WHAT WAS IN THAT WARM LITTLE POND? CONSEQUENCES OF SYNTHESIZING CONTEMPORARY BIOPOLYMERS BY ABIOTIC CHEMISTRY. A. E. Engelhart[1], K. Adamala[2], M.W. Powner[3], and J. W. Szostak[1], [1]Howard Hughes Medical Institute, Department of Molecular Biology and Center for Computational and Integrative Biology, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114, USA, [2]MIT Media Lab and McGovern Institute, Departments of Biological Engineering and Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139 [3]Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London, WC1H OAJ, UK. E-Mail for A.E.E: engelhart@molbio.mgh.harvard.edu. E-Mail for J.W.S.: szostak@molbio.mgh.harvard.edu.

The discovery of the dual informational and catalytic role of nucleic acids has resulted in a proliferation of interest in these molecules as candidates for the earliest (proto)-biopolymers. Recent advances in the synthesis of the constituent components of these polymers, the observation that alternative backbones can produce functional polymers, the discovery of monomers with more favorable self-assembly characterisics, and the expansion of the catalytic repertoire of these molecules by alternative metal ions have all led to considerable optimism for scenarios for the emergence of life in which nucleic acids played a key role, as well as the possibility that ancestral molecules to RNA existed as intermediates in the evolution of the RNA backbone.

While these advances are reason for optimism, model reactions for the prebiotic synthesis of RNA are plagued with difficulties, including chain termination (due to low chemical efficiency of synthesis or low processivity) and imperfect regiospecificity (some 2′-5′ linkages are produced in addition to the canonical 3′-5′ linkage; this lowers RNA duplex stability). These difficulties have been largely overcome by the use of highly evolved protein polymerases in contemporary life. Prior to the emergence of such catalysts, however, RNA must have been synthesized by simpler chemical means.

Here, I will show results from our recent work that suggest that the unique character of prebiotically-produced RNA (and related polymer) mixtures could have afforded very simple mechanisms for the emergence of RNA as the ancestral informational and catalytic biopolymer. Two recent examples from our work include 1) our observation that short, truncated fragments of ribozymes, while nonfunctional, can still assemble with complementary ribozyme fragments and undergo nonenzymatic primer extension (Figure 1, Ref. 1), resulting in recovery of function; and 2) our report that RNA, when substituted with prebiotically plausible (10-25%) levels of 2′-5′ linkages, can still form functional aptamers and enzymes (Figure 2, Ref. 2). Additionally, these low levels of 2′-5′ linkages allow for thermal strand separation of a ribozyme-length strand of RNA in the presence of the Mg^{2+} concentration required for known prebiotic RNA copying reactions. This could have been a key feature enabling the multiple-turnover replication of proto-RNA prior to the existence of strand-displacing enzymes. I will also discuss results from our recent work demonstrating that the interaction of model prebiotic catalyst mixtures with model protocells formed from fatty acid vesicles results in regulatory and functional behaviors that could have enabled the emergence of the earliest cellular life.

Our results suggest that the complex mixtures likely to have been found in prebiotic reactions could have facilitated, rather than impeded, the development of the earliest cellular life.

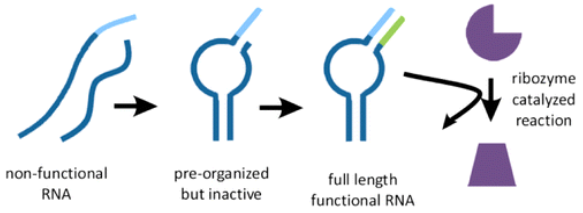

Fig 1. Truncated ribozyme fragments preorganize into non-functional assemblies, which can be elaborated into full-length, functional ribozymes by nonenzymatic primer extension. Figure from Ref. 1.

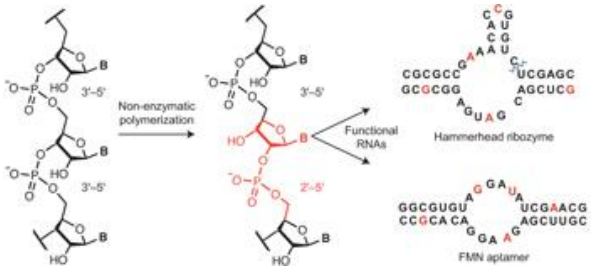

Fig 2. Functional RNAs (here, the FMN aptamer and hammerhead ribozyme), when substituted with prebiotically plausible levels of 2′-5′ linkages, retain binding and catalytic function. Figure from Ref. 2.

References: [1] Adamala K., Engelhart A.E., and Szostak J.W. (2015) *J. Am. Chem. Soc*, *137*, 483-489. [2] Engelhart A.E., Powner, M.W., and Szostak, J.W. (2013) *Nat. Chem.*, *5*, 390-394.