Leveraging Nature's Carrier: Albumin-Binding Dendritic siRNA for Enhanced Tumor Targeting

Small interfering RNA (siRNA) therapeutics are rapidly reshaping the landscape of precision medicine, offering the ability to silence disease-driving genes with exceptional specificity and durability. However, due to delivery barriers, the promise of siRNA therapy has largely been confined to the liver. Recent advances and mounting efforts are being poured into expanding siRNAs extrahepatically, to enable therapies for diseases in the heart, muscle, central nervous system, and even cancer. A recent study has demonstrated that extrahepatic delivery can be achieved by using an albumin-binding, Dendrimer-conjugated siRNA (D-siRNA) as the carrier, the chemistry originally developed in Hanadi Sleiman lab at McGill.

Published in *Molecular Therapy Nucleic Acids*, the study by Fakih et al. leverages the body's most abundant protein, albumin, as a natural transport vehicle. By conjugating siRNA with an amphiphilic dendritic structure (D-siRNA) that exhibits high-affinity albumin binding, the researchers developed a platform that not only prolongs time in circulation but also enables siRNA delivery to tumors (1, 2).

D-siRNA: a promising strategy to broaden the potential of siRNA delivery

The oligonucleotide therapeutic field has long been focused on expanding delivery to tissues beyond the liver. Various techniques, such as lipid nanoparticle based delivery and ligand conjugation strategies, are being explored to address the challenge of delivering siRNAs to extrahepatic sites (1, 3).

Additionally, despite holding immense potential for the oncology field due to their potency, durability, and selective targeting, which may help to limit chemotherapy side effects, siRNAs delivery to tumors have been challenging due in part to limited tissue penetration into tumor microenvironments and optimizing molecule stability and dosing (1, 4). Motivated by these challenges and the fact that albumin-binding is a clinically proven strategy for improving drug delivery to solid tumors, Fakih and his team began to explore how they could optimize siRNA delivery by harnessing albumin binding.

Dendritic siRNA (D-siRNA) is a modified siRNA molecule designed for improved delivery and efficacy in therapeutic applications, particularly in oncology. When siRNA is conjugated to the unique dendrimer-like conjugate made from various lipids, the highly branched tree-like structure bind albumin selectively and strongly (5, 6), protects the siRNA from degradation, boosts its stability, and enhances cellular uptake (5). Most importantly, when the dendritic moiety is attached to siRNA, it still enables selective binding to albumin in vivo and does not hinder therapeutic activity in various organs (2). This method aims to address the challenges of siRNA delivery, such as degradation in the bloodstream and inefficient cellular uptake.

The most unique property of D-siRNA molecules is their selective binding to albumin, the most abundant protein in the blood. This binding further enhances stability and reduces clearance by the kidneys, resulting in improved circulation and delivery to multiple tissues. Additionally, by leveraging albumin binding, D-siRNA can be directed to specific tissues, including tumors, where albumin is known to accumulate. These benefits arise from albumin's natural properties, like its long half-life, ability to avoid renal filtration, and its natural accumulation in sites of inflammation or high vascular permeability, such as tumors or arthritic joints (5, 7). Such properties have been observed with D-siRNAs as well as other albumin-binding conjugates (7).

Another benefit is that D-siRNA exhibits a favorable safety profile compared to other conjugates. At high doses, it causes no alterations in blood chemistry, complete blood counts, or histology, unlike other more hydrophobic conjugates which can alter readouts at high doses (2). Additionally, the reduced uptake of D-siRNA by immune cells minimizes cytokine responses and inflammation (2).

D-siRNA in a melanoma tumor model

Building on their previous work that showed dendritic conjugated D-siRNA exhibits exclusive binding to albumin upon intravenous or subcutaneous administration compared to other lipophilic conjugates, Fakih and his team hypothesized D-siRNA would show a prolonged plasma circulation due to albumin's extended circulation half-life. The results confirmed this, demonstrating that albumin-bound D-siRNA achieves extended circulation regardless of the administration method, potentially improving the drug's extrahepatic tumor distribution (1).

