conventional medicinal chemistry strategies, which are deeply entrenched in the “lock-and-key” paradigm of targeting rigid (and predominantly hydrophobic) binding pockets on proteins, have historically failed to hit the intrinsically disordered regions (IDRs) of proteins, leading to their classification of major oncogenic drivers as “undruggable.” The current review attempts to integrate the biophysical “chemical grammar” of phase boundaries with the rational development of small molecules that selectively modulate these droplets via hit-and-run mechanisms. We analyze the intermolecular forces—such as π-π stacking, cation- π interactions, and transient electrostatic networks—that determine the partitioning coefficient (Kp) of synthetic molecules into the dense phase. Moreover, we classify maximal therapeutic strategies into 3 further chemical actions either condensate disrupter, hardener (liquid-to-solid), selective partitioners (droplet drugging). Ultimately, we offer an analytical description of the basic screening tools that are required with respect to Fluorescence Recovery After Photobleaching (FRAP) kinetics, in vitro turbidity assays. This multidisciplinary manuscript combines cellular signaling networks with coordination and natural product medicinal chemistry in a modern roadmap to drug the un-enveloped proteome to avoid acquired chemotherapy resistance.

Keywords: Liquid-liquid phase separation; Biomolecular condensates; Onco-condensates; Drug partitioning (Kp); Intrinsically disordered proteins; Targeted protein degradation.

Received: 02-06-2026
Revised: 08-06-2026
Accepted: 10-06-2026
Published : 11-06-2026

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1. Introduction: The Paradigm Shift in Targeted Cancer Therapeutics

For over half a century, the cornerstone of rational drug discovery has been the traditional "lock-and-key" model, formalized by Emil Fischer. This structural framework dictates that a therapeutic agent must be a small, highly complementary ligand designed to bind with high affinity inside a deep, rigid, hydrophobic catalytic or allosteric pocket of a folded target protein. Output

While this strategy has resulted in a very large armory of FDA-approved enzyme inhibitors and receptor antagonists, it has reached an intellectual dead-end in modern oncology.

In fact, many of the strongest oncogenic drivers like master transcription factors (e.g. c-Myc, STAT3, SOX2), chromatin remodelers and fusion oncoproteins formed by chromosomal translocations (EWS-FLI1,NUP98-HOXA9) cannot find stable tertiary structures [17]. Rather, they consist solely of large Intrinsically Disordered Regions (IDRs) and low-complexity domains (LCDs), oscillating through an enormous conformational ensemble.

Lacking the defined geometrical pockets, such important regulatory proteins has always been dismissed as undruggable. Recent advances in Cellular Biophysics have broken this Gordian knot by revealing Liquid-Liquid Phase Separation (LLPS). Instead of functioning as a random soup of enzymes in free diffusion, the intracellular space is subjected to regulated thermodynamic demixing. Multivalent macromolecules spontaneously phase separate if local concentration (C) is above their critical saturation threshold (Csat) forming well-defined, membrane-less biomolecular condensates [1, 5]. They are nondelimited organelles that assemble to organize multiple metabolic reactions, and concentrate certain proteins and nucleic acids while excluding undesirable cellular clientele [5, 6].

Tumors often twist natural physical processes to build faulty cellular clusters [41]. Inside these thickened zones, survival signals get amplified while key gene controls freeze in place near cancer-linked enhancers [36, 37]; meanwhile, chemo agents find themselves shut out from DNA sites they need to reach [67]. Because of this shift, drug design is changing course- scientists now aim compounds not at rigid binding spots but at the fluid nature of condensate droplets, tweaking how they flow, pull, or resist motion [68, 69]. A blend of medicine science and biology helps turn phase separation ideas from odd lab findings into actual patient treatments. Step by step comes an analysis of how artificial molecules move through liquid layers, what molecular

traits guide where they gather, then what happens when those formless pockets within tumor cells break apart.

By combining the insights from both chemical and bioscientific points of view, this review aims to bridge LLPS translation from benchtop phenomena to bedside application. Here we chronologically assess how small molecules permeate through these liquid interfaces, what chemical rules govern selective partitioning, and the biological ramifications of puncturing these organelle-less organelles within human cancer.

