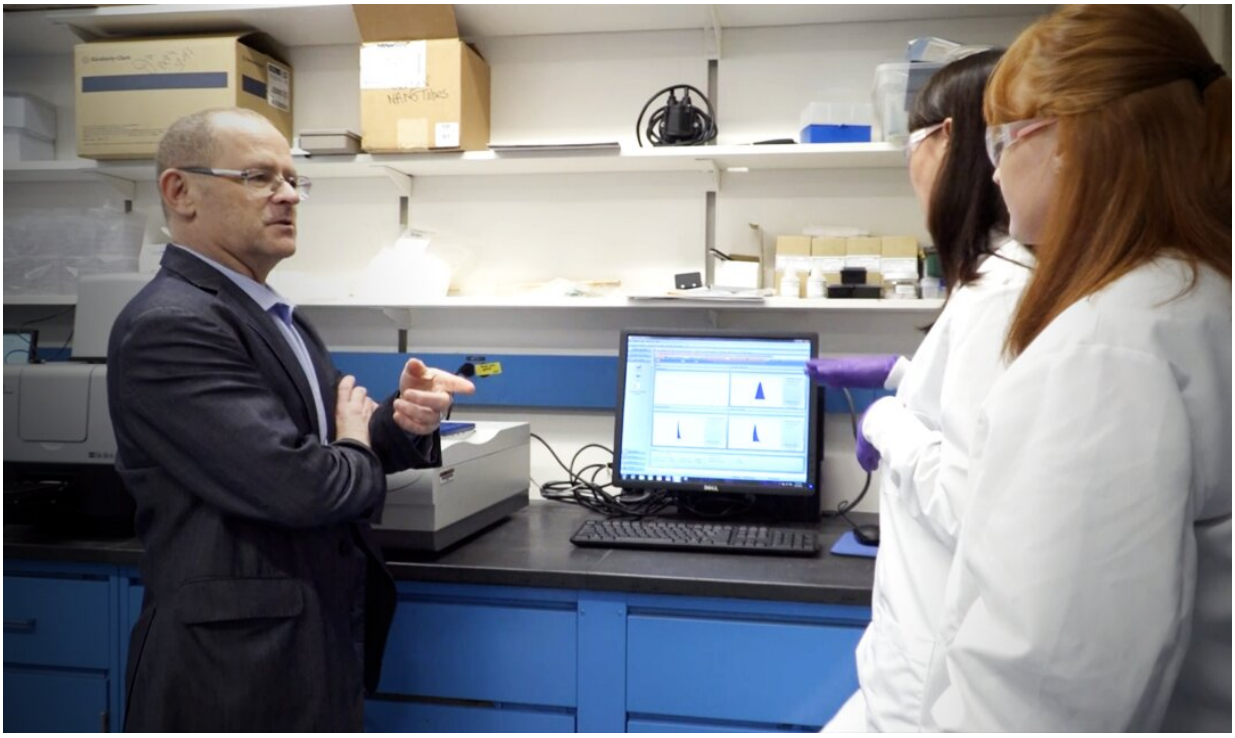
Salting down the cost of protein polymer drugs

January 6 2020, by Adam Dove



Credit: Carnegie Mellon University, Department of Chemical Engineering

Protein is big business. Not only does it make up a significant portion of every living thing—it's also a $150 billion per-year industry. Whether for food, medicine, or manufacturing, nearly all sectors have a need for proteins to create their products. But in the case of pharmaceuticals, the need for proteins also comes with a big cost, one that pharmaceutical

manufacturers desperately need to find their way around: the cost of protein purification. But now, thanks Alan Russell, professor of chemical engineering, and Ph.D. student Stefanie Baker, the pharmaceutical industry has an innovative way around this costly problem when manufacturing protein-polymer therapeutics. Russell, Baker, and their team have developed a novel method to purify the protein-polymer conjugates used in pharmaceuticals to ensure they perform properly, work that was recently published in *Nature Communications*.

"The purity of proteins and protein-polymer conjugates intended for therapeutic use is extremely important," says Baker. "Therapeutic proteins must be homogenous and have the same properties from batch to batch, otherwise, they won't have the same therapeutic effects time after time, and may in fact be harmful to the patients they're meant to help."

Currently, nearly all commercial proteins start their purification using a process of ammonium sulfate precipitation. From here, the struggle to separate one protein from another—especially in the case of a protein-polymer drug—gets really complicated. Conjugates must be separated from polymers, native proteins, and isomers. This has historically presented a real problem to scientists, and can account for more than half of the total cost of manufacturing protein drugs for patients. With Baker and Russell's new method, however, that cost can be significantly decreased.

"We have been interested in engineering the solubility of proteins by growing polymers from their surface," says Russell. "What if proteins could be engineered to make them soluble at extreme salt concentrations? The salt—ammonium sulfate—is used ubiquitously to concentrate proteins because it precipitates every protein at about 50% saturating concentration. We decided to challenge ourselves and see if

we could create a protein that dissolved in completely saturated ammonium sulfate."

Over the last year, the team has discovered that by growing covalent polymers from the surface of the proteins, they are able to greatly increase the solubility of these proteins in salt solutions. This way, the proteins will dissolve much more rapidly in the salt solution then their associated impurities, making them much easier to separate, and leaving behind only the pure, desired protein. It's a much quicker and more simple way to purify these compounds compared to the traditional methods. The team also collaborated with a leading group at the University of Florida, led by Professor Coray Colina. Colina and her students made computer models of the impact of salt on the protein conjugates to help understand how the right polymer could turn an arduous process into an easy one.

Now that their method has been proven to work, Baker and Russell will take the next step: proving that it works at the scale necessary for commercial production. And while this is a massive undertaking, the team is optimistic about just what this could mean for the future of biopharmaceuticals.

"The discovery that these proteins can be engineered to dissolve in a solution where every other protein cannot," says Russell, "may truly simplify how these conjugate drugs are made—and make them much more affordable in the future."

More information: Stefanie L. Baker et al. Transforming protein-polymer conjugate purification by tuning protein solubility, *Nature Communications* (2019). DOI: 10.1038/s41467-019-12612-9

Provided by Carnegie Mellon University, Department of Chemical Engineering