SUSTAINING LIFE WITH GENES AND PROTEINS DESIGNED DE NOVO

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Abstract:

The origin of life cannot be discovered, it has to be re-invented. This statement by Albert Eschenmoser emphasizes that we cannot go back in time to observe how life originated. Instead, we must devise alternative systems to probe what might have occurred in the past; and what may be possible in the future.

As a step toward reinventing life, we designed and constructed large collections of novel sequences with the goal of producing synthetic "genomes" capable of encoding entirely novel "proteomes." Millions of these novel sequences were expressed in *E. coli,* and proteins encoded by these genes were shown to fold into stable 3-dimensional structures. Moreover, several of the novel proteins bind biologically relevant metals, metabolites, and cofactors.

Most importantly, novel proteins from this artificial "proteome" provided essential functions necessary to sustain the growth of *E. coli.* In some cases, the novel proteins enable cell growth by rewiring gene regulation, while in other cases, the artificial protein provides an essential enzymatic activity required for nutrient assimilation or metabolism.

These results suggest that the molecular toolkit for life need not be limited to genes and proteins that already exist in nature; Instead, synthetic genomes encoding artificial proteomes can be constructed from sequences that never before existed on earth (or elsewhere). Ultimately, these findings suggest it may be possible to produce novel organisms – perhaps Eschenmoser's life reinvented – using genes and proteins designed entirely from scratch.