2. Biophysical Mechanics & "Chemical Grammar" of Phase Boundaries

Entropy-driven liquid-liquid phase separation (LLPS) of a homogenous cytosolic/nuclear solution into a dense and dilute phase is exclusively governed by transient multivalent interactions which are by nature weak and dynamic. As opposed to protein tertiary/quaternary structure which is dependent on strong localized hydrogen bonding and packing motifs, the thermodynamic parameters driving LLPS are instead encoded in the linear sequence of Intrinsically Disordered Regions (IDRs). The organization, distribution and density of residues in disordered regions follow a highly deterministic "grammar" [1, 16].

2.1 The Atomic Forces Stabilizing Condensates

The dense phase of a biomolecular condensate is stabilized through a web of breaking and making of intermolecular forces that dynamically interconvert.

1. **π- π Stacking Interactions:** Interactions of stacking of plane electronic clouds of aromatic amino acid residues Tyrosine (Tyr), Phenylalanine (Phe) and Tryptophan (Trp) [18].

2. **Cation-π Interactions:** Cation-π interactions arise when a guanidinium or amine group enriched with a positive charge interacts with the electron-rich face of an adjacent aromatic ring. This refers to the Arg and Lys side-chain constituent residues [16, 17]. They can contribute significantly to the stability of LLPS.

3. **Electrostatic Patterning:** Electrostatic patterning is defined as a dense clustering of alternating positive and negative charged residues (e.g. Aspartate/Glutamate interacting with Lysine/Arginine) form salt bridges that are temporary and allow for maintaining liquid-like clustering [19].

4. **Hydrophobic and Hydrogen Bonding Networks:** Weak, cooperative hydrogen bonds along the uncoiled peptide backbone, and the exclusion of water molecules surrounding the hydrophobic patches, provide the thermodynamic driving force (- ΔG) that is needed to overcome the entropic loss associated with condensation [19, 20].

2.2 Phase Diagram and Saturation Thermodynamics

Entrance into a phase-separated state will therefore always be contingent on local conditions and is often described using a biophysical phase diagram [2, 6]. The line which demarcates this

precise coexistence region is called the binodal curve, where the chemical potentials of the dilute and dense phases are equal. This structural boundary can be written as:

$$C_{sat} \alpha\ 1/x$$

Where C_{sat} is the critical saturation concentration required for phase separation and 1/x is the Flory-Huggins interaction parameter, which depends on temperature, ionic strength, pH, and macromolecular crowding agents [4]. Should mutation or transcriptional upregulation increase the intracellular concentration of an oncoprotein past its respective Csat, an onco-condensate will spontaneously nucleate [5, 6].