To assess tumor delivery, the researchers used a melanoma tumor model injected with D-siRNA (exclusive albumin binding) or DCA-siRNA (a lipid-conjugated siRNA that is not selective to albumin binding). One day after injection, fluorescence imaging showed increased D-siRNA distribution within tumors. Delivery of D-siRNA to tumor parenchyma cells (the actual cancer cells inside a solid tumor) was

elevated by 4.2 times, and overall delivery to antigen-presenting cells, including macrophages and dendritic cells, doubled (1). Conversely, DCA-siRNA resulted in greater liver uptake. These results indicate that D-siRNA significantly enhances delivery to both tumor parenchyma and resident immune cells, leading to a higher tumor-to-liver ratio compared to DCA-siRNA, the authors state. Moreover, the ability to deliver beyond the tumor microenvironment and reach the parenchyma cells is noteworthy, emphasizes Fakih.

“It allows for gene modulation in both the TME cells and the cancerous cells themselves, significantly widening the potential reach of the therapy,” he says. However, the fact that the amount of siRNA delivered to the tumor was still orders of magnitude less than what is typically delivered to the liver or other organs was a surprise, Fakih explains.

“From a ‘glass half-empty’ perspective, this shows our technology, despite being functional, is far from optimized and can certainly be improved,” Fakih says. “Looking at it with a ‘glass half-full’ lens, this result also showed us that sometimes you only need a few potent siRNA molecules to have a measurable impact. This shifted our perspective, highlighting the potential for high efficacy even with limited delivery.”

To determine if the improved tumor delivery translated to functional gene silencing, the researchers evaluated Htt knockdown in tumor-bearing mice, as a control target. The mice received two doses of either D-siRNA, DCA-siRNA, or non-targeting D-siRNA. The tumors treated with D-siRNA showed robust Htt silencing at over 40%, whereas those treated with DCA-siRNA revealed a minimal silencing effect. These results highlight that D-siRNA is capable of both efficient delivery and significantly higher gene silencing in solid tumors (4).

The study also explored the therapeutic potential of D-siRNAs in combination with the immune checkpoint inhibitor PD-1 within a melanoma tumor model. Tumors often exploit PD-1, which stands for programmed cell death protein 1, and which acts as a type of off-switch on immune cells. PD-1 inhibitors are drugs that block this off-switch, allowing immune cells to stay active and kill cancer cells. Additionally, the inhibition of JAK (a protein that plays a critical role in cell signaling) has recently been found to have a crucial role in supporting immunotherapy treatments in cancers such as Hodgkin lymphoma and non-small cell lung cancer (1). Fakih and his team recently developed a potent JAK1-selective siRNA capable of robust JAK1 silencing in both mouse and human tissues (8). To determine if this creation could augment PD-1 inhibition, melanoma-bearing mice were treated with either D-siRNA that specifically targeted JAK1, DCA-siRNA that also targeted JAK1, or non-targeting D-siRNA control. The results showed that mice receiving only the D-siRNA targeting JAK1 had a significantly improved response to PD-1 treatment, resulting in slower tumor growth compared to those receiving the non-targeting D-siRNA (1).

Opening the door: next steps in D-siRNA technology

The findings show a new path for applying siRNA technology beyond the liver, particularly in solid tumors. According to the authors, “The binding of D-siRNA to albumin presents a promising strategy for overcoming systemic tumor delivery challenges that have historically limited the therapeutic potential of siRNA” (4). Fakih says this could open the door to new therapeutic strategies in cancer treatment that could have fewer side effects and be more potent, durable, and selective than what’s currently available.

“It provides a proof-of-concept that this technology is viable and ready for further development, which could attract more research and industry investment into this area,” he says.

