Enhancing Biopreparedness Through a Model System to Understand the Molecular Mechanisms that Lead to Pathogenesis and Disease Transmission

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The science of biopreparedness to counter biological threats hinges on understanding the fundamental principles and molecular mechanisms that lead to pathogenesis and disease transmission. The vision to address this challenge is to create a powerful and user-friendly platform to elucidate the fundamental principles of how molecular interactions drive pathogen-host relationships and host shifts. The team will enable groundbreaking discoveries by integrating a wide range of structural, genomics, proteomics, and other advanced omics measurements, along with evolutionary and artificial intelligence predictions. To make sure the system is applicable to real-world problems, it will be developed in the context of a tractable model system, the small, abundant, and accessible photosynthetic cyanobacteria, and their constantly co-adapting viral pathogens, cyanophages. This model will maintain the system's applicability to real-world problems and techniques, but the overall focus will be on elucidating general principles of detecting, assessing, and surveilling molecular interaction, adaptation, and coevolution that are system agnostic and therefore extensible to any other viral-host interaction.

Objectives are to (1) identify the molecular complexes that comprise the cyanobacteria redox macromolecular subsystem and how they dynamically change with bacteriophage infection in situ, using cryo-electron tomography; (2) profile regulatory changes during infection using proteomics, multiomics, and experimental validation, and integrate the data with in situ structures; (3) use genomics and metagenomics to determine environmental and population factors across time scales that impact the interactions between marine cyanobacteria and their cyanophage parasites, predicting the evolutionary origins of in situ structural and functional interactions, convergence and coevolution; and (4) develop a data integration and transformation platform that facilitates the integration of in situ, proteomic, and evolutionary measurements of molecular interactions to surveil diverse hosts and parasites in various environmental contexts.

This powerful and user-friendly platform will enhance connections between the often-siloed fields of structure, molecular phenotype, and evolutionary genomics that are key to biopreparedness, but in need of integration. Researchers will do this by building a navigation tool to facilitate the effective use of globally distributed experimental data for integrated analysis and predictive modeling. The impact of the project will be to develop, implement, and test a platform to assess host-pathogen molecular interactions, adaptation to hosts and host shifts, and coevolution between hosts and pathogens. A successful project outcome will transform researchers' ability to study any host-pathogen interaction, encourage diverse community contributions, and gain fundamental insights into how proteins adapt to new contexts. This ability will be critical for designing early interventions to address future threats. Researchers will build surveillance training capability, aiming for a fair and equitable response to future pandemics and biothreats.