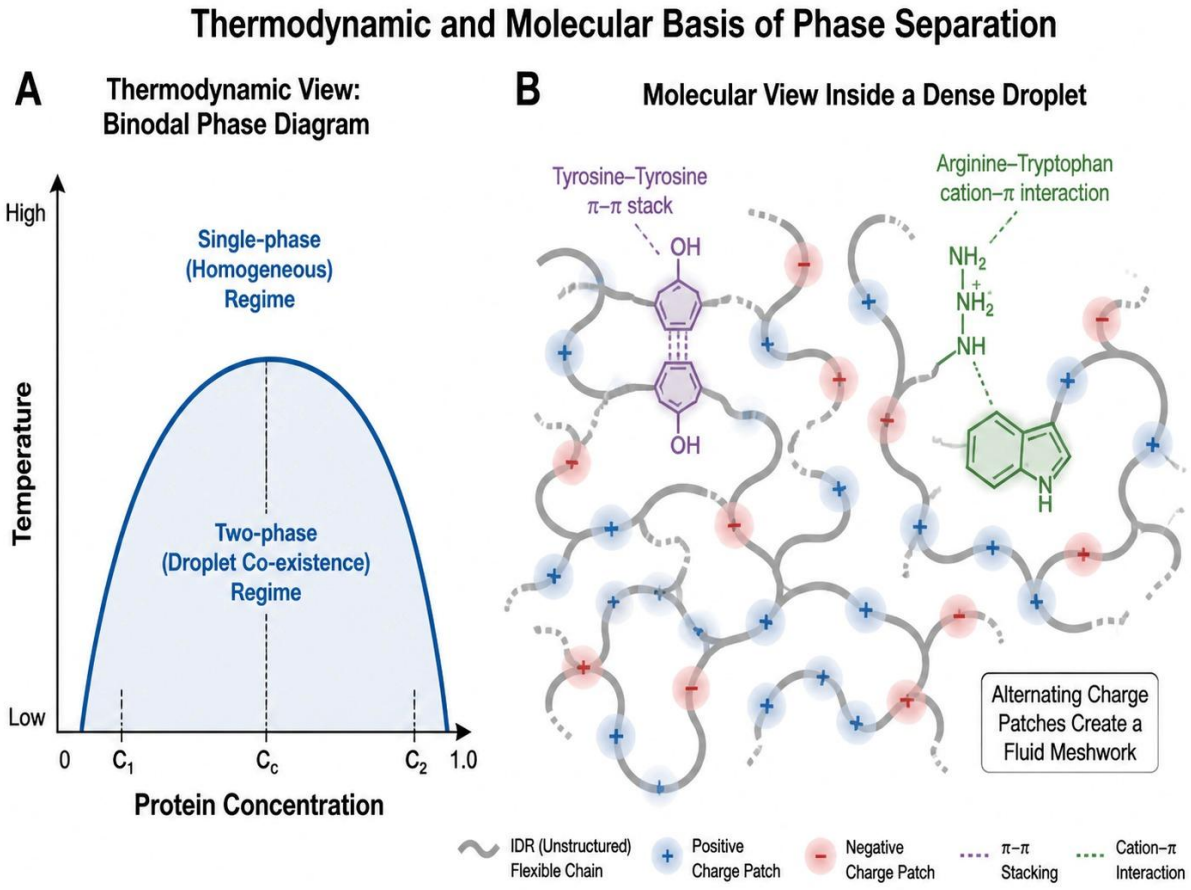

Diagram 1: Biophysical Architecture of LLPS

3. Pathological Onco-Condensates in Cancer Hallmarks

The physiological circuits that govern LLPS become systematically disintegrated under a hostile microenvironment. Malignant cells take advantage of their abnormal biomolecular condensates to direct various hallmark traits of cancer, thereby transforming compartmentalization into a mechanism for their own survival [41].

3.1 Super-Enhancer Hierarchies and Transcriptional Hyper-Activation

Pathological phase separation is most strikingly manifested in the super-enhancers (SEs) of tumor nuclei: dense clusters of genomic elements that control the expression of master oncogenes. In healthy settings, transcriptional coactivators such as Mediator Complex Subunit 1 (MED1) and Bromodomain-Containing Protein 4 (BRD4), are derived from their extensive IDRs to nucleate small, transitory transcription droplets that assemble with RNA Polymerase II (Pol II) in a synchronous mode of burst-like transcription [36, 38].

Notably, this process is grossly hyper-activated in cancer cells.

- The c-Myc Onco-Condensate: Mutants containing hotspot mutations in the YEATS domain of the histone acetylation reader ENL (often found in pediatric acute myeloid leukemia) show abnormal self-association patterns, which result in formation of localized high-affinity condensates on chromatin [39]. Recent studies have shown that nascent RNA molecules serve as a functional cofactor to bind to a basic patch within the mutated YEATS domain and promote the nucleation of these condensates, enabling chromatin looping, and maintaining the undifferentiated, rapidly proliferative status of the cell through the formation of these condensates [39].

Gain-of-Function Mutant ENL Condensates: Mutants containing hotspot mutations in the YEATS domain of the histone acetylation reader ENL (often found in pediatric acute myeloid leukemia) show abnormal self-association patterns, which result in formation of localized high-affinity condensates on chromatin [39]. Recent studies have shown that nascent RNA molecules serve as a functional cofactor to bind to a basic patch within the mutated YEATS domain and promote the nucleation of these condensates, enabling chromatin looping, and maintaining the undifferentiated, rapidly proliferative status of the cell through the formation of these condensates [39].

