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HFSP CASESTUDY

Early Career Research Grant: Mechanosensing Response in Archaea

Multi-scale functional investigations into mechanosensing response in archaea

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Human Frontier Science Program Organization (HFSPO)

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Project Title	**Multi-scale functional investigations into mechanosensing response in archaea**
Starting Year	2021
Principal Investigator	Alex Bisson
Collaborators	Vikram Alva Kullanja, Tanmay Bharat
Countries	US, UK, India
Disciplines	Cell Biology, Molecular Biology, Biophysics, Evolutionary and Computational Biology
Task	Investigate when, how and why cell division in archaea forms multicellular structures under pressure
Key output	Experimental evidence that archaea reproducibly form multicellular, contiguous structures under pressure, without the need for any additional specific interventions

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

Archaea are among the oldest forms of cellular life and play essential roles in global carbon and nitrogen cycles. They thrive in extreme environments and are central to current hypotheses about the evolutionary origins of eukaryotic cells. Archaea have long been viewed as strictly unicellular organisms with relatively simple developmental behaviors.

This HFSP-funded project challenged that long-standing view by revealing that mechanical forces can trigger coordinated, tissue-like development in archaea. Specifically, the project demonstrated that mechanical compression can induce archaeal cells to divide without separating, forming multicellular structures that resemble rudimentary tissues rather than isolated single cells. This discovery opened a new field at the interface of archaeal biology, mechanobiology, and evolutionary theory, raising fundamental questions about mechanical sensing, cell–cell interactions and the evolutionary origins of multicellularity.

2 The Project

The project originated from an unexpected observation made in the laboratory of one of the collaborators. Under mechanical compression, archaeal cells continued to divide, but the daughter cells failed to separate. Under normal growth conditions, archaeal cell division produces discrete, separated cells. Under compression, they instead remained physically linked and developed into coordinated multicellular structures. This led to the hypothesis that mechanical stress acts as a biologically meaningful signal for archaea, capable of reshaping growth patterns and triggering collective behaviors. The HFSP project aimed to establish mechanosensing in archaea as a tractable biological process and to identify mechanisms linking mechanical stress to cellular and developmental outcomes.

To this end, an interdisciplinary and international team was assembled, integrating:

- Microbiology to characterize archaeal growth and physiology,
- Molecular and structural biology, including cryo-based methods, to analyze cellular organization,
- Evolutionary and computational biology to place findings in a broader evolutionary context.

Investigating archaeal mechanobiology was a speculative and risky project. There was little precedent for multicellular behavior in archaea, and the underlying mechanisms of mechanical sensing were largely unknown. Given HFSP's reputation as a risk-taking funder that supports internationally collaborative projects, it was a natural fit, and they successfully secured an Early Career Research Grant.

The project required experimental innovation, including the controlled application of physical forces at scales relevant to microbial cells, and multi-scale analysis spanning proteins, cell structure, and emergent collective behaviors.

HFSP funding provided the flexibility and trust-based support needed to pursue this frontier science project. It benefited from HFSP's minimal bureaucracy, which allowed partners to adjust resource allocation as the research unfolded, including shifting funds between groups when needed. Measured against the project's ambition and frontier character, the scientific work progressed surprisingly smoothly without major hurdles and the hypothesis could be confirmed experimentally. Interviewees noted that HFSP's hands-off approach places greater weight on researchers' intrinsic motivation, which can in some circumstances be a double-edged sword and makes it particularly important to identify researchers with the right mindset and motivation.

3 Outcomes and Impact

The project demonstrated that multicellular, tissue-like behavior can occur in archaea and that mechanical compression is sufficient to trigger this coordinated development. This phenomenon had not been described previously. Rather than being an anomaly, the results suggested a general principle: under mechanical stress, archaeal cells may resist environmental pressure by forming multicellular structures, potentially improving resilience through collective organization.

The work culminated in a high-profile publication, providing validation of both the phenomenon and its scientific significance. The findings challenged existing assumptions about archaeal biology and expanded the conceptual space for studying the origins of multicellularity.

The discovery opened multiple new research directions. Key questions include how archaea sense mechanical forces, which molecular pathways link force detection to altered division and adhesion behaviors, and whether similar stress-induced multicellularity exists across diverse archaeal lineages and environments. The project has continued beyond the initial grant, with collaborators pursuing these questions and expanding the mechanobiology toolkit for archaeal systems.

More broadly, the results contribute to evolutionary debates on the origins of complex life. They suggest that mechanical environments – compression, confinement and physical stress – may have been underappreciated drivers of early multicellular evolution, alongside chemical and genetic factors.

In addition to scientific outcomes, the project had significant value for the investigators' careers and networks. It fostered collaborations that persisted beyond the project's duration and crossed disciplinary boundaries. Because it was an Early Career Research Grant, the scientists involved were relatively young and benefited particularly from the interdisciplinary experience, access to networks, and the prestige that comes with an HFSP grant. For some, it helped them establish a foothold in a new interdisciplinary field at the interface of microbiology, mechanobiology, and evolution.

4 Role of HFSP and Conclusion

Without HFSP, the project would not have been possible in this form, because this kind of international collaboration could not have been funded otherwise. Moreover, the project's interdisciplinary and ambitious nature would have made it difficult to secure funding from other sources.

Equally important was HFSP's responsive funding model with low administrative burden. The consortium was able to distribute the grant flexibly, shift funds between groups without administrative barriers and use remaining resources to explore follow-up directions. Regular HFSP meetings also provided an important platform for community building, particularly valued by early-career researchers.

In conclusion, this project exemplifies HFSP's mission to enable frontier research that reshapes biological understanding. By demonstrating mechanically induced multicellular development in archaea, it opened a new field of archaeal mechanobiology and provided fresh perspectives on the evolutionary origins of multicellularity.

5 Sources

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Claessen, D. et al. (2014). Bacterial solutions to multicellularity: a tale of biofilms, filaments and fruiting bodies. Nature Reviews Microbiology.

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