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## Exploring the Evolutionary Accident Hypothesis: Are Extant Protein Folds the Fittest or the Luckiest?

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**Introduction:** Considering the range of functions proteins perform, it is surprising they fold into a relatively small set of structures or “folds” that facilitate such function. One explanation is that only a minority were fit enough to emerge from Darwinian selection during the early evolution of life. Alternatively, perhaps only a fraction of all possible folds were trialed [1]. Understanding proto-catalyst selection will aid understanding of the origins and early evolution of life.

To investigate which explanation is correct, we study a protein evolved *in vitro* to bind ATP by Jack Szostak (Fig. 1) [2]. This protein adopts a fold which is absent from nature [3]. We are testing whether this fold would have possessed the capability to evolve that would have been essential to survive natural selection on early Earth. Folds that couldn’t improve their fitness and evolve to perform new functions would have been replaced by rivals that could.

To determine whether the fold is evolvable, we are attempting to change the function of the protein by rationally redesigning to bind GTP. Two design strategies in the region of the nucleobase have been implemented to provide hydrogen bonding partners for the ligand i) an insertion ii) a MET to ASN mutation. Redesigns are being studied computationally at Ames Research Center including free energy of binding calculations. Binding affinities of promising redesigns are to be validated by experimental collaborators at FortéBio using Super Streptavidin Biosensors.

If the fold is found to be non-evolvable, this may suggest that many structures were trialed, but the majority were pruned on the basis of their evolvability [1]. Alternatively, if the fold is demonstrated to be evolvable, it would be difficult to explain its absence from nature without considering the possibility that the fold simply wasn’t sampled on early Earth. This would not only further our understanding of the origins of life on Earth but also suggest a common phenomenon of proto-catalyst evolution.

### References

[1] Chaput JC and Szostak JW (2004) *Chemistry & Biology* 11:865-874. [2] Keefe AD and Szostak JW (2001) *Nature* 410:715-718. [3] Lo Surdo P, Walsh MA, and Sollazzo M (2004) *Nature Structural & Molecular Biology* 11:382-383.

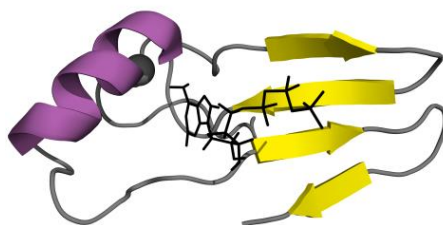


Figure 1: The novel fold of an ATP-binding protein evolved via mRNA display.