Chemists concoct new agents to easily study critical cell proteins

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They are the portals to the cell, gateways through which critical signals and chemicals are exchanged between living cells and their environments.

But these gateways -- proteins that span the cell membrane and connect the world outside the cell to its vital inner workings – remain, for the most part, black boxes with little known about their structures and how they work. They are of intense interest to scientists as they are the targets on which many drugs act, but are notoriously difficult to study because extracting these proteins intact from cell membranes is tricky.

Now, however, a team of scientists from the University of Wisconsin-Madison and Stanford University has devised a technology to more easily obtain membrane proteins for study. Writing this week (Oct. 31) in the journal *Nature Methods*, the group reports the development of a class of agents capable of extracting complex membrane proteins without distorting their shape, a key to understanding how they work.

"The proteins are embedded in the membrane to control what gets into the cell and what gets out," explains Samuel Gellman, a UW-Madison professor of chemistry and a senior author of the paper along with Brian Kobilka of Stanford and Bernadette Byrne of Imperial College London. "If we want to understand life at the molecular level, we need to understand the properties and functions of these membrane proteins."

The catch with membrane proteins and unleashing their potential,

however, is getting insight into their physical properties, says Gellman.

Like other kinds of proteins, membrane proteins exhibit a complex pattern of folding, and determining the three-dimensional shapes they assume in the membrane provides essential insight into how they do business.

Proteins are workhorse molecules in any organism, and myriad proteins are known. Structures have been solved for many thousands of so-called "soluble" proteins, but only a couple of hundred membrane protein structures are known, Gellman notes. This contrast is important because roughly one-third of the proteins encoded in the human genome appear to be membrane proteins.

To effectively study a protein, scientists must have access to it. A primary obstacle has been simply getting proteins out of the membrane while maintaining their functional shapes. To that end, Gellman's group has developed a family of new chemical agents, known as amphiphiles, that are easily prepared, customizable to specific proteins and cheap.

"These amphiphiles are very simple," says Gellman. "That's one of their charms. The other is that they can be tuned to pull out many different kinds of proteins."

The hope, according to Gellman, is that the new technology will facilitate research at the biomedical frontier.

The development of the amphiphiles was conducted in close collaboration with groups like Kobilka's, which specializes in techniques that help resolve the three-dimensional structures of proteins found in cell membranes.