08 Accelerator Grants

Assessing the morphological space of self-assembling abiotic chemistries as potential confounding biosignatures

Accelerator Grant

- Henderson Cleaves, Dept. of Chemistry, The Howard University, Washington, USA
- Sean McMahon, School of Physics and Astronomy, University of Edinburgh, UK
- Mark Van Zuilen, Marine Biodiversity Lab, Stichting Naturalis Biodiversity Center, Leiden, Netherlands
- **Sudha Rajamani, Dept. Of Biology, Indian Institute of Science Education and Research (IISER) Pune, India**

The integration of Sudha Rajamani into the team will greatly expand the scope of this work by providing a large reference dataset of nonbiological self-assembled systems with bio-similar morphologies. The diversity of molecules in the "prebiotic soup" likely provided molecules resembling extant biomolecules. Some of these straight chain fatty acids (8–20 carbon atoms), are endowed with properties that allow them to self-assemble into cell-like structures under prebiotic environmental conditions. Such molecules may have been selected for incorporation into protocells. The diversity of amphiphiles in the prebiotic soup likely resulted in heterogeneous membranes that could have been central to the emergence of cellular life. Of particular interest are mixed amphiphilic systems that robustly formed membranes under plausible prebiotic planetary conditions. This highlights the importance of characterizing such molecules for their role in life's emergence, and also for searching for life in our solar system, as structures formed from inherent properties of nonbiologically produced molecules may provide evidence of true cells. Some of these self-assembled structures may be stages on the way to life, which is interesting in itself, while others may simply represent propensities of matter to self-organize in non-life producing ways. It is crucial to be able to distinguish between life, emerging life, and simple abiotic systems with no propensity to give rise to life.

We will systematically characterize hybrid amphiphile systems, with a focus on molecules that merge the amphiphilic properties of lipids with biological building blocks. This includes nucleolipids, formed by combining nucleobases/nucleos(t)ides with fatty acids, allowing for the integration of informational and structural roles in early cellular life, as well as aminolipids, composed of amino acids and lipids, which could have contributed to membrane stability and functionality under prebiotic conditions. We have demonstrated synthesis of N-acyl amino acids (NAAs) under early earth conditions and their assembly into vesicles. When mixed with fatty acid derivatives, NAAs produce vesicles over a wide pH range and assemble into compartments under plausible early earth conditions. This work will explore prebiotic hybrid amphiphiles and characterize assemblies that they produce under diverse environmental conditions and compare them with modern and fossil cell morphologies. We will generate a comprehensive catalog of structures that can be used to discern primordial life on extraterrestrial bodies.

Resurrecting the multiple origins of tyrosine kinase activity and phosphotyrosine recognition

Accelerator Grant

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- Brian Metzger, Dept. of Biological Sciences, Purdue University, West Lafayette, USA
- **Arun Shukla, Dept. of Biological Sciences and Bioengineering, Indian Institute of Technology Kanpur, India**

A major goal of evolutionary biology is to determine the mechanisms responsible for generating new biological functions. Molecular systems are particularly attractive for this work due to their experimental tractability and integration into organismal traits. All cells are exposed to a diverse array of stimuli to which they must detect and respond for their growth and survival. Organisms often accomplish this using signal-transduction cascades through protein post-translational modification. While all organisms can use phosphorylation of serine and threonine residues for this purpose, tyrosine phosphorylation is found primarily in eukaryotes and evolved later in history. In addition, the evolution of tyrosine phosphorylation occurred several times independently, offering the rare opportunity to compare the molecular mechanisms responsible for the evolution of a new function and address key questions about the repeatability of evolution across scales. However, the structural basis by which tyrosine phosphorylation evolved in any case is unknown.

Here we propose to use ancestral state reconstruction coupled with X-ray crystallography and cryogenic electron microscopy to identify the structural basis by which tyrosine kinase activity evolved across multiple independent origins. We will use recent advancements in structural biology to visualize the overall architecture, fine details, and molecular dynamics of kinases just prior to and just after the emergence of tyrosine phosphorylation activity. In addition, we will structurally characterize plausible intermediates for one instance—thus identifying not only the structural basis for this new function, but also the specific amino acid substitutions and their individual structural impacts.

This HFSP Accelerator project extends the explanatory power of the original project, which focused on the genetic, molecular, and evolutionary mechanisms underlying the repeated emergence of pY signaling, by adding detailed knowledge of the structural impacts of these historical changes. There is thus synergy gained by creating both structure-function and genotype-phenotype connections within a single system. Furthermore, by identifying the structural impacts of individual historical mutations, this work would provide unprecedented insights into the structural basis by which any new molecular function has evolved.

Mechanisms and origins of glycosylation in giant viruses

Accelerator Grant

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- Cristina De Castro, Dept. of Chemical Sciences, University of Naples Federico II, Italy
- Hiroyuki Ogata, Institute for Chemical Research, Kyoto University, Japan
- **Suvarn Kulkarni, Dept. of Chemistry, Indian Institute of Technology Bombay, India**

This HFSP Accelerator project will strengthen and expand the original research into the glycobiology of three marine giant viruses, CroV, ChlorV, and BigV, through the inclusion of an expert in synthetic carbohydrate chemistry.

The first task of the proposal focuses on the structural elucidation of viral glycans. In order to independently assess the structures of viral glycans, it will be highly advantageous to produce relevant amounts of these natural compounds in high purity. In addition, chemical synthesis of viral glycans will allow us to identify interacting proteins from the virus or host via binding assays. The second task aims to decipher the assembly pathway of viral glycans and requires azido-labeled derivatives, which can be difficult to obtain in case these viruses use unusual monosaccharides. Hence, the added expertise will help us to overcome labeling problems by developing new synthesis protocols. Importantly, the third task can now be expanded to studying the biochemistry of viral glycosyltransferases, because the substrates needed for enzymatic assays will become available through the additional team member.

Indirectly, the fourth task will also benefit from the added expertise, as phylogenetic analyses require reliable experimental data from chemical, biochemical, and cell biology approaches, resulting in an improved overall accuracy of computational predictions.

Suvarn Kulkarni is an expert in the chemical synthesis of bacterial glycans, which are composed of highly diverse and complex monosaccharide units, working on state-of-the-art procedures to maximize the yield of target molecules while reducing the number of synthetic steps and the use of toxic organic solvents. Kulkarni has developed several one-pot synthetic strategies and has access to a solid-phase synthesizer ‘Glyconeer 3.1’, that can assemble oligosaccharides of virtually any size. The integration of Suvarn Kulkarni is therefore ideally suited to facilitate and expand our research on the mechanisms and origins of glycosylation in giant viruses.