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Project Report: Delivery of Organic Materials to Planets

Scripps Research Institute
Executive Summary
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Astrobiological research seeks to define and elaborate the life-originating conditions, processes, and events that prevailed early in Earth's history. This means confronting and understanding the immensely complex chemistry that was responsible for that wondrous transition ?perhaps 3–4 billion years ago? from Earth's pre-biotic, inanimate molecules to living organisms.

What is life? What are the requirements for its origins and evolution? How can living systems be identified elsewhere in the Universe? These are some of the most fundamental questions in astrobiology. Under the auspices of the Scripps Research Institute, a multi-institutional research team has been assembled to explore a variety of interdisciplinary experimental approaches to self-reproducing molecular systems and Darwinian chemistry. Through the design and study of diverse and novel chemical systems in the laboratory, we seek to garner a better understanding of life and its origins.

In the past year our team has continued to make significant discoveries and progress in several areas of research. At the University of Florida, our group has established a multidisciplinary research program that addresses issues relevant to astrobiology from several distinct but interrelated perspectives. In the area of Darwinian chemistry, we have explored whether the polyelectrolyte nature of the nucleic acid backbones are fundamentally important to the functioning of the genetic system by building and studying alternative genetic systems from non-ionic backbones. There have also been recent suggestions that specific base pairing in DNA might be possible without hydrogen bonding between two DNA strands. Contrary to that suggestion, it has been shown that hydrogen bonding is critical to genetic molecules operating in water. Other studies include expanding the artificial genetic system to incorporate alternative genetic molecules; and developing polymerases that incorporate thiol functionality in an artificial genetic system, thus setting the stage for in vitro evolution experiments with an unnatural genetic system. We have also been actively involved in protein data mining and informatics and have established collaborative efforts with other members of the Astrobiology Institute. In studies that have been catalyzed by the NAI focus group efforts in evogenomics, examples of changes in protein function that result from coupling "nonstationary" divergent evolution of protein sequences to their three dimensional structures have been developed. Furthermore, a comprehensive survey was conducted of adaptive evolution in the global proteome and reconstructed evolutionary intermediates have been exploited to search for

compensatory changes in protein structure. An intriguing new computational tool was developed for dating events in the molecular record, and its value in detecting pathways from an in silico analysis of genomic/proteomic sequence data has been demonstrated. In collaboration with the Jet Propulsion Laboratory we are developing chemical technology for detecting benzenecarboxylic acids that are thought to be the most likely Martian organic compounds on the accessible surface of the planet.

Our group at the University of Texas at Austin is interested in generating novel self-replicating biopolymers in order to better identify self-replicating molecular ensembles that may be encountered on other planets. Such biopolymer systems may not exactly resemble the systems that first arose on Earth (indeed, it may be impossible to determine exactly what happened on the early Earth), but they should serve as important doppelgangers that can reveal what would have been possible both on Earth and, potentially, on other planets. The effort in this field of research has centered on the design and evolution of an autocatalytic replication system based on nucleic acids. The approach to this research has been to initially select a deoxyribozyme ligase short enough to be amenable to engineering. This deoxyribozyme ligase was then converted into an allosteric enzyme, a feature that may have been important in the evolution of a metabolism based on nucleic acid catalysts. In order to demonstrate the feasibility of generating autocatalytic replication systems in general, a 'ping-pong' cleavage reaction, based on a cyclized deoxyribozyme, was engineered. This novel system demonstrates kinetic behavior consistent with autocatalysis and exponential growth. By combining the insights garnered from engineering the deoxyribozyme ligase with those garnered from the cleavage cycle, it is expected that it should be possible to develop an autocatalytic ligase cycle yielding a milestone in any origins scenario.

It is also postulated that prebiotic replicators and complex catalysts in a putative RNA world would have segued to peptide-based catalysts. To understand how this may have occurred, several models for the transition have been investigated. It has been shown that peptides can template the ligation of nucleic acids, and thus may have served as important cofactors in a prebiotic or RNA world. It has also been demonstrated that peptides can act as powerful effectors to regulate the activities of nucleic acid catalysts, a function that would again have been important in any complex RNA metabolism.

