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Proteins as we don't know them – creating primordial-like proteins from ancient amino acids

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Billions of years of evolution have shaped the intricate and complex structures of proteins that facilitate most processes in modern biology. All known organisms utilize essentially the same universal genetic code, comprised of 20 amino acids, to encode the huge diversity of proteins necessary for life. Thanks to thousands of three-dimensional structures, scientists have gained a good idea of how proteins function, at least in broad strokes. However, our understanding of 'how proteins work' is likely biased by mostly looking at those proteins that are easily crystallizable and have been optimized by evolution over eons. We are speculating that polypeptides in principle may be able to take on properties and form structures that are different from what has generally been observed in biology so far.

Instead of studying modern biology, we are investigating potential scenarios of how the earliest primordial proteins could have originated. We use high throughput selection and evolution in a test tube to isolate novel proteins from vast libraries of synthetic randomized polypeptides. We have generated novel proteins from scratch – proteins that nature has never seen before. In contrast to their modern-day counterparts, these artificial proteins have not undergone natural evolution and can serve as a model for primordial-like proteins. Furthermore, we are using our in vitro selection strategy to test hypotheses on the potential predecessors of the standard genetic code. We are comparing libraries of polypeptides from different likely earlier amino acid alphabets for the ability to form structured proteins and perform simple biological functions.

While we will not be able to prove a specific history of protein-based life, these experiments are testing the feasibility of plausible evolutionary scenarios and might reveal protein properties and structures as we have not seen them before.