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Safer, more effective gene therapy

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Athens, Ga. – The potential of gene therapy has long been hampered by the risks associated with using viruses as vectors to deliver healthy genes, but a new University of Georgia study helps bring scientists closer to a safe and efficient gene delivery method that doesn't involve viruses.

Assistant professor of chemistry Yan Geng and her colleagues in the UGA Franklin College of Arts and Sciences have created a novel synthetic gene vector that packages DNA into well-defined nanostructures that allow it to efficiently deliver genes without triggering immune responses. The study, primarily carried out by doctoral student Jennifer Haley, appears in the June issue of the journal Molecular BioSystems and also may have implications for cancer treatment and vaccine development.

"We've developed a very versatile approach to creating synthetic gene delivery vectors," said Geng, a Georgia Cancer Coalition Distinguished Scholar and a researcher in the UGA Cancer Center. "Our approach is relatively simple – using simple chemical reactions to create a new class of packaging molecules that wrap up genes on their own – and has the potential to be very useful in real-world, clinical applications."

Gene therapy involves replacing abnormal, disease-causing genes with normal genes. To do this, genetically modified viruses often are used. The viruses do a remarkable job of inserting the new genes into hosts, Geng said, but they're inherently dangerous. So while the use of viruses as gene delivery vectors has been efficient, it also has led to unexpected and tragic complications, some of which were fatal. Synthetic vectors,

which use synthetic molecules to package genes, are generally safer than viral vectors, Geng said. The downside is that they're not nearly as efficient. For millions of years, viruses have evolved into a small size, a rich variety of shapes – spherical, disk-like, and sometimes long filaments, and sophisticated mechanisms to facilitate the easy entrance of their DNA into cells.

"In nature, viruses are precisely self-assembled by their coating proteins and genome," Geng said. "We have to learn from nature and engineer a safer yet efficient gene delivery system for medical use."

Synthetically packaging long strands of DNA into compact, small structures has long been a challenge, but Geng's team has developed a unique combinative self-assembly method that allows scientists to control precisely the size and shape of the vector. The Geng team synthesized small peptides – which are short chains of amino acids – that bind to genes and emulate natural proteins to minimize potential immune reactions. The researchers then attach the small peptides onto a biocompatible polymer scaffold to create a clustered effect. The clustered peptides of the combined molecule will automatically assemble with DNA, while the polymer wraps around the assembly, creating a protective shell. The researchers have discovered that the assembly process is extremely sensitive to the clustered arrangement of the gene-binding peptides. To change the shape and size of the vectors, the researchers simply change the attachment density of the peptides on the polymer scaffold, resulting in shapes that vary from spherical to donut shaped to long filaments.

"These gene vectors also can be further conjugated with targeting molecules, which will allow us to deliver the right genes to the right spot in our body," Geng added.

With the synthesis of the vector complete, the scientists now plan to

assess how effective it is in integrating genes into cancer cells. Geng said her ultimate goal is to use tumor-suppressor genes to treat cancer. Another possibility is to use the synthetic vectors to introduce genes that boost the immune system.

"Our research is still at an early stage," Geng said, "but we've developed a very promising system."

Source: University of Georgia