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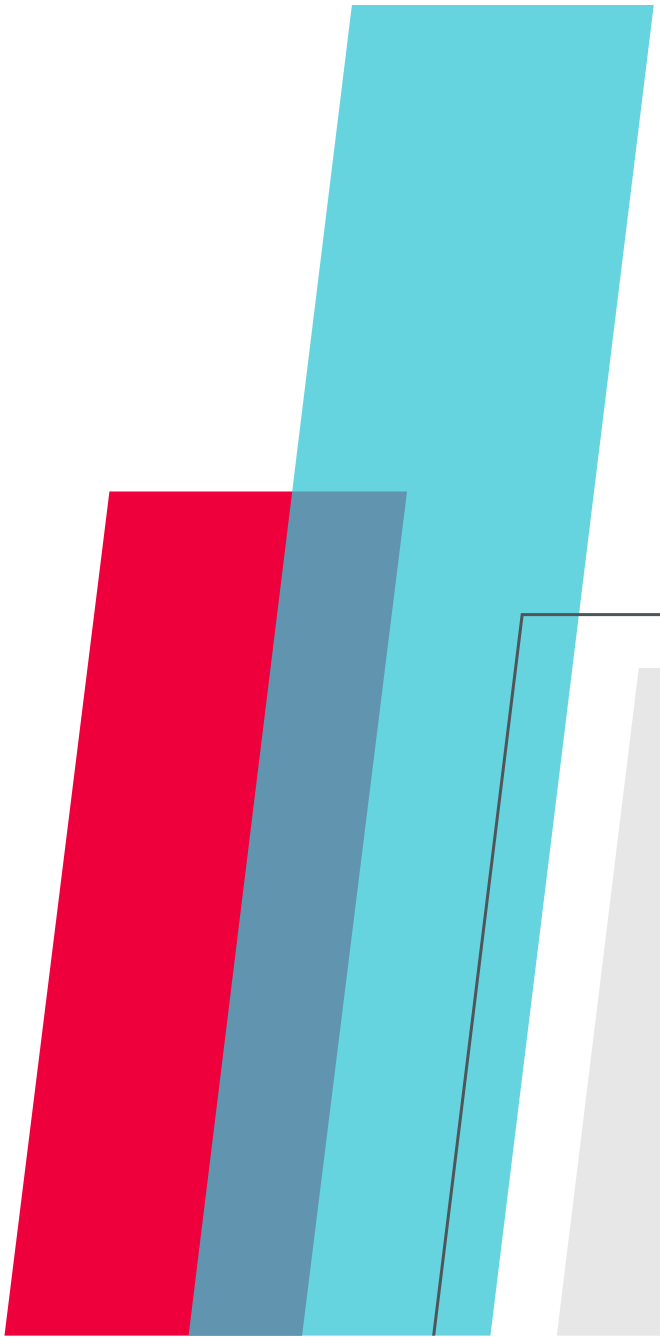
HFSP CASESTUDY

Research Grant: Phase separation and Dewpoint Therapeutics

Phase separation of glycolytic machinery as a fundamental mechanism in energy metabolism



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Client
Human Frontier Science Program Organization (HFSPO)

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Project Title	**Phase separation of glycolytic machinery as a fundamental mechanism in energy metabolism**
Starting Year	2019
Principal Investigator	Anthony Hyman
Collaborators	Daniel A. Colón-Ramos,
Countries	Germany, USA
Disciplines	Cell Biology, Biophysics, Soft Matter Physics, Molecular Biology
Task	Understand how phase separation underpins cellular organization
Key output	Explanation and experimental evidence for the functioning of phase separation as a widespread mechanism in cells

In addition to the cited documents, interviews with the researchers and HFSP data were used as sources. Furthermore, quantitative analyses were carried out using the Dimensions Database.

1 Overview

The case study examines an entire research trajectory advanced by Anthony Hyman and Clifford P. Brangwynne that focuses on phase separation. Both researchers received several HFSP grants on different topics, which helped propel their careers. The grant highlighted in this case study is only the most recent in that series of HFSP awards and is used as a springboard to explore the research topic of phase separation, its scientific and economic impacts, with particular attention to the founding of Dewpoint Therapeutics.

The research idea behind this specific project emerged from a simple observation: for decades, cellular organization was understood primarily in terms of membrane-bound compartments. However, many cellular functions occur in regions that lack surrounding membranes, raising fundamental questions about how cells achieve spatial and temporal control over complex biochemical reactions. This HFSP-funded project addressed this conceptual gap by investigating phase separation as a fundamental physical mechanism underlying cellular organization. It focused on the idea that cells can form dynamic, liquid-like condensates through phase

separation, allowing specific proteins and enzymes to concentrate transiently in defined regions. By studying phase separation in the context of glycolytic machinery and cellular metabolism, the project contributed to a paradigm shift in cell biology and laid the groundwork for new approaches in biomedical research and drug discovery.

