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Peixuan Guo, PhD, Dane and Mary Louise Miller Endowed Chair in biomedical engineering with students in his lab at the Vontz Center for Molecular Studies

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Publish Date: 04/20/11
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Building From The Ground Up, Researchers Construct RNA Nanoparticles To Safely Deliver Long-Lasting Therapy To Cells

CINCINNATI—Nanotechnology researchers have known for years that RNA, the cousin of DNA, is a promising tool for nanotherapy, in which therapeutic agents can be delivered inside the body via nanoparticles. But the difficulties of producing long-lasting, therapeutic RNA that remains stable and non-toxic while entering targeted cells have posed challenges for their progress.

In two new publications in the journal *Molecular Therapy*, University of Cincinnati (UC) biomedical engineering professor Peixuan Guo, PhD, details successful methods of producing large RNA nanoparticles and testing their safety in the delivery of therapeutics to targeted cells.

The articles, in advance online publication, represent "two very important milestones in RNA nanotherapy," says Guo.

"One problem in RNA therapy is the requirement for the generation of relatively large quantities of RNA," he says. "In this research, we focused on solving the most challenging problem of industry-scale production of large RNA molecules by a bipartite approach, finding that pRNA can be assembled from two pieces of smaller RNA modules."

Guo, Dane and Mary Louise Miller Endowed Chair of biomedical engineering, serves as director of the National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer Platform Partnership Program at UC. He has focused his research on RNA for decades, pioneering its use as a versatile building block for nanotechnology, or for the engineering of functional systems at the molecular scale. In 1987, he discovered a packaging RNA (pRNA) in the bacteriophage phi29 virus which can gear a motor to package DNA into the viral protein shell. In 1998, his lab discovered that pRNA can self-assemble or be engineered into nanoparticles to gear the motor.

In his most recent research, Guo and colleagues detail multiple approaches for the construction of a functional 117-base pRNA molecule containing small interfering RNA (siRNA). siRNA has already been shown to be an efficient tool for silencing genes in cells, but previous attempts have produced chemically modified siRNA lasting only 15-45 minutes in the body and often inducing undesired immune responses.

"The pRNA particles we constructed to harbor siRNA have a half life of between five and 10 hours in animal models, are non-toxic and produce no immune response," says Guo. "The tenfold increase of circulation time in the body is important in drug development and paves the way towards clinical trials of RNA nanoparticles as therapeutic drugs."

Guo says the size of the constructed pRNA molecule is crucial for the effective delivery of therapeutics to diseased tissues.

"RNA nanoparticles must be within the range of 15 to 50 nanometers," he says, "large enough to be retained by the body and not enter cells randomly, causing toxicity, but small enough to enter the targeted cells with the aid of cell surface receptors."

In the paper, "Assembly of Therapeutic pRNA-siRNA Nanoparticles Using Bipartite Approach," Guo and his colleagues used two synthetic RNA fragments to create the 117-base pRNA, which was able to further assemble with other pRNA molecules and function in the bacteriophage phi29 viral motor to package DNA.

"The two-piece approach in pRNA synthesis overcame challenges of size limitations in chemical synthesis of RNA nanoparticles," Guo wrote. "The resulting nanoparticles were competent in delivering and releasing therapeutics to cells and silencing the genes within them. The ability to chemically synthesize these nanoparticles allows for further chemical modification of RNA for stability and specific targeting."

The second publication, "Pharmacological Characterization of Chemically Synthesized Monomeric phi29 pRNA Nanoparticles for Systemic Delivery," builds on that research, demonstrating that modified three-dimensional pRNA nanoparticles were readily manufactured through the two-piece approach. The modified nanoparticles were resistant to common enzymes that can attack and degrade RNA and remained chemically and metabolically stable.

Furthermore, when delivered to target cells in an animal model, the nanoparticles were non-toxic and did not induce an immune response, enabling the nanoparticles to bind to cancer cells in vivo.

Previous studies have encased therapeutic siRNA in a polymer coating or liposome for delivery to cells.

"To our knowledge, this is the first naked RNA nanoparticles to have been comprehensively examined pharmacologically in vivo and demonstrated to be safe, as well as deliver itself to tumor tissues by a specific targeting mechanism," he says. "It suggests that the pRNA nanoparticles without coating have all the preferred pharmacological features to serve as an efficient nanodelivery platform for broad medical applications."

Co-authors of "Assembly of Therapeutic pRNA-siRNA Nanoparticles Using Bipartite Approach" include Yi Shu, Mathieu Cinier, Sejal Fox and Nira Ben-Johnathan of the University of Cincinnati.

Co-authors of "Pharmacological Characterization of Chemically Synthesized Monomeric phi29 pRNA Nanoparticles for Systemic Delivery" include Sherine Abdelmawla and Songchuan Guo of Kylin Therapeutics and Purdue University, Limin Zhang, Sai M Pulkuri, Prithviraj Patankar, Patrick Conley, Joseph Trebley and Qi-Xiang Li of Kylin Therapeutics.

This study was funded by National Cancer Institute, National Institute of Biomedical Imaging and Bioengineering, National Institute of General Medical Sciences and Kylin Therapeutics Inc. Guo is co-founder of Kylin Therapeutics.

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