3.2 Evasion of Proteasomal Degradation and Tumor Suppression

While also increasing the number of active pathways, onco-condensates shut down many tumor-suppressing mechanisms. For example, the commonly known tumor suppressor p53 is often structurally modified or otherwise inactivated as a result of inappropriate phase transitions that happen in human cancers [41]. Normally, wild-type p53 preserves cellular stability by managing the processes of DNA repair and/or apoptotic cell death. Yet due to mutations in the core portion of its DNA-binding domain, the structural disorder of p53 is dramatically increased and leads to p53 experiencing a phase change to inactive, solid-like amyloid aggregates in the cytoplasm or nucleus [90]. This type of physical phase change effectively removes the main protector of the cell, resulting in problems with the stability of the cell's genome and accelerating the process of tumor development [41, 90].

3.3 Cytoplasmic Stress Granules and Chemotherapy Sequestration

During treatment with chemotherapy, radiation, or hypoxia, cancer cells form cytoplasmic membrane-less structures known as Stress Granules (SG), which contain RNA binding proteins such as G3BP1 and TIA1 that are involved in the accumulation of mRNAs that have stopped being translated as well as essential signalling kinases. The presence of SGs provides a mechanism for the virus to delay or prevent apoptosis because the viral cells will have temporarily stopped producing proteins but will still remain metabolically active. These SGs also provide a dense liquid phase that acts as a physical barrier to the delivery of the drugs [67, 68].

Hydrophobic chemotherapeutic agents can be excluded from entering the SG or, if they do enter, never reaching their target intracellular locations due to the droplet's surface tension preventing the active drug from entering the target. Thus, SGs provide a mechanism by which multiple drugs can contribute to the development of multi-drug resistance (MDR) [41,68].

4. Medicinal Chemistry Strategies: "Drugging the Droplet"

Discovering that onco-condensates are responsible for causing malignant phenotypes has completely changed the way we create and design targeted drugs. Because of the untraditional, ill-defined nature in which these assemblies form, it is necessary for the medicinal chemist to optimize the macro-pharmacological parameters of synthetic molecules in order to change the underlying material states of the droplet themselves [68]. There are three general categories of therapeutic interventions to deal with this type of condensates.

4.1. Modality I: Disruption of Condensates (Dissolution)

The purpose of this type of intervention is to disrupt the weak intermolecular forces stabilizing the condensates such that they will dissolve back into a homogeneous, dilute state. The classical biophysical probe for this type of mechanism is 1,6-Hexanediol (HD), an aliphatic diol that can easily enter the condensed meshes and disrupt transitory hydrophobic interactions [68]. Although 1,6-Hexanediol itself would be too non-specific and cytotoxic for use in the clinic, it does provide a model for validating structures of potential therapeutic compounds. In fact, through the use of more sophisticated synthetic methods today, the majority of new drug discovery platforms are utilizing complex polyphenolic scaffolds and planar, multi−ringed aromatic compounds (such as modified flavones like Myricetin and Quercetin) as primary sources of target substances to develop their drugs [70].

These molecules feature extended π-electron clouds and strategically placed hydroxyl groups that intercalate directly into the Arginine-Tyrosine networks of onco-condensates, breaking down the multivalent interactions and displacing trapped oncoproteins from their genomic loci [41, 69].

4.2 Modality II: Induced Phase Transition (Condensate Hardening)

Instead of dissolving the droplet, this modality forces a rapid liquid-to-solid phase transition, effectively freezing the condensate into an inactive, crystalline, or fibrillar aggregate. By locking the components into a rigid matrix, the dynamic mobility of the trapped enzymes is completely halted [68]. For instance, small-molecule screens have identified specific compounds (such as certain structural iterations of the LipoShield chemical pipeline) that accelerate the hardening of cytoplasmic stress granules [68, 70]. Once frozen, the granules lose their ability to dynamically release survival mRNAs, forcing the cancer cell to undergo programmed apoptosis.

