New polymer allows researchers to study how proteins fold, function

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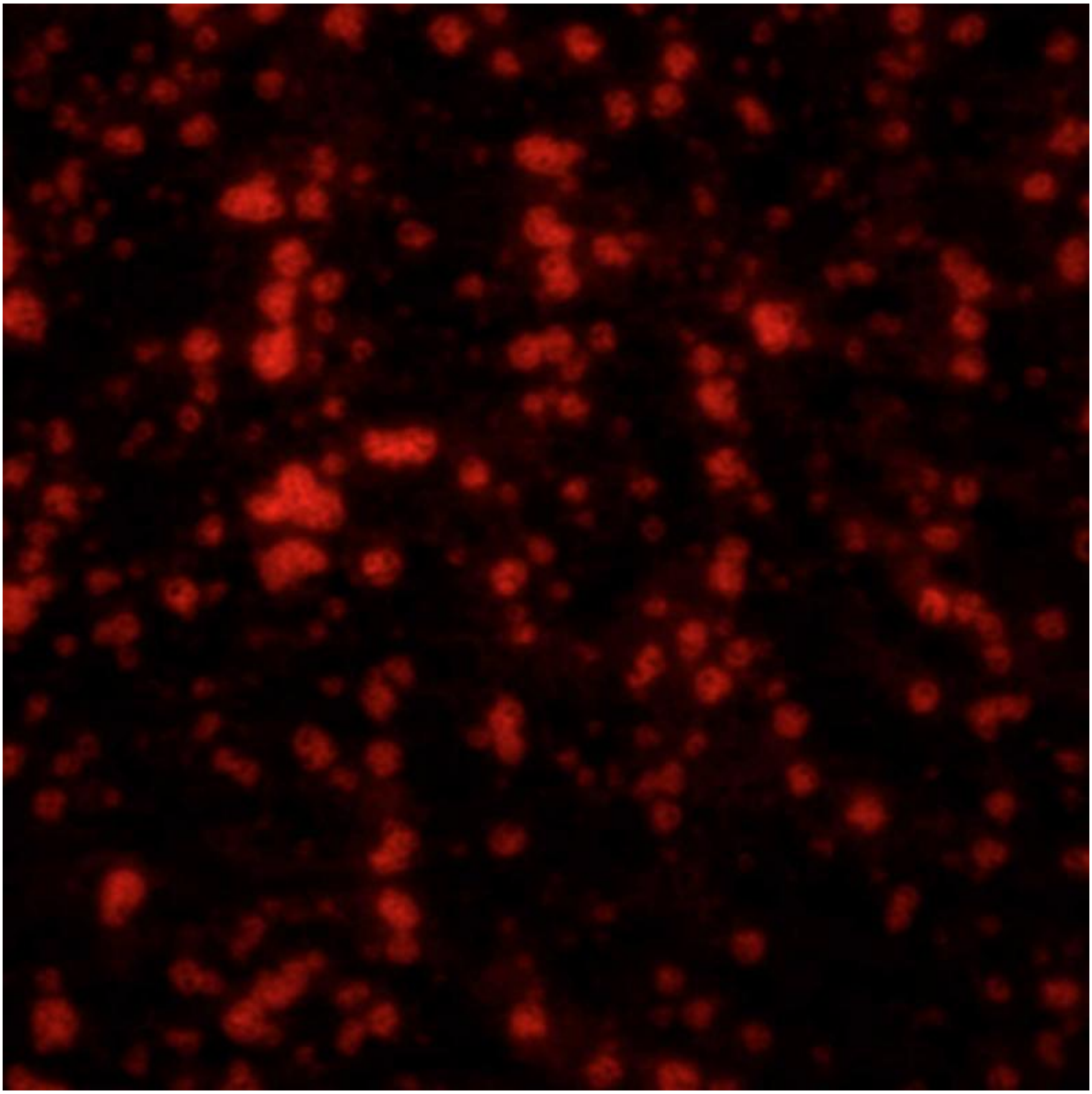

esicles containing the phospholipid DMPE-rhodamine B after Ramamoorthy's polymer has been added. Phospholipids are fatty acids that are critical components of all cell membranes. The polymer breaks the vesicles to form sushi-like nanodiscs. Credit: Ayyalusamy Ramamoorthy

University of Michigan biophysicists and chemists have created a new polymer that mimics a cell membrane, allowing proteins found within cell membranes to fold and function naturally in the synthetic material.

This could give researchers the opportunity to study how proteins behave in cells being ravaged by Alzheimer's disease and cancer. The polymer may also be useful for drug delivery systems: It's not harmful to living tissues, and can form large nanodiscs, ranging from approximately eight to 60 nanometers in diameter.

"This kind of nanodisc has been demonstrated by others to be the best mimic for cell membranes, but the main problem with previous nanodiscs is that they're too small—only as big as 20 nanometers in diameter," said lead author Ayyalusamy Ramamoorthy, the Robert W. Parry Collegiate Professor of Chemistry and Biophysics. "We have been able to open the disc to form a bigger, sushi-like disc up to 60 nanometers, a dramatic achievement."

Proteins found in the cell membrane are difficult to study by biophysical and biochemical approaches: they sit in a lipid bilayer environment within cell membranes, which is hard to mimic. The Ramamoorthy lab at U-M has designed and synthesized the new polymer, which forms lipid nanodiscs to provide a suitable environment in which these proteins can fold and become structured naturally.

The synthetic polymer breaks large onion-like multilayered lipid

structures to form small pieces of lipid bilayers called "nanodiscs." These nanodiscs are shaped like sushi, with the polymer wrapping around a patch of lipid bilayer. When researchers want to study a particular membrane protein, they can reconstitute that protein into the polymer nanodisc in order to examine the protein's structure, protein-to-protein interactions and drug-protein interactions, among other actions.

Researchers then use a technique called nuclear magnetic resonance imaging to image the protein at an atomic level within the nanodisc. These techniques are being developed in the Ramamoorthy lab to study the structures of an enzyme called cytochrome P450, responsible for metabolizing many kinds of medicine, and also to monitor the aggregation of amyloid proteins that are implicated in Alzheimer's disease and type 2 diabetes.

The newly discovered polymer and its ability to form lipid nanodisc will have significant impacts in the atomic-resolution structure determination and functional analysis of a variety of proteins found in the cell membrane.

The study was published in Wiley-VCH and Ramamoorthy's group has filed for a U.S. patent on the polymer.

More information: Thirupathi Ravula et al. Bioinspired, Size-Tunable Self-Assembly of Polymer-Lipid Bilayer Nanodiscs, *Angewandte Chemie International Edition* (2017). DOI: 10.1002/anie.201705569

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