A goal of the research program at the Scripps Research Institute is to design, discover, and understand the primary factors responsible for directing self-organization of inanimate molecules into the animate chemistry of living systems. The approach has been to rationally design and recreate various forms of autocatalytic peptide networks in the laboratory and to study how the interplay of molecular information and nonlinear catalysis can lead to self-organization and expression of emergent properties. Recently a series of studies on reciprocal autocatalytic peptide networks, which illustrates how self-reproduction can emerge from mutually autocatalytic set of chemical reactions has been completed. Considering the important role of parasites in the Darwinian evolution of species, the work at Scripps has sought to recreate molecular parasites in the laboratory and has resulted in the design and

characterization of the first parasitic peptide network, demonstrating the emergence of a host–parasite relationship among similar molecular species. The group is also engaged in studies establishing the possibility of information transfer–catalysis from nucleic acids to peptides. These lines of investigation have led to the design and characterization of nucleic–acid dependent peptide ligases that display significant rate enhancements of peptide fragment condensation reactions in the presence of specific PNA sequences.

One of the central objectives of this research program is to understand the process of self–organization and the emergence of complex behavior in informational nonlinear systems, which are believed to be the first step in transitioning inanimate molecules into animate chemical systems. Ongoing studies centered on the design and construction of complex and adaptive molecular ecosystems systems continue to yield new insights about the interplay between molecular information, nonlinear catalysis, and system self–organization. Recently, a theoretical framework for multi–peptide network formation was established and experimentally validated, and it was shown, experimentally, how species within a subsystem interact and self–organize to vary each other's production.

Pioneering efforts continue in the design of novel abiotic molecular replicators. Autocatalysis and chemical amplification are characteristic properties of living systems, and they give rise to behaviors such as increased sensitivity, responsiveness, and self–replication. A new type of self–replicating system has been devised in which an autocatalytic chemical system was designed based on molecular recognition and encapsulation. Nature has long recognized the inherent benefits of compartmentalization, and it is widely believed to be an important, if not essential, characteristic of living systems. The compartment designed in this work is a reversibly formed molecular capsule in which a reagent is sequestered. Reaction products displace the reagent from the capsule into solution, and the reaction rate is accelerated. The resulting self–regulation is sensitive to the highly selective molecular recognition properties of the capsule. The autocatalytic behavior of this system is thus an emergent property of the system as a whole, rather than a property of specific molecules within the system.

A primary goal is to synthesize alternative nucleic acids (ANAs) to attempt the optimization of polymer structure subject to the constraints of prebiotic availability, template–directed reproduction, replication–conservative mutation, and fitness. ANAs have been identified by taking small steps in "structure–space" away from RNA (the best model for a molecule bearing features both universal and unique to life) that may avoid some of the problems inherent in fulfillment of the aforementioned constraints. Specifically, attention is focused on examining ANAs with novel changes to base–pairing domains, backbone charges, and the sugar portion of the nucleic acids. These studies are expected help to define chemical parameters for molecular evolution. Moreover, this research program addresses whether nucleic acid–like molecules are sufficient to enable the origin of life and what limitations exist for life elsewhere in the Universe based on a single biopolymer (e.g., RNA) rather than multiple biopolymers (DNA, RNA, proteins, carbohydrates).

It has been shown that a nonstandard base-pair can provide a vast improvement in the efficiency of non-enzymatic template directed synthesis over the canonical A•T base-pair. In effect, the new nonstandard base-pair suggest improved fitness for non-enzymatic (prebiotic) template-directed reactions in comparison to the natural A•T base-pair. Furthermore, the way in which tethered cations affect DNA topology has been assessed, thus providing a better understanding of the electrostatic contributions of protein-DNA interactions. A new method for selecting DNA aptamers that incorporate alternative nucleic acids was also recently discovered, paving the way for the evolution and selection of prebiotically relevant nucleic acid catalysts.