4.3 Modality III: Selective Drug Partitioning ("Droplet Drugging")

One way in which to manipulate the properties of an onco-condensate is by taking advantage of its highly concentrated environment (Modality III). By adjusting specific structural properties of the drug through the targeted design, scientists can modify how much the drug will accumulate inside of a specific target onco-condensate (the amount of drug will depend on the drug's Kp value (condensate partition constant).

$$K_p = C_{dense} / C_{dilute}$$

The Kp value of a drug reflects how well the drug partitions between two phases: the Kp value is calculated by dividing the concentration of small molecule drug within the onco-condensate by the small molecule drug concentration in the surrounding cytoplasm or nucleoplasm .

Recent advances in machine learning and virtual screening have demonstrated a link between the structural properties of the drug and the Kp value of the drug [69]. Molecules with a high frequency of conjugated aromatic rings, low topological polar surface area (TPSA), and localized positive charges have Kp values greater than 1 in transcriptional condensates [67]. Recent clinical data confirmed this principle, with Sunitinib (and other multi-kinase inhibitors) shown to spontaneously partition at truly remarkable levels into nuclear condensates (e.g. nucleolus, MED1 super-enhancers) [67, 69]. Even though these molecules were designed to bind to enzyme targets, the high local concentrations dramatically increased the extent of target occupancy and the overall therapeutic index [67, 69].

