

Science & Technology

Protein engineering may be the future of science

Designing new proteins could become as significant as tweaking DNA

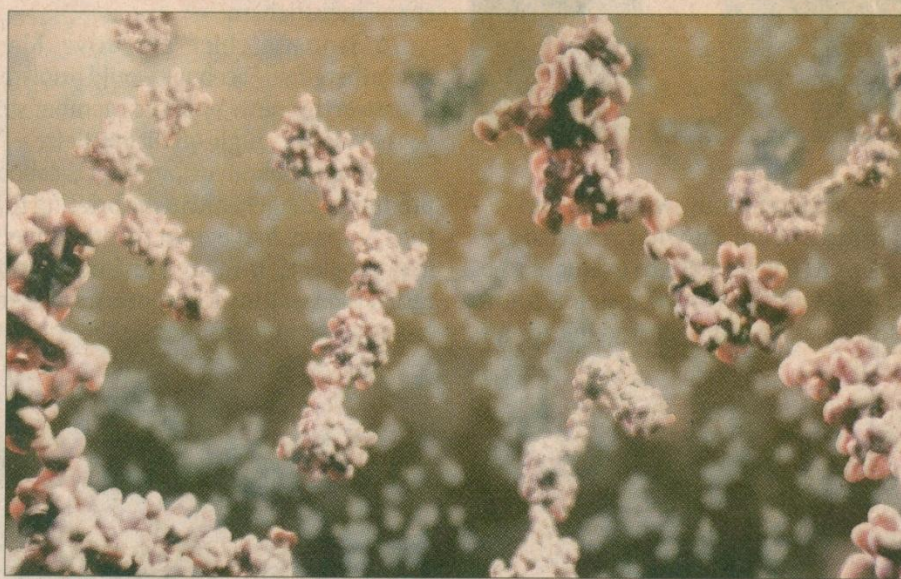
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SCIENTISTS ARE INCREASINGLY betting their time and effort that the way to control the world is through proteins. Proteins are what makes life animated. They take information encoded in DNA and turn it into intricate three-dimensional structures, many of which act as tiny machines. Proteins work to ferry oxygen through the bloodstream, extract energy from food, fire neurons, and attack invaders. One can think of DNA as working in the service of the proteins, carrying the information on how, when and in what quantities to make them.

Living things make thousands of different proteins, but soon there could be many more, as scientists are starting to learn to design new ones from scratch with specific purposes in mind. Some are looking to design new proteins for drugs and vaccines, while others are seeking cleaner catalysts for the chemical industry and new materials.

David Baker, director for the Institute for Protein Design at the University of Washington, compares protein design to the advent of custom tool-making. At some point, proto-humans went beyond merely finding uses for pieces of wood, rock or bone, and started designing tools to suit specific needs.

Now, it's possible to make a similar transition on a molecular scale, since scientists can create proteins with structures that nature never produced. "They can transcend the natural protein universe," said William DeGrado, a chemist at the University of California, San Francisco.



People have been talking about protein engineering for decades. But until the last couple of years, carrying it out was a dauntingly complex problem. There are no simple rules to predict how proteins fold into their various 3D structures. So even if you could design a protein with just the right shape for some job, there would be no obvious way to know how to make it from protein's building blocks, the amino acids.

But over many years, scientists have been chipping away at the problem, DeGrado said. Unlike in other more widely publicised fields, there haven't been any celebrated milestones (such as the completion of the \$3 billion human genome project). Nor have there been any single, surprise breakthroughs such as CRISPR—a component of yogurt bacteria that revolutionised the ability to manipulate genes. But now some scientists think

designing proteins will become at least as important as manipulating DNA has been in the past couple of decades.

What's recently changed is the ability to decipher the complex language of protein shapes. There's a very simple way that the linear chemical code carried by strands of DNA translates into strings of amino acids in proteins. But then the laws of physics come into play. The proteins snap into folded structures because amino acids are attracted or repelled by others many places down the chain.

University of Washington's Baker said that when he was starting his career some 30 years ago, senior scientists tried to steer him away from protein engineering because there was no guarantee he would make any appreciable progress in his lifetime. But he said he liked the challenge and the interdisciplinary nature of the quest,

which combined computer science, biology, chemistry and physics. Since then, scientists have advanced their understanding of the physics of proteins, and computing power has increased. Baker started a translation system called Rosetta, but—realising that he was running out of computer power at his university—he engaged citizens to lend their computers in a project called Rosetta@home.

Baker and colleagues then devised a sort of game called Foldit, in which citizen scientists could try figure out how certain proteins would fold. They eventually enlisted the help of more than a million people, he told me. That won them the ability to predict how smaller proteins would fold, but larger ones were still too complex. According to the magazine *Science*, they got a boost from scientists studying how evolution has led to the proteins we already have. Most genetic mutations that affect the structure of proteins will lead to something that doesn't work, and the death of whatever inherited it. But certain combinations of different mutations will lead to a modified version of the same thing, allowing new proteins to evolve.

And finally, their biological Rosetta stone is working. UCSF's DeGrado said his lab is looking at how to create new medicines with better stability—on the shelf and in the body. He's also studying Alzheimer's disease and similar neurological conditions, which are characterised by brain proteins that fold up incorrectly into toxic deposits.

Baker's lab is working on an equally diverse set of applications, including a vaccine that would simultaneously protect against all strains of the influenza virus, and a system to break down gluten, in the hope of helping people with celiac disease. Others are looking for proteins that help convert solar energy to fuel. Baker pointed out that there are 20 to the 200th possible proteins—more than the number of atoms in the universe. Evolution has produced just a minute fraction. So, there's room to expand.

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