Fakih says the study is merely a demonstration that the technology works and has a functional therapeutic outcome, but many questions remain unanswered. The team is currently focused on validating the technology by expanding the range of targets it can go after in tumors and assessing its universality by testing its delivery to other types of tumors and cancers. This has been most recently reported in a preprint where D-siRNA targeting IRS2 for breast cancer has been developed (9).

“We hope our work inspires further chemical innovation to improve the delivery of siRNAs to solid tumors. We also hope others will utilize the current technology to assess interesting cancer targets that were previously untestable due to delivery limitations,” he says.

Other preclinical studies highlighting the power of albumin binding for delivery include work examining improved delivery and efficacy of siRNAs in arthritis treatment. Mice injected with another albumin-binding conjugate showed a reduction in the cartilage-degrading enzyme MMP13 by over 60% (10). In post-traumatic osteoarthritis (PTOA) mouse models, this decreases pain, preserves cartilage, and lowers inflammatory markers (10). Similar efficacy is observed in rheumatoid arthritis (RA) models, which reduce joint swelling and bone erosion, as well as in guinea pig models of PTOA, highlighting the translatability of these findings (10). Some studies have also reported that albumin binding enhanced productive tumor delivery of siRNA to multiple breast cancer models (9, 11).

Collaboration: the perfect ingredient for innovation and helping patients

The research was a highly collaborative effort among the Sleiman Lab, the Khvorova Lab, and the Harris Lab. Fakih says that coordinating the efforts of the three labs was a pleasant and exciting experience, and his co-authors were extremely motivated, experienced, and supportive, making the process enjoyable and the outcome impactful.

“Getting input from researchers who are experts in different fields is not only extremely helpful but also eye-opening. It allowed us to advance the research more efficiently and create a more well-rounded study,” Fakih says. “This collaboration encouraged us to think about different aspects of the technology and scientific questions at play. Perspectives from chemists, biologists, and clinicians are the perfect ingredients for scientific innovation that can ultimately improve healthcare and help patients.”

siRNA and the future of cancer care

The development of albumin-binding dendritic siRNA (D-siRNA) may represent a significant advancement in the field of oligonucleotide therapeutics, enabling effective systemic delivery and gene silencing in solid tumors beyond the liver. By using albumin as a natural carrier, D-siRNA achieves improved tumor targeting, enhanced cellular uptake, and reduced toxicity compared to traditional approaches. While validation across a range of targets and assessing its universality are needed, the technology lays important groundwork for future research, offering hope for more potent, selective, and safer cancer treatments.

“The key takeaway [from the study] is that siRNAs can, and will, be applied to improve cancer care. It is only a matter of time until the field figures it out,” Fakih says.

References:

