UT researchers' innovation addresses major challenge of drug delivery

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A new physical form of proteins developed by researchers at The University of Texas at Austin could drastically improve treatments for cancer and other diseases, as well as overcome some of the largest challenges in therapeutics: delivering drugs to patients safely, easily and more effectively.

The protein formulation strategy, developed by faculty and students in the Cockrell School of Engineering's Department of Chemical Engineering, is unprecedented and offers a new and universal approach to drug delivery – one that could revolutionize treatment of cancer, arthritis and infectious disease.

"We believe this discovery of a new highly concentrated form of proteins – clusters of individual protein molecules – is a disruptive innovation that could transform how we fight diseases," said Keith P. Johnston, a chemical engineering professor and member of the National Academy Engineering. "It required integration of challenging contributions in fundamental science and engineering from three of our chemical engineering research groups."

The research, led by Johnston, Chemical Engineering Professor Thomas M. Truskett and Assistant Professor Jennifer Maynard, was published online recently ahead of a print version to appear soon in the *ACS Nano* journal.

"The real challenge in developing therapeutics is how do you deliver

them to patients." Maynard said.

Typically, protein biopharmaceuticals are administered intravenously at dilute concentrations in a hospital or clinic. Scientists and engineers have long tried to produce safe drugs at higher concentrations, so that a patient could self-inject the drugs at home, similar to an insulin shot. But doing so has been stymied by the fact that proteins, in high-concentration formulations, form aggregates that could be dangerous to patients and gels that cannot be injected.

The Cockrell School research team has introduced a new physical form of proteins, whereby proteins are packed into highly concentrated, nanometer-sized clusters that can pass through a needle into a patient to treat disease. The novel composition avoids the pitfalls of previous attempts because drug proteins are clustered so densely that they don't unfold or form dangerous aggregates.

"This general physical concept for forming highly concentrated, yet stable, protein dispersions is a major new direction in protein science," Johnston said.

A key advance came in 2004, when Truskett predicted that protein-based drugs in solution would be stable if they could somehow be formulated at ultra-high concentrations. At that time, Johnston had nanoparticles of concentrated stable protein but didn't know how to disperse them in an injectable form.

In 2009, the team formed protein nanoclusters in water simply by properly adjusting the pH (to lower protein charge) and adding sugar to crowd protein molecules together. Upon dilution or subcutaneous injection into a mouse the proteins separate back to individual stable molecules with biological activity. Once injected, the protein in the bloodstream attacks targeted cells and tumors similarly as for protein

delivered via IV therapy. To provide a roadmap for improving the design of nanoclusters, chemical engineering graduate students, Andrea Miller and Ameya Borwankar worked with Truskett and Johnston to develop a new thermodynamic theory.

Another breakthrough for the team came in 2009 when a chemical engineering senior, Brian Wilson, created a transparent dispersion of extremely concentrated protein, which was later found to be formed of nanoclusters.

"Through Brian's discussions about the research both inside and outside of the classroom, numerous undergraduate students at UT are now realizing the enormous opportunities they have to contribute to science, engineering and human health when they get involved in research projects," Johnston said.

Since the research began in 2004, three patent applications have been filed through the university's Office of Technology Commercialization.

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