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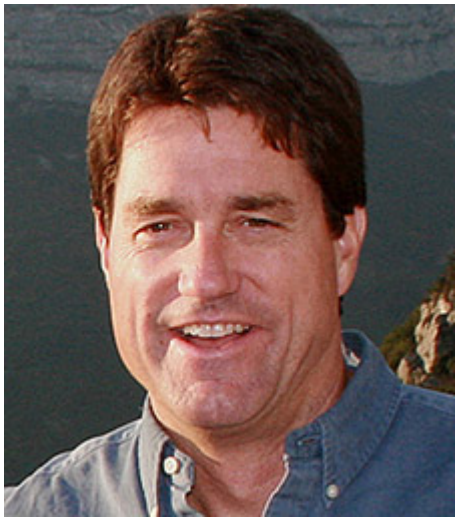
# Chemical Disguise Transforms RNAi Drug Delivery

## Chemistry trick may herald transformational next-generation RNAi therapeutics aimed at cancer, viral infections and more

Small pieces of synthetic RNA trigger a RNA interference (RNAi) response that holds great therapeutic potential to treat a number of diseases, especially cancer and pandemic viruses. The problem is delivery — it is extremely difficult to get RNAi drugs inside the cells in which they are needed. To overcome this hurdle, researchers at University of California, San Diego School of Medicine have developed a way to chemically disguise RNAi drugs so that they are able to enter cells. Once inside, cellular machinery converts these disguised drug precursors — called siRNNs — into active RNAi drugs. The technique will publish Nov. 17 in *Nature Biotechnology*.



*Steven Dowdy, PhD*

"Many current approaches use nanoparticles to deliver RNAi drugs into cells," said Steven F. Dowdy, PhD, professor in the Department of Cellular and Molecular Medicine and the study's principal investigator. "While nanotechnology protects the RNAi drug, from a molecular perspective nanoparticles are huge, some 5,000 times larger than the RNAi drug itself. Think of delivering a package into your house by having an 18-wheeler truck drive it through your living room wall — that's nanoparticles carrying standard RNAi drugs. Now think of a package being slipped through the mail slot — that's siRNNs."

The beauty of RNAi is that it selectively blocks production of target proteins in a cell, a finding that garnered a Nobel Prize in 2006. While this is a normal process that all cells use, researchers have taken advantage of RNAi to inhibit specific proteins that cause disease when overproduced or mutated, such as in cancer. First, researchers generate RNAi drugs with a sequence that

corresponds to the gene blueprint for the disease protein and then delivers them into cells. Once inside the cell, the RNAi drug is loaded into an enzyme that specifically slices the messenger RNA encoding the target protein in half. This way, no protein is produced.

As cancer and viral genes mutate, RNAi drugs can be easily evolved to target them. This allows RNAi therapy to keep pace with the genetics of the disease — something that no other type of therapy can do. Unfortunately, due to their size and negatively charged chemical groups (phosphates) on their backbone, RNAi drugs are repelled by the cellular membrane and cannot be delivered into cells without a special delivery agent.

It took Dowdy and his team, including Bryan Meade, PhD, Khirud Gogoi, PhD, and Alexander S. Hamil, eight years to find a way to mask RNAi's negative phosphates in such a way that gets them into cells, but is still capable of inducing an RNAi response once inside.

In the end, the team added a chemical tag called a phosphotriester group. The phosphotriester neutralizes and protects the RNA backbone — converting the ribonucleic acid (RNA) to ribonucleic neutral (RNN), and thus giving the name siRNN. The neutral (uncharged) nature of siRNNs allows them to pass into the cell much more efficiently. Once inside the cell, enzymes cleave off the neutral phosphotriester group to expose a charged RNAi drug that shuts down production of the target disease protein. siRNNs represent a transformational next-generation RNAi drug.

"siRNNs are precursor drugs, or prodrugs, with no activity. It's like having a tool still in the box, it won't work until you take it out," Dowdy said. "Only when the packaging — the phosphotriester groups — is removed inside the cells do you have an active tool or RNAi drug."

The findings held up in a mouse model, too. There, Dowdy's team found that siRNNs were significantly more effective at blocking target protein production than typical RNAi drugs — demonstrating that once siRNNs get inside a cell they can do a better job.

"There remains a lot of work ahead to get this into the clinics. But, in theory, the therapeutic potential of siRNNs is endless," Dowdy said. "Particularly for cancer, viral infections and genetic diseases."

The siRNN technology forms the basis for Solstice Biologics, a biotech company in La Jolla, Calif. that is now taking the technique to the next level. Dowdy is a co-founder of Solstice Biologics and serves as a Board Director.

Additional study co-authors include Caroline Palm-Apergi, Arjen van den Berg, Jonathan C. Hagopian, Aaron D. Springer, Akiko Eguchi, Apollo D. Kacsinta, Connor F. Dowdy, Asaf Presente, Peter Lönn, Manuel Kaulich, Naohisa Yoshioka, Edwige Gros and Xian-Shu Cui, UC San Diego School of Medicine.

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