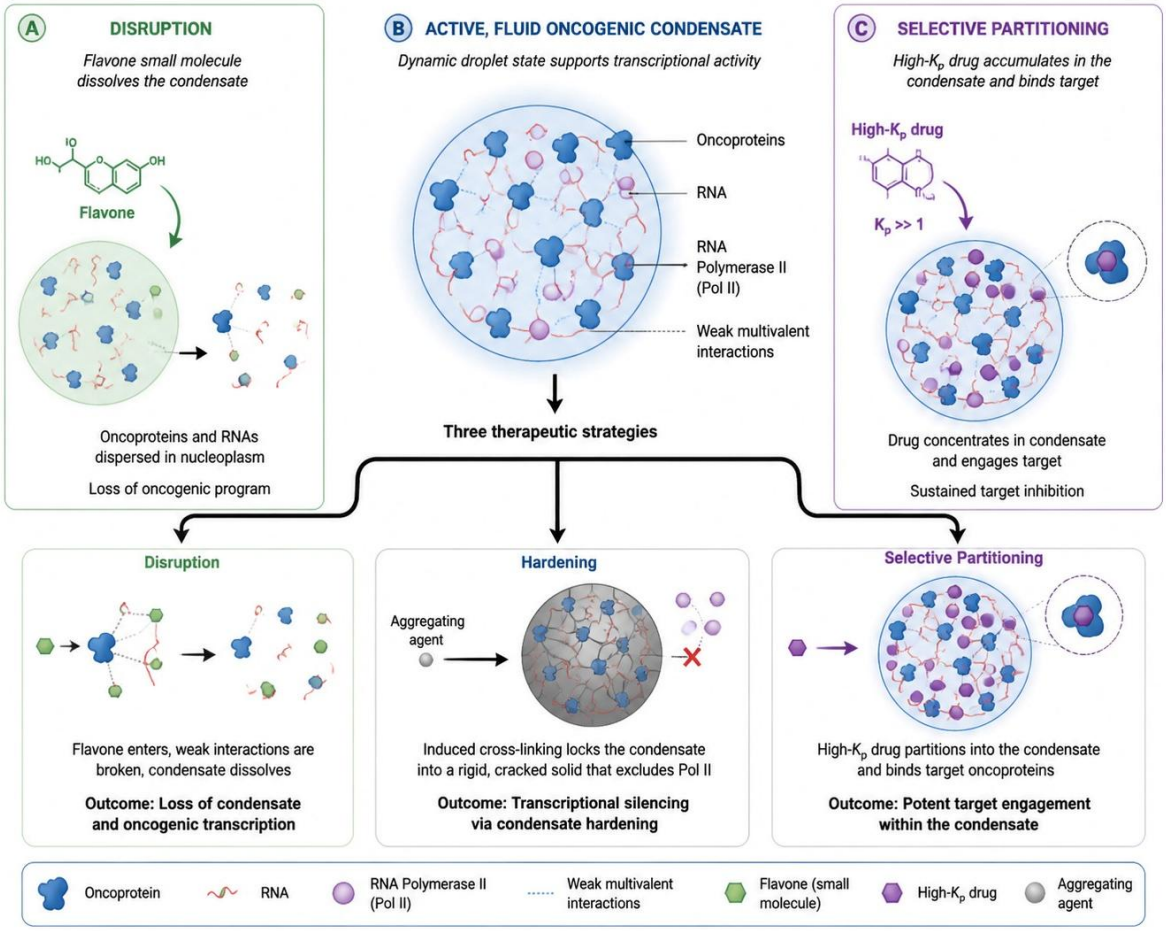

Diagram 2: Therapeutic Modalities of Onco-Condensate Modulation

Table 1: Comparative Profile of Small-Molecule Condensate Modulators

Compound Class / Lead Scaffold	Primary Molecular Target	Biophysical Mechanism of Action	Downstream Biological Outcome	Key Reference Source (Extracted Bibliography)
Aliphatic Diols *(e.g., 1,6-Hexanediol)*	FUS / Nuclear Speckles	Non-specific disruption of weak aliphatic hydrophobic networks	Immediate dissolution of structural nuclear droplets	[3, 68]
Polyphenolic Flavonoids *(e.g., Myricetin)*	MED1 / Super-	Intercalation into π-π, cation- π stacks	Dissolution of SE-hubs; downregulation of *c-Myc*	[41, 69]

	Enhancer Hubs	within IDR meshes		
Planar Anthraquinones *(e.g., Mitoxantrone)*	Nucleolar / NPM1 Condensates	High passive partitioning (K_p > 10) into highly electrostatic phases	Localized DNA intercalating action inside ribosomal factories	[67, 69]
Kinase Inhibitor Derivatives *(e.g., LY2835219)*	Oncogenic Transcription Factors	Rapid clearing of aberrant multi-component assemblies via targeted degradation	Delivery of intact onco-condensates to the lysosome	[67, 70]

5. Toolbox to Evaluate: Effects of Condensate Dynamics

Upon verifying that NCE (small molecules or peptides) modify onco-condensates usually require very thorough large battery of analytical and biophysical tests as well as validating that the test compound causes the modulation or effects of true phase separation as opposed to the nonspecific or irreversible precipitation of proteins. [89]

5.1 Fluorescence recovery after photobleaching (FRAP) kinetics

FRAP is a gold standard method for probing the internal viscosity and molecular dynamics of biomolecular condensates [3]. Imaging Cells Performs: High resolution confocal microscopy of cells with fluorescently tagged oncoprotein (e.g. GFP-Myc)

The recovery timeline is evaluated via:

$$T_{1/2} \alpha\ 1/D$$

If the condensate remains in a healthy, liquid-like state, unbleached fluorescent molecules will diffuse very quickly from surrounding droplet to bleached zone leading to recovery curve with short half-life ($T_{1/2}$) and high diffusion co-efficient (D) [88]. When the test compound used by a chemistry student hardens the condensate to solid or a crystal state, further internal diffusion of molecules is stopped and fluorescence recovery curve is flat [20, 88]. On the contrary, if the compound is a disrupter, the droplet will quickly shrink and disappear from view before bleaching can be performed [41, 68].

5.2 In Vitro Turbidity and Phase Migration Assays

Quantitative high-throughput screening (HTS) of condensate disrupters of recombinant IDR proteins can be carried out after purification and reconstitution of the IDR protein in cell-free buffers containing crowding

agents such as Dextran or Ficoll [89]. Phase separation is induced by varying the concentration of salts or by temperature, and the solution becomes turbid or “suspensive” due to the presence of very small droplets that scatter light.