2 The Project

At the outset of the project, phase separation was regarded by many biologists as an obscure or marginal concept, primarily discussed in the context of polymer physics or soft matter theory. The observation that certain cellular components appeared to behave like liquid droplets – forming, fusing and dissolving dynamically – suggested a fundamentally different mode of intracellular organization. The project aimed to test whether phase separation could serve as a general organizing principle for cellular metabolism. Specifically, it examined whether glycolytic enzymes and related molecular assemblies form phase-separated condensates that regulate metabolic flux by spatially organizing enzymatic reactions.

Addressing this question required an unusually close integration of disciplines. The project combined:

- Cell-biological experiments to visualize and manipulate intracellular condensates,
- Biophysical and theoretical modeling to describe their material properties,
- Molecular biology to link phase behavior to specific protein features and interactions.

The project carried significant scientific risk. At the time, there was no consensus that phase separation played a functional role in living cells, let alone in central metabolic pathways. There was also no established methodological framework for distinguishing functionally relevant condensates from experimental artifacts.

HFSP's support allowed the team to pursue this high-risk idea without needing to present extensive preliminary data, and instead allowed them to focus on the fundamental question of how cells organize biochemical reactions in space and time.

3 Outcomes and Impact

The project provided compelling evidence that phase separation is a widespread and functionally relevant mechanism in cells. It demonstrated that proteins can self-organize into liquid-like condensates whose formation and dissolution are regulated by biochemical and physical parameters. In the context of metabolism, these findings suggested that metabolic components can be dynamically concentrated within condensates, enabling rapid and reversible control of metabolic activity. This represented a conceptual shift away from static views of enzyme localization toward a dynamic, materials-based understanding of cellular organization. More

broadly, the project helped establish biomolecular condensates as a central concept in modern cell biology, influencing research on gene regulation, signaling, stress responses and neurodegenerative disease.

The impact of the project and the entire research trajectory extended far beyond its immediate scientific findings. It contributed to the emergence of a new research field at the interface of cell biology and physics. Major research initiatives, including large interdisciplinary clusters focused on the “physics of life,” were subsequently established, attracting substantial public and private investment.

One of the most striking outcomes, not of the project itself but the larger research trajectory, was its translation into biotechnology. Insights gained from fundamental studies of phase separation directly inspired a new approach to drug discovery: rather than targeting individual proteins, therapeutic strategies could aim to modulate the physical properties of biomolecular condensates. The company Dewpoint Therapeutics was co-founded in Boston by Clifford P. Brangwynne and colleagues to exploit the therapeutic potential of phase separation biology. Headquartered in Cambridge, Massachusetts, Dewpoint has grown to a team of several dozen scientists and industry professionals, combining expertise in cell biology, medicinal chemistry, structural biology and computational modeling.

Since its inception, Dewpoint has attracted substantial venture capital and strategic investment, raising more than USD 150 million in early financing rounds. Investors have included leading life-science venture firms such as Polaris Partners and Third Rock Ventures. In addition, Dewpoint has entered into high-value strategic collaborations with major pharmaceutical companies, including Bayer and Merck, to develop therapeutics targeting disease-associated biomolecular condensates. These partnerships, reportedly valued in the hundreds of millions of dollars in potential milestone payments, underscore the perceived medical and commercial relevance of condensate biology.

Although clinical-stage products are still in development, Dewpoint has already had notable impact on the biomedical innovation landscape. It has established condensate-targeted therapeutics as a credible and investable domain within drug discovery, catalyzed industrial interest in phase separation biology and contributed to the creation of high-skilled jobs at the interface of physics, biology and medicine. In scientific and industry media, Dewpoint is frequently described as a “pioneer of condensate therapeutics” or a “phase-separation drug discovery company,” and is regularly cited as a leading example of how curiosity-driven fundamental research can generate transformative commercial platforms.

4 Role of HFSP and Conclusion

HFSP played a decisive role in enabling not only the concrete project but the whole research trajectory. By supporting interdisciplinary, high-risk research focused on fundamental principles rather than immediate applications, HFSP created the conditions for a conceptual breakthrough

with long-term impact. By funding Anthony Hyman and Clifford P. Brangwynne, HFSP also enabled them to pursue more ambitious ideas and advance their scientific careers.

The aspect of international collaboration and mobility was highlighted as particularly valuable, as it helped establish connections that proved exceptionally beneficial in the long term. The commercialization pathway initiated by the underlying HFSP-supported research illustrates how high-risk, interdisciplinary basic science can ultimately reshape pharmaceutical strategies and stimulate significant private-sector investment.

In conclusion, this project exemplifies HFSP's mission to generate transformative biological knowledge by funding bold, interdisciplinary research. By establishing phase separation as a fundamental mechanism of cellular organization, it reshaped cell biology and opened new pathways for biomedical innovation and subsequent commercialization.

5 Sources

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