Condensate-targeted drug discovery powered by phenotypic signatures

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Introduction

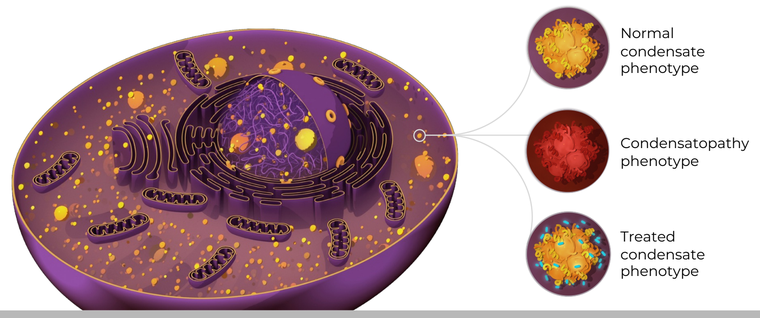
Biomolecular condensates are dynamic membraneless organelles that arise through phase separation mediated by multivalent interactions and concentrate specific biomolecules. Unlike traditional membrane-bound organelles, condensates display remarkable flexibility and adaptability, serving as critical regulators of diverse cellular functions, such as RNA metabolism, transcriptional processes, and signal transduction pathways.

Misregulation or dysfunction of condensates (which we call condensatopathies)[1] have been implicated in a wide range of diseases, including neurodegenerative disorders, cancer, metabolic diseases, and infectious diseases. Furthermore, condensates are enriched in biomolecules previously considered undruggable. Therefore, **condensates are an untapped source of therapeutic targets.** By focusing drug discovery efforts on condensates, we can expand the available target space, opening novel opportunities for therapeutic development.

Dewpoint Therapeutics is at the forefront of condensate-targeted drug discovery. High content, high-throughput imaging techniques provide multidimensional phenotypic data that offer critical insights into the disease status and the mechanisms of action (MoA) of condensate modifying drugs (c-mods)[1]. Here we use phenotypic signatures to accelerate the identification and optimization of c-mods.

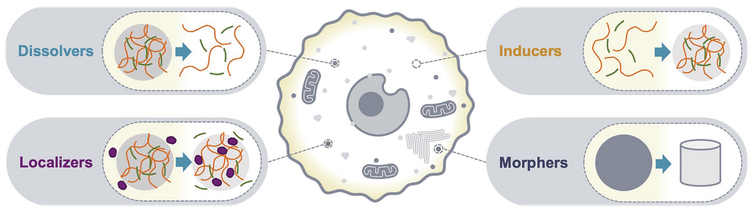
Advantages of targeting condensates

- Address undruggable targets
- Utilize novel MOAs
- Reverse multi-system dysfunction
- Potential for disease modification



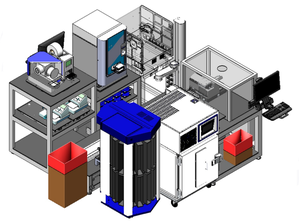
Background

C-mods cover a wide chemical space and a diversity of MoAs,[1] including direct and indirect interactions with the condensate. Finding c-mods requires sensitive, target agnostic methods. We monitor changes in the optical phenotype of target condensates in our high-throughput screening pipeline. We find the following phenotypic classes of c-mods[2]:

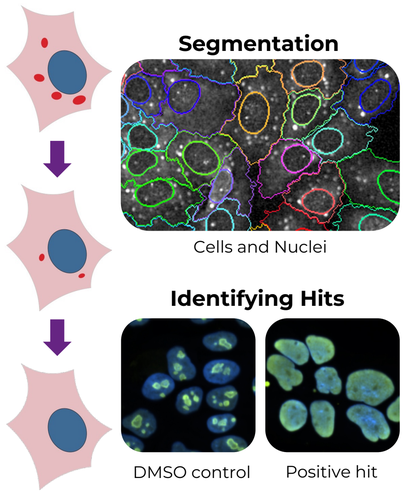


Methods

High content, high-throughput capabilities enable compound profiling using multi-condensate signatures

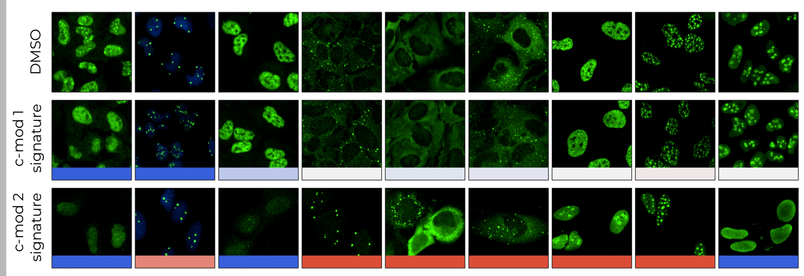


- Cells expressing fluorescently-labeled proteins are treated with small molecules
- High content, high-throughput imaging provides multidimensional phenotypic data that offers critical insights into the disease status and MoAs of c-mods
- AI/ML and conventional methods identify changes in the condensate signature

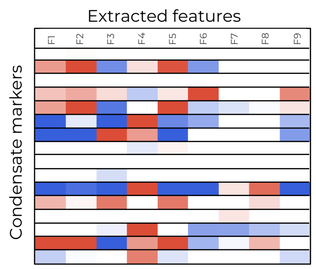


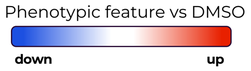
Results

Condensate signatures decode information locked in dense phenotypic data



Condensate signature of a c-mod





Condensate signatures encode function, capturing features of high content images that predict therapeutically-relevant properties such as biological function and toxicity.

Results

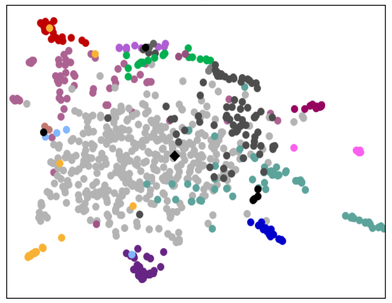
Condensate signatures decode small molecule activity based on condensate profile perturbations

Condensate signatures can:

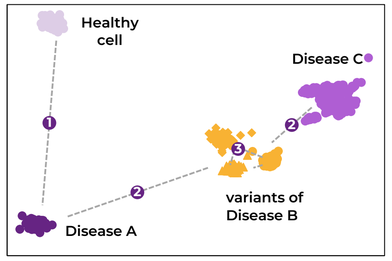
- distinguish between c-mods targeting different pathways
- infer MoAs
- identify pathways enriched with hit compounds
- nominate additional promising compounds targeting the same pathways
- recognize chemotypes associated with mechanisms that differentially impact condensate perturbations
- profile cell state, capturing perturbations that distinguish between healthy and diseased states
- discover selective c-mods that perturb condensates in specific disease states

Work done in collaboration with QuantumBlack

Decoding MoAs



Decoding disease relevant cell states



1. Healthy and diseased states
2. Distinct diseases
3. Subtypes of diseases

Future Directions and References

The growing understanding of condensate biology, coupled with advances in imaging technologies and innovative drug discovery methodologies, is accelerating progress towards development of novel therapeutics for undruggable diseases.

1. Mitrea DM, et al, Nat. Rev. Drug Discovery (2022)
2. Patel A, et al, Front. Mol. Biosci. (2022)

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