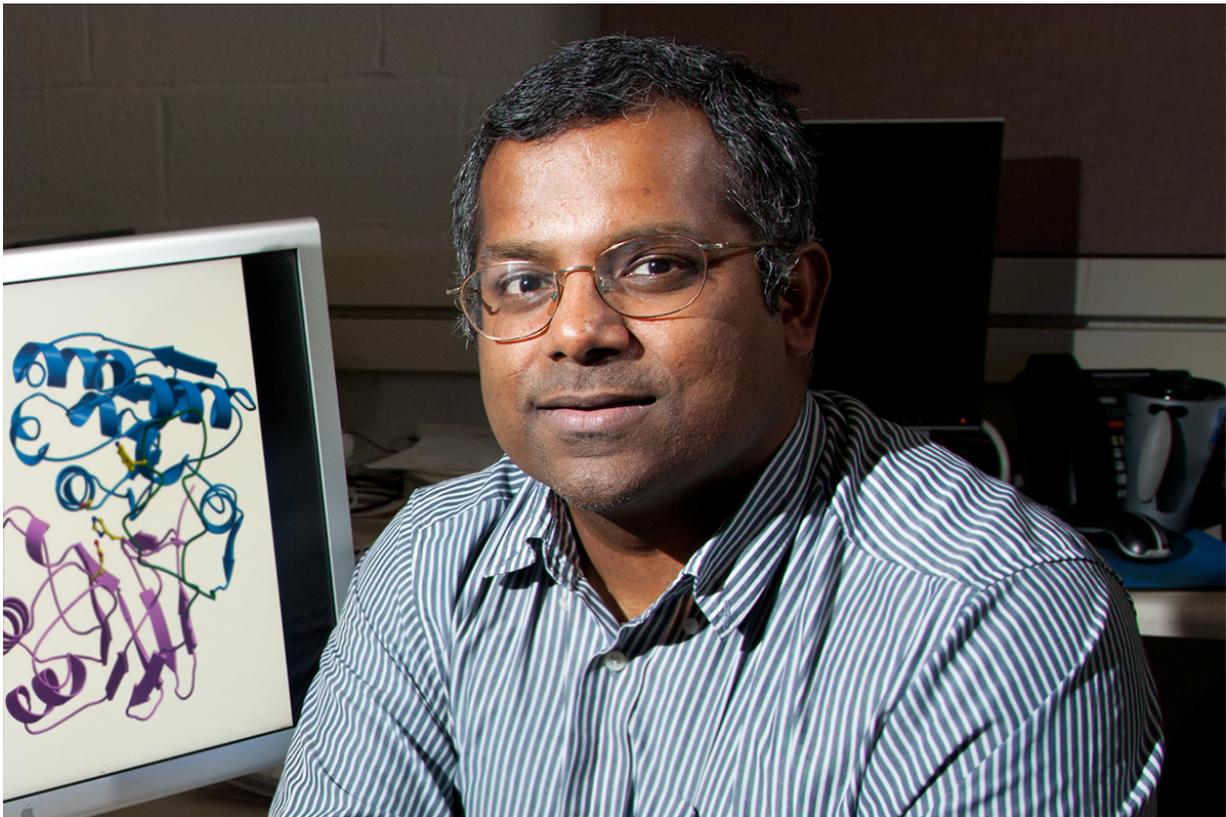


Team finds new way to attach lipids to proteins, streamlining drug development

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University of Illinois biochemistry professor Satish Nair and his colleagues found a way to use a microbial enzyme to efficiently transform proteins by adding lipid (fat) molecules to them. Credit: L. Brian Stauffer

Protein-based drugs are used in the treatment of every kind of malady,

from cancer to heart disease to rheumatoid arthritis. But the proteins are almost always modified with chemical appendages that help them navigate through the body or target specific tissues. A new study reveals an efficient means of attaching lipids (fat molecules) to peptides (the building blocks of proteins). This can improve the molecules' drug-delivery capabilities.

The new findings are reported in the *Proceedings of the National Academy of Sciences*.

"Medicinal chemistry has focused on using [peptides](#) as scaffolds for drugs because of the ease of their production and the chemical diversity of their amino-acid [building blocks](#)," said University of Illinois biochemistry professor Satish K. Nair, who led the new research with Thomas Cheatham and Eric Schmidt of the University of Utah.

"However, peptides are generally ineffective drugs because they are poorly absorbed, cannot penetrate the blood-brain barrier and are easily broken down," Nair said.

Attaching lipids "improves all of these properties, enabling peptides to be more druglike," he said. Current methods for attaching lipids to peptides require the use of either harsh chemical solvents or expensive biological catalysts.

Nair and his colleagues focused on a little-known group of enzymes isolated from water-dwelling bacteria that have the remarkable ability to add lipids to a wide variety of proteins. The team performed a series of experiments on one family of these enzymes to discover how they recognize and interact with the peptides they modify.

The researchers discovered that one type of enzyme recognizes a simple, two-amino-acid sequence within its [target proteins](#). They added this motif to two peptides selected at random and exposed the peptides to the

enzyme. This caused the enzyme to add a [lipid](#) appendage to the proteins. The transformation was fast and efficient.

"Now that we have a very efficient way of attaching lipids to peptides, this opens up the possibility of using this approach to make large libraries of molecules that are more druglike than peptides," Nair said.

More information: Molecular basis for the broad substrate selectivity of a peptide prenyltransferase, *PNAS*,

www.pnas.org/cgi/doi/10.1073/pnas.1609869113

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