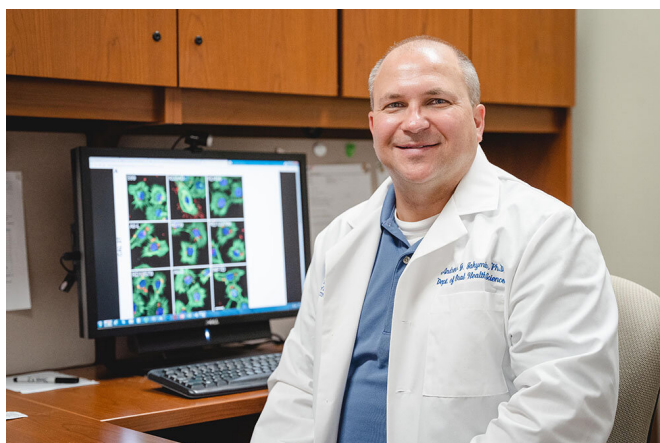


Chemical changes to peptide siRNA-carrier enhance gene silencing for future cancer drugs

24 May 2021, by Caroline Wallace



Dr. Andrew Jakymiw and his team found a peptide carrier with heightened potential to deliver a cancer therapeutic for oral cancer. Credit: Marquel Coaxum

MUSC Hollings Cancer Center researchers are exploring the use of peptide carriers for the delivery of small RNA drugs as a novel treatment for cancer. The team's recent work, published online March 19 in the *Molecular Therapy—Nucleic Acids* journal, lays the foundation for developing a clinically relevant peptide carrier RNAi-based drug treatment strategy for human oral cancer.

According to the American Cancer Society, the estimated risk of developing [oral cancer](#) in the U.S. is 1 in 60 for men and 1 in 140 for women. Cancer therapies face multiple challenges, including off-target side effects and low efficacy. RNAi-based therapeutics have great potential to overcome these specific treatment challenges.

Andrew Jakymiw, Ph.D., who is also an associate professor in the Oral Health Sciences Department at MUSC, focuses on the study of RNA interference (RNAi)-based therapies for oral

cancer. RNAi is a method of gene silencing that specifically targets, or tags, messenger RNA (mRNA) for degradation. mRNA contains the genetic code needed to make proteins. Small interfering RNA (siRNA) are the pieces of RNA that can bind to specific regions on mRNA that stop proteins from being made. Scientists are figuring out how to use this to target and silence disease-causing genes. Decades of research have shown that certain proteins are overexpressed in cancer and drive [cancer cell growth](#). The goal of the RNAi drug treatment strategy is to "turn off" the proteins that promote cancer development.

Jakymiw said that although the principle is biologically sound, there are many technical challenges with siRNA delivery. "For example, rapid renal excretion, degradation by RNases, low intracellular uptake, endosomal entrapment and low release of the siRNA cargo from the delivery platform are all challenges that we must consider when modifying a peptide siRNA carrier," he said.

To harness the gene silencing capabilities of siRNA, scientists must get the siRNA into the appropriate cells. The siRNA must be attached to a larger molecule to protect it during delivery to the desired location. Peptide carriers are an attractive tool for delivering siRNA, because they are affordable and easy to modify.

In earlier studies, the Jakymiw laboratory found that the original peptide carrier they designed, called 599, could deliver the siRNA cargo into cancer cells and turn off a targeted cancer gene, which inhibited tumor growth in a mouse cancer model.

"We originally designed the 599 peptide so that it could help the siRNA cargo penetrate the cell and escape endosomes more easily. However, by looking at the three-dimensional arrangement of the

amino acids in the 599 peptide, in particular their stereochemistry, we were able to make additional changes that beneficially affected the peptide carrier's capabilities," said Jakymiw.

Charles Holjencin, a dual D.M.D./Ph.D. student in the Jakymiw lab, used confocal fluorescence microscopy and observed that one of the modified 599 siRNA-loaded peptide carriers, called RD3AD, was arranged around the cancer cells in a clear pattern that he had not seen with the original 599 peptide carrier.

"Charles's keen observations through confocal work allowed us to identify an important intracellular delivery mechanism," said Jakymiw.

The modified RD3AD peptide carrier was delivering the siRNA drug by adhering to and potentially moving along cell surface protrusions, called filopodia. Entry into the cell via filopodia is a very efficient way for small biological complexes to enter cells; some viruses and bacteria also use this entry method. Since the siRNA-loaded RD3AD peptide carrier was able to enter cancer [cells](#) more efficiently, the research team saw improved gene silencing. This meant that the peptide carrier had heightened potential to deliver a cancer therapeutic, Jakymiw explained.

One of the next steps will be to test the RD3AD peptide in animal cancer models. Additionally, the researchers want to understand the mechanisms associated with this form of drug delivery more fully. For example, an unanswered question is what protein is the peptide carrier interacting with on filopodia? If this molecule is overexpressed in cancer, then this could be a valuable therapeutic target, especially for aggressive cancers, which typically have increased numbers of filopodia.

While [cancer cells](#) were the biological target for improving this drug delivery system, peptide carriers, such as RD3AD, have more applications than just in [cancer](#) therapies. In fact, [peptides](#) such as RD3AD could be used to deliver siRNA in any instance where gene silencing is desired for the treatment of a disease.

Now that the Jakymiw lab understands how to

harness the specific amino acid stereochemical modifications in their peptide designs, the [carrier's](#) abilities are not limited to just siRNA. Other nucleic acid cargoes can be delivered by these peptide carriers, which opens future options for more targeted delivery of other forms of therapeutic molecules to treat challenging diseases.

"I look forward to collaborating with members of the Hollings Cancer Center in future studies related to how filopodia can be exploited for the enhancement of drug delivery, especially in the treatment of aggressive cancers," said Jakymiw.

More information: Charles E. Holjencin et al, Advancing peptide siRNA-carrier designs through L/D-amino acid stereochemical modifications to enhance gene silencing, *Molecular Therapy—Nucleic Acids* (2021). DOI: [10.1016/j.omtn.2021.03.013](https://doi.org/10.1016/j.omtn.2021.03.013)

Provided by Medical University of South Carolina

APA citation: Chemical changes to peptide siRNA-carrier enhance gene silencing for future cancer drugs (2021, May 24) retrieved 23 September 2021 from <https://medicalxpress.com/news/2021-05-chemical-peptide-sirna-carrier-gene-silencing.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.