

# DDN

EXPLORING  
DRUG DISCOVERY  
AND DEVELOPMENT

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## A PRESCRIPTION

# for art

Creating art may help treat Parkinson's disease  
and other neurodegenerative diseases.



Telomerase: The Protector  
of Chromosomes

Asthma Patients Breathe  
a Little Easier

# Targeting Cancer with RNA Therapeutics

A unique cell-penetrating peptide nanoparticle delivers RNA directly to tumor cells, avoiding a decade-old problem with therapeutic RNA delivery.

Andrew Fire and Craig Mello won the Nobel Prize for their discovery of RNA interference (RNAi) in 2006, invigorating the field of RNA therapeutics. Scientists hoped that this new technology would usher in an era of RNA therapeutics targeted to diseased tissues, but a major limitation soon emerged. RNAs delivered to the body went straight to the liver, bypassing their target tissues along the way.

“Everybody thought this was it. This was going to be the greatest thing to deliver RNA and then have it knock down or silence the production of pathologic proteins. It turned out that this was a lot harder than folks thought,” said Samuel Wickline, chief scientific officer at Altamira Therapeutics and professor of cardiovascular sciences, molecular physiology and pharmacology, and medical engineering at the University of South Florida.

Scientists soon learned that the most important factor for RNA delivery was the carrier or delivery agent. For the past 15 years, Wickline has been developing a cell-penetrating peptide-based nanoparticle that can deliver RNA to targeted tissues.

## Perfecting targeted delivery

Before joining the University of South Florida, Wickline served as a professor at Washington University. During that time, Wickline conceived the idea to develop a nanoparticle to selectively target and penetrate tumors.

Cancer and other diseases induce inflammation that causes the vasculature of afflicted tissues to become leaky. Wickline and his team leveraged this to their advantage. They developed a nanoparticle that targeted inflamed tissue, but their initial approach to use a natural cell-penetrating peptide was ineffective at delivering siRNA. Next, Wickline and his team shortened the peptide nanoparticle, but it still could not transfect cells. Undeterred, Wickline and his team at Washington University incrementally modified their peptide nanoparticle, eventually landing on one that

avoids the liver and selectively targets and penetrates inflamed tissue.

“We may have gotten a bit lucky in terms of the extrahepatic delivery based on the actual size of these particles, which turned out to be around 50 to 60 nanometers — a sweet spot for avoiding the liver,” said Wickline.

His team also coated their nanoparticle in albumin, which helped stabilize the nanoparticle and maintain its size. Typically, scientists package RNA in lipids and include other agents, such as polyethylene glycol. However, the liver rapidly takes up lipid nanoparticles, making them less useful for systemic delivery to other organs and tissues.

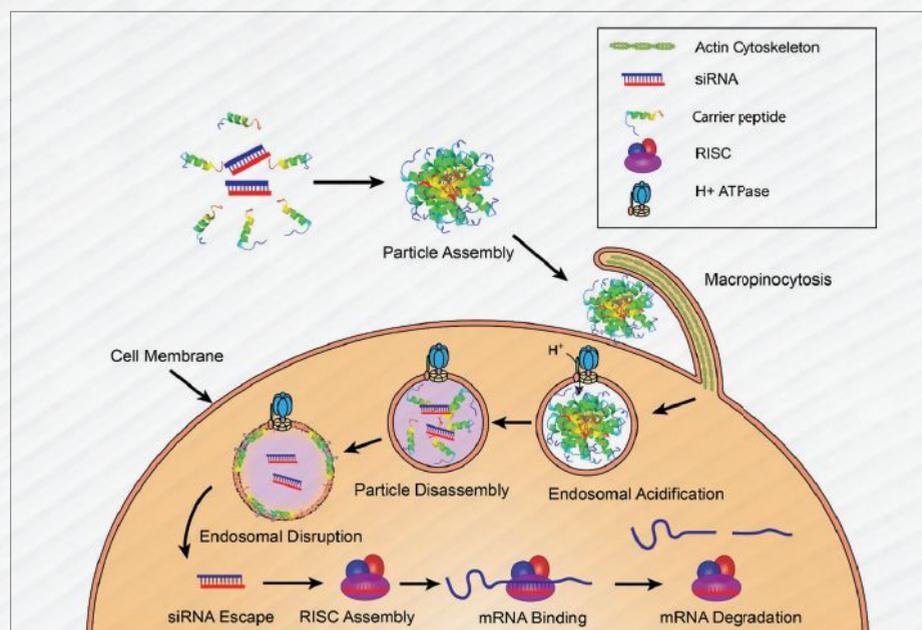
Wickline’s use of albumin had a second purpose: “It protects the nanoparticle and makes it stealthy. It’s the stealthiest system without having to use polyethylene glycol, which can cause immune system reactions in certain individuals.”

## How it works

Wickline’s cell-penetrating peptide nanoparticle can carry and deliver any type of RNA, including siRNA or mRNA. “We can actually induce proteins with the same peptide nanoparticle that we use to inhibit protein production. Either one can be done, and they can both be done simultaneously,” said Wickline.

To form the nanoparticle, the RNA payload is complexed with the peptide, resulting in a stable polyplex. Once inside the cell, the nanoparticle is temporarily encapsulated within an endosome until falling cellular pH levels disassemble the protein-RNA nanoparticle, releasing the RNA and peptide components. These components permeabilize the endosome, allowing the RNA to escape fully and engage with cytoplasmic cellular machinery to modify protein expression.

“We wanted to make sure that the nanoparticles were nontoxic and biologic in the sense that they look like something else that circulates in the bloodstream. They are made out of the same amino acids, proteins,



Cell-penetrating peptides assemble and encapsulate RNA to form a peptide-based nanoparticle. A cellular endosome encases the protein nanoparticle. As pH levels inside the cell fall, the endosome and protein nanoparticle disintegrate, releasing the RNA payload. The siRNA stimulates cellular machinery in the cytoplasm to block protein expression.

and RNA elements that are common to the body’s own cells,” said Wickline.