The mixture is read in a UV-Visible spectrophotometer for optical density (OD) or turbidity at 600 nm (A_{600}). The instant disruption of the condensate by a condensate-disrupter molecule leads to a sharp and instant drop in the absorbance of the solution [68]. The IC_{50} values for novel chemical scaffolds can be precisely calculated by the pharmaceutical chemist by performing HTS using this simple and fully-automated assay before conducting expensive assays using cultured cells [68].

6. Current Bottlenecks & Translational Challenges

Although the therapeutic potential of manipulating biomolecular condensates is great, there are still various biophysical and pharmacological challenges which need to be overcome by candidate molecules before they can go through clinical trials:

1. The Specificity Dilemma vs. Pan-Condensate Toxicity: Because healthy mammalian cells rely on LLPS for foundational cellular house-keeping, such as forming the nucleolus for ribosome biogenesis, assembling nuclear speckles for RNA splicing, and organizing the postsynaptic density in neurons [4, 5], a small molecule must display meticulous selectivity. The drug must differentiate between the structural grammar of a malignant onco-condensate and a physiological condensate. Broad, non-specific disrupters will display narrow therapeutic windows and severe systemic toxicities [41].

2. The Non-Linear "Hook Effect": Since condensates are often formed by multivalent networks, the dose-response curves for phase modulators can be non-linear: at low concentrations there is no effect, whereas at intermediate concentrations these allosteric bridges both stabilise and promote phase separation. Only at higher concentrations does the phase modulator saturate individual valencies, by doing this disrupting the condensate assembly [16]. This biphasic behavior becomes complicated for traditional pharmacokinetic modeling and can be challenging when clinically escalating doses during a trial.

3. In Vivo Validation and Microenvironment Complexity: Most screening assays are optimized towards simple, cell-free, in vitro conditions with a single purified protein [89]. The inside of a human tumor is more like a complex, multi-component matrix - comprising hundreds of distinct proteins and diverse RNA species - with local fluctuations in, e.g., ATP levels [5]. A compound with a high partition coefficient (Kp) in a test tube might nonetheless fail in vivo because it binds non-specifically to serum albumin or cannot penetrate dense, hypoxic, solid tumor microenvironments [67, 90].

ACKNOWLEDGEMENTS

The authors express their sincere gratitude to JIS University, Agarpara, Kolkata, West Bengal, India, for providing academic support, library facilities, and access to scientific resources for the preparation of this review article.

AUTHOR CONTRIBUTIONS

Ramshankar Goswami: Conceptualization, literature review, data collection, manuscript drafting, critical analysis of scientific literature, and preparation of the final manuscript.

Rudrajit Maji: Literature survey, content validation, manuscript review, editing, and scientific interpretation of the reviewed studies.

Both authors have read and approved the final version of the manuscript.

FUNDING

No external funding was received for the preparation of this review article.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

DATA AVAILABILITY STATEMENT

No new datasets were generated or analyzed during the preparation of this review article. All information presented in this manuscript has been compiled from previously published scientific literature and publicly available sources.

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7. Conclusion & Future Perspectives

In this decade of precision medicine, a novel, model-changing concept, liquid-liquid phase separation (LLPS), has arrived in the history of modern medicine, particularly for elucidating cancer pathogenesis and treatment. For nearly 50 years, the scientific community was mired in struggling to inhibit or disrupt so-called master oncogenic transcription factors due to their lack of traditional, rigid structural pockets, targets amenable to conventional small-molecule

drugs and/or antibodies. However, by applying insights from polymer physics and material science, the community's approach toward drug discovery has been transformed.

Rather than remaining at the level of qualitative description, we must now advance into an era of quantitative and predictive approaches by employing deep-learning platforms to control, adjust or eliminate condensates by tuning key features such as TPSA and electronic distribution in conjunction with shape complementarity to modulate droplet partitioning. The marriage of emerging cellular, genetic and pathological insights regarding aberrant and disease-relevant condensates with the synthetic capabilities and analytical workflows of the modern bioscientist and pharmaceutical chemist, respectively, promises to generate new advances in treating devastating cancers and other human maladies through next-generation Condensate-Modifying Therapies (cMTs).

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