Genetic code used to engineer a living protein

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Yale University researchers have successfully re-engineered the protein-making machinery in bacteria, a technical tour de force that promises to revolutionize the study and treatment of a variety of diseases.

"Essentially, we have expanded the genetic code of *E. coli*, which allows us synthesize special forms of proteins that can mimic natural or disease states," said Jesse Rinehart of the Department of Cellular and Molecular Physiology and co-corresponding author of the research published in the August 26 issue of the journal *Science*.

Since the structure of DNA was revealed in the 1950s, scientists have been working hard to understand the nature of the genetic code. Decades of research and recent advances in the field of synthetic biology have given researchers the tools to modify the natural genetic code within organisms and even rewrite the universal recipe for life.

"What we have done is taken synthetic biology and turned it around to give us real biology that has been synthesized," Rinehart explained.

The Yale team — under the direction of Dieter Söll, Sterling Professor of Molecular Biophysics and Biochemistry, professor of chemistry and corresponding author of the paper — developed a new way to influence the behavior of proteins, which carry out almost all of life's functions. Instead of creating something new in nature, the researchers essentially induced phosphorylation, a fundamental process that occurs in all forms of life and can dramatically change a protein's function. The rules for protein phosphorylation are not directly coded in the DNA but instead

occur after the protein is made. The Yale researchers fundamentally rewrote these rules by expanding the *E. coli* genetic code to include phosphoserine, and for the first time directed protein phosphorylation via DNA.

This new technology now enables the production of human proteins with their naturally occurring phosphorylation sites, a state crucial to understanding disease processes. Previously, scientists lacked the ability to study proteins in their phosphorylated or active state. This has hindered research in diseases such as cancer, which is marked by damagingly high levels of protein activation.

"What we are doing is playing with biological switches — turning proteins on or off — which will give us a completely new way to study disease states and hopefully guide the discovery of new drugs," Rinehart said.

"We had to give some very ancient proteins a few modern upgrades," Söll said.

Söll and Rinehart now are attempting to create proteins in states known to be linked to cancer, type 2 diabetes, and hypertension. Both men, however, stressed the technique can be done for any type of protein.

"Dr. Söll and his colleagues have provided researchers with a powerful new tool to use in uncovering how cells regulate a broad range of processes, including cell division, differentiation and metabolism," said Michael Bender, who oversees protein synthesis grants at the National Institute of General Medical Sciences of the National Institutes of Health.

Provided by Yale University

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