The ability of the nanoparticle to selectively target inflamed tissues opens its applicability to a slew of pathologies where tissue vasculature is compromised. Recognizing the therapeutic potential of his peptide nanoparticle, Wickline formed a company called Trasir Therapeutics.

As other scientists learned Wickline’s technology, they began to apply it to their research. Today, Wickline’s peptide-RNA nanoparticle has been tested in numerous preclinical research models, including pancreatic cancer, ovarian cancer, lung cancer, metastatic melanoma, adult T cell leukemia/lymphoma, necrotizing enterocolitis, rheumatoid and osteoarthritis, atherosclerosis, and more.

## A meeting of minds

With the success of his peptide nanoparticle and the re-emerging interest in RNA technology, Wickline sought to transition his discovery to the clinic. He turned to Thomas Meyer, CEO and founder of Auris Medical, who has 14 years of experience in the drug delivery industry and is now CEO and chairman of Altamira Therapeutics.

“It was a meeting of similar mindsets,” said Meyer. “We immediately had a very good discussion. My impression was that here was someone who has been working very hard on bringing something from the scientific bench to patients, but has been largely confined to an academic setting.” Meyer and his team at Auris Medical were also working on a cell-penetrating peptide for the treatment of acute hearing loss, so they shared a mutual interest.

Wickline presented his cell-penetrating peptide nanoparticle for targeted RNA delivery to Meyer. “I have to admit, I had that feeling of well, it almost sounds too good to be true. I was very impressed. It was exciting,” said Meyer. After conducting his own research and speaking with other experts in the field, Meyer got on board.

“It’s amazing when you look at the technology

— how it actually works. It solves a few hurdles or barriers that other people have been grappling with for years,” said Meyer. Together, Wickline and Meyer merged Trasir Therapeutics and Auris Medical to forge a new company called Altamira Therapeutics, which is dedicated to delivering RNA therapeutics to tissues other than the liver.

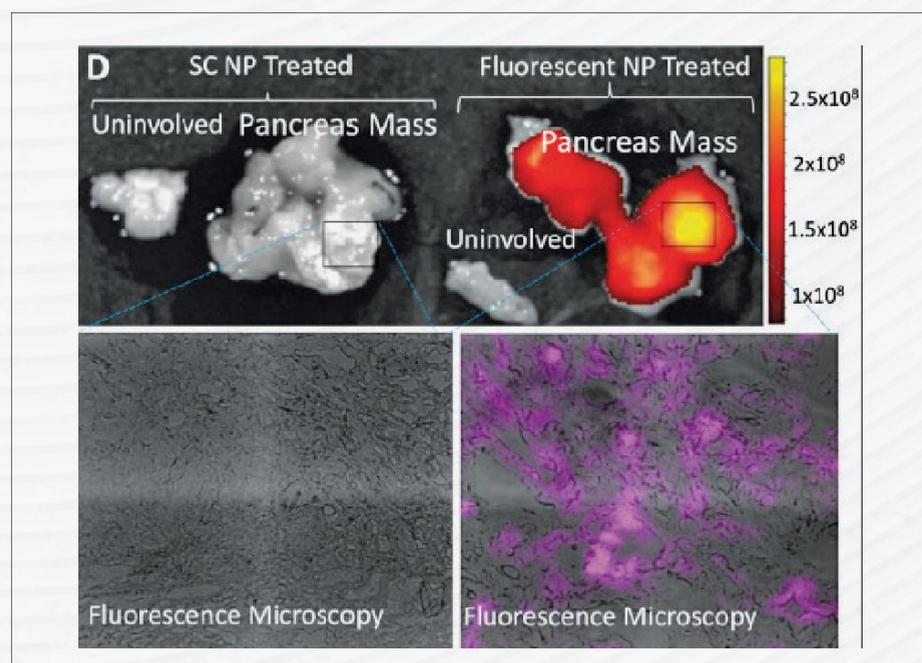
Meyer and Wickline mapped out their plan, and selected a target with high unmet medical need and good developmental feasibility. In July 2021, they launched a program to move their cell-penetrating nanoparticle toward a clinical proof of concept using an siRNA that targets KRAS-driven colorectal cancer.

“You can have a fantastic drug or substance, but if you don’t get it to the right place, in the right quantity, at the right time, you may miss the whole potential of it,” said Meyer. “This is really about delivery: effective, efficient, and safe delivery. It’s exciting to help move this forward towards clinical applications.”

Wickline’s cell-penetrating peptide nanoparticle solves a decade-old problem with RNA delivery: it avoids the liver. The platform is simple to use and modular, enabling scientists to add any single or combination of RNA they desire, an attractive feature for precision medicine. Allowing scientists to simply exchange RNA and use the same nanoparticle peptide for delivery, regardless of the disease, offers a lot of versatility.

Meyer and Wickline plan to submit an investigational new drug application in late 2022. In the meantime, they continue to expand the capabilities of their cell-penetrating peptide as they investigate the delivery of other types of RNA payloads and disease models.

“To develop a whole platform for extrahepatic delivery of nucleotides, like siRNA or mRNA, to me, would be huge, not only for this particular field in cancer but for many other fields as well,” said Wickline. “The ability to deliver RNA extrahepatically would fulfill the promise of the RNA silencing approach, and I think we have something to offer there.”



The cell-penetrating protein nanoparticle targets only an inflamed pancreatic tumor mass, as shown by IVIS imaging (top) and fluorescent imaging (bottom) in a preclinical mouse model of pancreatic cancer.