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Synthetic biology using genomes and proteomes designed *De Novo*

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Abstract

The entire collection of genes and proteins in all living systems comprises a minuscule fraction of sequence space. (For example, the collection of all 100-residue proteins would contain $20^{100}=10^{130}$ sequences -- far grater than the number of atoms in the universe.) From this enormous diversity of possible sequences, billions of years of evolution have selected a very small collection of 'molecular parts' that sustain living organisms (only ~4,000 genes in *E. coli* and ~23,000 in humans.) These considerations might lead one to assume that sequences capable of sustaining life must be unusual or somehow special. Is this true? Or can sequences designed 'from scratch' sustain the growth of living cells? To address these questions, we designed and constructed a collection containing millions of artificial proteins (a model 'proteome') encoded by a library of synthetic genes (an artificial 'genome'). Structural studies show that many (perhaps most) of our novel proteins fold into stable 3-dimensional structures. Next, we used genetic selections to demonstrate that several of these novel proteins provide biochemical functions essential for the growth of *E. coli*. Thus, artificial sequences that never existed in nature possess activities that sustain life. This initial foray into artificial genomics suggests (i) the molecular toolkit for life need not be limited to genes and proteins that already exist in nature; (ii) the construction of artificial genomes composed of non-natural sequences is within reach; and (iii) it may be possible to devise synthetic organisms using *de novo* designed proteins encoded by novel genomes.

Biography

Michael Hecht grew up in New York City. He received a BA in Chemistry from Cornell University and a Ph.D. in Biology from MIT. He then did post-doctoral research in Biochemistry at Duke Medical School. In 1990, Hecht joined the faculty at Princeton, where is a Professor of Chemistry and holds an affiliated appointment in Molecular Biology. He teaches courses ranging from Introductory Chemistry to graduate seminars on protein folding and design. In addition to teaching and research, Prof. Hecht is the Master of Forbes College, one of the six residential colleges at Princeton University.