Novel Properties Arising from Interactions Between Lipid Compartments and Biopolymers. Aaron Engelhart[1,2,3], Katarzyna P. Adamala[1,3], and Jack W. Szostak[1], [1]Massachusetts General Hospital, Simches Research Center, 185 Cambridge Street, Boston, MA 55414, [2]e-mail:enge0213@umn.edu, [3]Current Address: University of Minnesota, Molecular and Cellular Biology 5-178, 420 Washington Avenue SE, Minnapolis, MN, 55455.

In contemporary life, the central role of each biomolecule is fairly well-defined: nucleic acids carry information, proteins perform regulatory and catalytic functions, and lipids afford a means of compartmentalization. However, exceptions to these rules exist and have attracted intense attention among prebiotic chemists – perhaps the most-studied exception is the fact that nucleic acids can act as catalysts (e.g., ribozymes) as well as regulatory molecules (i.e., riboswitches). The utility of nucleic acids in such unexpected roles has inspired a generation of researchers to examine the prospect of an "RNA world," and great progress has been made towards this end. Similarly, very short protein catalysts, such as dipeptides, have been shown to act as catalysts. The utility of these ultrashort peptide catalysts suggests that peptides synthesized by noncoded dehydration reactions could have played a role in prebiotic chemistry as well.

While these primitive catalysts appear likely to have been useful in primitive life, modern life ultimately converged on largely protein-based mechanisms of catalysis and regulation, due to the greater effectiveness and broader utility of coded, ribosomally-synthesized proteins in these roles. Recently, we have observed that both nucleic acid and peptide catalysts can exhibit unexpected, novel behaviors as a result of their compartmentalization within fatty acid vesicles – models of primitive cells. In this talk, I will discuss our recent results demonstrating properties of potentially substantial utility to early life that arise from interactions between lipid compartments and both peptide and nucleic acid catalysts.

In particular, we have recently demonstrated the upregulation of ribozyme activity as a fatty acid vesicle grows, as a model of primitive homeostatic behavior [1]; growth of a fatty acid vesicle containing a dipeptide catalyst at the expense of those lacking the same catalyst, as a model of primitive Darwinian fitness [2]; and that a protein enzyme, when encapsulated within a fatty acid vesicle, can perform transformations on a water-insoluble substrate that are otherwise impossible in bulk aqueous solution, as a model of how primitive catalysts, such as ribozymes, might have performed transformations on hydrophobic substrates that are performed today by coded protein enzymes [3].

Taken together, we suggest these results indicate that, far from being a passive barrier, primitive cell membranes could have played a central role in early cellular biochemistry, enabling primitive biopolymers to exhibit a far wider suite of catalytic and regulatory behaviors than would be possible until the advent of coded protein synthesis with a full complement of modern amino acids.

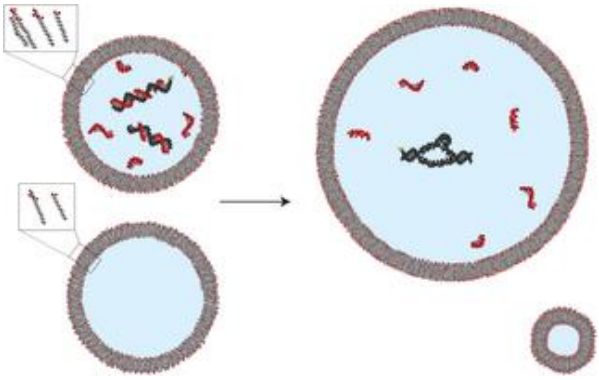

Figure 1. Regulation of enzyme activity in model protocells by dissociation of short complementary oligonucleotides.

Mixed fatty acid-glycerol ester-phospholipid vesicles that contain split ribozymes (black) and high concentrations of short oligonucleotides (red) exhibit no ribozyme activity, due to inhibition by duplex formation between the ribozyme fragments and complementary oligonucleotides (top left). When mixed with vesicles lacking phospholipid (bottom left), the phospholipid-containing vesicles grow at the expense of the phospholipid-lacking vesicles. This growth results in dilution of vesicle contents, inhibitor dissociation, and ribozyme reconstitution (right), increasing catalyst activity in the enlarged vesicles.

Figure and caption from [1].

References: [1] Aaron E. Engelhart, Katarzyna P. Adamala, and Jack W. Szostak. *Nature Chemistry*, 8, 448-453 (2016). doi:10.1038/nchem.2475. [2] Katarzyna P. Adamala and Jack W. Szostak. *Nature Chemistry*, 5, 495-501 (2013). doi:10.1038/nchem.1650. [3] Katarzyna P. Adamala, Aaron E. Engelhart, and Jack W. Szostak. *Nature Communications* (2016). doi:10.1038/ncomms11041.