

Researchers create new 'smart' nanocapsule delivery system for use in protein therapy

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the delivery of healthy proteins directly into human cells to replace malfunctioning proteins — is considered one of the most direct and safe approaches for treating diseases. But its effectiveness has been limited by low delivery efficiency and the poor stability of proteins, which are frequently broken down and digested by cells' protease enzymes before they reach their intended target.

In what could signal a major advance in [protein](#) therapeutics, researchers at the UCLA Henry Samueli School of Engineering and Applied Science have developed a new intracellular delivery platform that uses nanocapsules made up of a single-protein core with a thin polymer shell that can be engineered to either degrade or remain stable based on the cellular environment.

Their research appears Dec. 29 in the January 2010 edition of the journal *Nature Nanotechnology* and is currently available online.

"For proteins in general, it's very difficult to cross the cell membrane. The protease will usually digest it, making stability an issue," said lead study author Yunfeng Lu, a UCLA professor of chemical and biomolecular engineering. "Here, we've been able to use this new technology to stabilize the protein, making it very easy to cross the cell membrane, allowing the protein to function properly once inside the cell. This is one of our biggest achievements."

Nanocapsules are submicroscopic containers composed of an oily or

aqueous core — in this case a single protein — surrounded by a thin, permeable polymer membrane roughly several to tens of nanometers thick. The membranes of the nanocapsules used in the new UCLA delivery method can degrade or remain intact depending on the size of the molecular substrates with which their embedded protein must interact.

Non-degradable nanocapsules are more stable, and small molecular substrates can readily diffuse to the protein embedded inside. The capsule's non-degradable skin meanwhile protects the cargo from protease attacks and stabilizes the protein from other factors, like varying temperatures and pH levels.

However, a non-degradable skin may also prevent substrates of larger molecular weight from reaching the embedded protein. In order for the protein to be able to interact with a large substrate, a degradable skin can also be used.

When the protein nanocapsule is taken in by the cell, it will stay within the endosome initially. Endosomes generally have lower pH levels than the outside cellular environment; the lower pH triggers the degradation of the polymer skin layer, releasing the protein cargo intracellularly.

The research team, led by study co-author Yi Tang, a UCLA professor of chemical and biomolecular engineering, has also demonstrated that such skin layers can also be degraded by incorporating components that are sensitive to proteases. This approach will also allow for a more targeted delivery of the proteins.

The new study has shown that multiple proteins can now be delivered to cells with high efficiency and activity but low toxicity, allowing for potential applications in protein therapies, vaccines, cellular imaging, tumor tracking, cancer therapies and even cosmetics.

"Covering the protein payload with a polymeric shell provides added stability in circulation, where there are plenty of proteases to degrade the naked protein," said Lily Wu, professor of medical and molecular pharmacology at the David Geffen School of Medicine at UCLA and an author of the study. "This will clearly be advantageous in improving efficacy of delivery.

"Further, the ability to deliver cargo intracellularly and to control the release of the protein cargo by pH or other environmental parameters is very important," she said. "Improving safety, efficiency and targeted delivery of protein payload is the holy grail of modern medicine. This new technology holds promise in all these aspects and that's why it is so exciting to me."

"Right now, a lot of protein therapeutics available only act outside of the cell because it's been difficult to deliver the proteins inside the cell," said Tatiana Segura, a UCLA professor of chemical and biomolecular engineering and a study co-author.

The team hopes the new technology will serve as a delivery platform for any type of protein or protein drug. Though the study, when originally submitted, described the use of the technology with five different proteins, in the short time since, the team has expanded to more than two dozen different proteins.

"I think the important next step is to apply this technology in a relevant, preclinical disease model," Wu said. "Based on the promising results of improved efficiency of delivery into cells, I anticipate improved efficacy in preclinical animal models as well.

"In the long run, the hope is to develop new technology that can make a difference in the lives of patients," she said. "I feel extremely fortunate to be able to collaborate with this elite group of chemical engineers on

this exciting project."

Provided by University of California - Los Angeles

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