Protein sex provides a prescription for power

SCIENCE

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PASADENA, Calif. — Some scientists have an unusually strong interest in unnatural sex.

Frances Arnold, for example, gets turned on by sex between proteins. But the millions of natural proteins in the biological world aren't enough to satisfy her.

"These proteins are all existing for one purpose, and that is to contribute to the ability of their own organisms to survive and reproduce," she says. "I don't want to tie my molecules to survival of the organism. I want something that will do something non-natural."

And so Dr. Arnold, a professor of chemical engineering at the California Institute of Technology in Pasadena, has embarked on a program of inducing unnatural chemical sex to produce proteins that nature either discarded or never imagined.

You can't blame nature for not making every possible protein, Dr. Arnold points out. Proteins are long chains of molecular building blocks known as amino acids. A typical protein chain contains about 300 amino acid links, and each link can be any of 20 amino acids. The number of possible combinations exceeds human comprehension, dwarfing the number of stars in the sky, atoms in the universe, grains of sand in Santa Monica and the population of China, India and Plano all added together.

Say you were counting the number of atoms in the universe. When you get to 1, you've reached a higher percentage of all the atoms than the percentage of protein possibilities you'd have after counting them for a trillion years — at a rate of a trillion a second.

Of course, not all those possibilities will make good proteins, as Dr. Arnold explained at a recent Caltech colloquium. To do anything useful, the protein's amino acid chain has to fold up into a precise shape, suitable for interacting with other molecules. Without the proper folds, a protein does nothing. Most of the possible proteins, it turns out, don't fold at all.

Nature's strategy is to find one protein that works, and then make new ones with slight variations. That way a few basic shapes can provide numerous proteins for conducting a wide range of tasks.

Such variations depend on simple changes, or mutations, in the DNA storing the protein's genetic blueprint. One mutation alters a single amino acid somewhere in the chain. So you might think the way to make new proteins would be just replacing an amino acid here and there with another one.

Sadly, as few as four such changes typically render the resulting protein unfoldable and therefore useless. So changing the links at random is a poor strategy.

It seems that in addition to mutations, you need another way to modify the DNA's genetic information. Such as sex.

After all, mixing up DNA is what sex is all about. When organisms mate, mother and father both provide half their offspring's genes. The DNA is shuffled in the process, recombining DNA segments to make new genes that can differ from those in either parent.

There's no reason, Dr. Arnold argues, why human scientists can't shuffle DNA in test tubes and make new genes — that is, blueprints for new proteins.

"I propose that you can breed proteins just like you can breed cats and dogs," she says.

In fact, she attempts the molecular equivalent of breeding cats *with* dogs — taking segments from two distinct proteins for "parents," and producing from their DNA the blueprint for a new offspring protein unlike anything found in nature.

The trick, of course, is making a new protein that does something useful, such as curing a disease or neutralizing a poisonous pollutant. And shuffling protein DNA at random is not a very good bet to come up with a marketable protein.

But as Dr. Arnold points out, you don't have to shuffle DNA at random. You can look at the structure of the parent proteins and see how they're folded, noting which amino acid links seem to be keeping the folded structure in place. When you break up the pieces to recombine, you can slice them in a way that will preserve the parts that are critical for the folds.

This approach gives Dr. Arnold an advantage over evolution, which relies on random shuffling to search for new proteins. "So I actually have the potential to breed at a much larger scale than can happen in nature," she says.

Recent work in her lab has already demonstrated success at shuffling segments of DNA blueprints in test tubes and then quickly identifying new combinations that make useful proteins. By taking segments from proteins with similar shapes, Dr. Arnold can produce protein children with the same basic folded 3-D backbone, but with many mutations that provide new capabilities.

So far, nobody has tried to stop scientists from pursuing this sort of research, probably because no politicians realize how powerful it could be.

"This process that I've talked to you about, creating new proteins, is equally valid for all levels of complexity in biology," says Dr. Arnold, "not just proteins, but whole protein pathways, regulatory circuits, metabolic systems, whole organisms and even whole ecosystems."

In other words, science has figured out how to harness the power of evolution, the force that populated the planet. And just as some of evolution's other products demonstrate, such power can produce bad things, but many good things as well.