Project Proposal: A "Focused Research Organization" to Systematically Study Bacteriophage Genes and their Functions

Systematically sequencing the genome and studying the function of genes from all viruses that infect a set of model bacteria with significant scientific, biotechnological, and human health relevance will enable the development of phage-gene libraries that can in turn enable the faster development of genetic tools for advancing molecular biology.

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Problem Statement

Viruses have been evolving host-modifying factors for billions of years. This wealth of naturally engineered proteins holds the key to unlocking the full potential of the cell. Virus-derived genetic tools have driven most key advances in molecular biology, from recombinant DNA to CRISPR genetic engineering. Although most such transformative discoveries have resulted from the study of bacteriophages (viruses of bacteria), phage research has relied primarily on inferential work rather than systematic approaches to discern the functions of phage genes. With serendipity as the primary engine of discovery, experimental approaches have not kept pace with phage genome sequencing over the past decade. Consequently, the vast majority of phage genetic diversity is still entirely unexplored.

Project Concept

We have built a high throughput screening platform to characterize phage genes and completed a pilot of the entire pipeline, from gene selection through functional screening and mechanistic follow- up (manuscript in preparation and available upon request). Our FRO will scale this platform and use it to chemically synthesize and test all non-redundant phage genes from two clinically relevant families of bacteria (Enterobacteria and Mycobacteria) which collectively host ~40% of all isolated phages, allowing us to test a large swathe of phage genetic diversity in a set of model species. The phage-gene library generated from this process will enable us to pursue the following objectives: 1) discover new molecular tools with revolutionary potential (eg. broadly understanding the principles of protein detection in antiviral immunity could yield a generalizable protein-targeting framework without some of the pitfalls of antibodies), 2) develop therapeutic avenues for antimicrobial resistant infections inspired by natural antiviral defense and counter-defense strategies, 3) build an inventory of phage design principles and engineering methods for therapeutic, industrial, and microbiome-directed applications, and 4) gain a complete understanding of interactions between phage and their hosts.

What is a Focused Research Organization?

Focused Research Organizations (FROs) are time-limited mission-focused research teams organized like a startup to tackle a specific mid-scale science or technology challenge. FRO projects seek to produce transformative new tools, technologies, processes, or datasets that serve as public goods, creating new capabilities for the research community with the goal of accelerating scientific and technological progress more broadly. Crucially, FRO projects are those that often fall between the cracks left by existing research funding sources due to conflicting incentives, processes, mission, or culture. There are likely a large range of project concepts for which agencies could leverage FRO-style entities to achieve their mission and advance scientific progress.

This project is suited for a FRO-style approach because to achieve our scientific goals, we will need to scale our platform ~10,000-fold from 104-5 assays in the pilot to ~108-9 assays at the FRO. Massively parallelizing these assays will involve a highly systematic effort with a tightly coordinated and dedicated team, a substantial initial investment in gene-library synthesis and platform engineering, and long publishing timelines, which are qualities unsuitable for traditional grant funding. For these reasons, an FRO is the ideal (and probably the only viable) structure for this project.

How This Project Will Benefit Scientific Progress

Paradigm shifts in biology have often started with the humble bacteriophage. With $10^{8\text{-}9}$ prospects across the oldest and most diverse host-pathogen interface in the biosphere, our FRO presents abundant opportunities for making impactful discoveries, and will pioneer a new field of functional metaviromics. Moreover, the phage-gene libraries we will create are analogous to small-molecule screening libraries, consisting of 104-105 phage-derived natural products that can be used to find potentiators or suppressors of any cellular stressor of interest. We expect these resources to enable discovery far beyond the scope and timeline of our FRO.

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