1. Fakih HH, Tang Q, Summers A, Gross KY, Rachid MO, Okamura K, Martinez N, Sleiman HF, Harris JE, Khvorova A. Albumin-binding dendritic siRNA improves delivery and efficacy to solid tumors in a melanoma model. Mol Ther Nucleic Acids. 2025 May 24;36(3):102579. doi: 10.1016/j.omtn.2025.102579. PMID: 40606645; PMCID: PMC12213268.
2. Fakih HH, Tang Q, Summers A, Shin M, Buchwald JE, Gagnon R, Hariharan VN, Echeverria D, Cooper DA, Watts JK, Khvorova A, Sleiman HF. Dendritic amphiphilic siRNA: Selective albumin binding, *in vivo* efficacy, and low toxicity. Mol Ther Nucleic Acids. 2023 Nov 17;34:102080. doi: 10.1016/j.omtn.2023.102080. PMID: 38089931; PMCID: PMC10711485.
3. Egli M, Manoharan M. Chemistry, structure and function of approved oligonucleotide therapeutics. Nucleic Acids Res. 2023 Apr 11;51(6):2529-2573. doi: 10.1093/nar/gkad067. PMID: 36881759; PMCID: PMC10085713.
4. Wang B, Gatlin JT, Anand P. Dendritic siRNA conjugate riding albumin for targeted delivery to solid tumors. Mol Ther Nucleic Acids. 2025 Aug 13;36(3):102657. doi: 10.1016/j.omtn.2025.102657. PMID: 40838192; PMCID: PMC12362386.
5. Lacroix A, Fakih HH, Sleiman HF. Detailed cellular assessment of albumin-bound oligonucleotides: Increased stability and lower non-specific cell uptake. J Control Release. 2020 Aug 10;324:34-46. doi: 10.1016/j.jconrel.2020.04.020. Epub 2020 Apr 21. PMID: 32330572.
6. Lacroix A, Edwardson TGW, Hancock MA, Dore MD, Sleiman HF. Development of DNA Nanostructures for High-Affinity Binding to Human Serum Albumin. J Am Chem Soc. 2017 May 31;139(21):7355-7362. doi: 10.1021/jacs.7b02917. Epub 2017 May 18. PMID: 28475327.
7. Colazo JM, Hoogenboezem EN, Keech MC, Francini N, Shah V, Yu F, Lo JH, Sorets AG, McCune JT, Cho H, DeJulius CR, Michell DL, Maerz T, Vickers KC, Gibson-Corley KN, Hasty KA, Crofford L, Cook RS, Duvall CL. Albumin-binding RNAi Conjugate for Carrier Free Treatment of Arthritis. bioRxiv [Preprint]. 2023 Dec 28:2023.05.31.542971. doi: 10.1101/2023.05.31.542971. PMID: 37333210; PMCID: PMC10274717.
8. Tang Q, Fakih HH, Zain Ui Abideen M, Hildebrand SR, Afshari K, Gross KY, Sousa J, Maebius AS, Bartholdy C, Søgaard PP, Jackerott M, Hariharan V, Summers A, Fan X, Okamura K, Monopoli KR, Cooper DA, Echeverria D, Bramato B, McHugh N, Furgal RC, Dresser K, Winter SJ, Biscans A, Chuprin J, Haddadi NS, Sherman S, Yıldız-Altay Ü, Rashighi M, Richmond JM, Bouix-Peter C, Blanchard C, Clauss A, Alterman JF, Khvorova A, Harris JE. Rational design of a JAK1-selective siRNA inhibitor for the modulation of autoimmunity in the skin. Nat Commun. 2023 Nov 4;14(1):7099. doi: 10.1038/s41467-023-42714-4. PMID: 37925520; PMCID: PMC10625637.
9. Tocheny CE, Buchwald JE, Dahlke CD, Fakih HH, Morgan JS, Summers A, Wisniewski CA, Jackson SO, Lee JS, Card MA, Echeverria D, Peterson C, Mercurio AM, Khvorova A, Shaw LM. Therapeutic delivery of albumin-binding siRNA targeting IRS2 to diverse cell types reduces mammary tumor growth. bioRxiv [Preprint]. 2025 Aug 1:2025.07.29.667434. doi: 10.1101/2025.07.29.667434. PMID: 40766531; PMCID: PMC12324365.

10. Colazo JM, Keech MC, Shah V, Hoogenboezem EN, Lo JH, Francini N, Cassidy NT, Yu F, Sorets AG, McCune JT, DeJulius CR, Cho H, Michell DL, Maerz T, Vickers KC, Gibson-Corley KN, Hasty KA, Crofford LJ, Cook RS, Duvall CL. siRNA conjugate with high albumin affinity and degradation resistance for delivery and treatment of arthritis in mice and guinea pigs. Nat Biomed Eng. 2025 Aug;9(8):1366-1383. doi: 10.1038/s41551-025-01376-x. Epub 2025 May 16. PMID: 40379798; PMCID: PMC12354308.
11. Hoogenboezem, E.N., Patel, S.S., Lo, J.H., Cavnar, A.B., Babb, L.M., Francini, N., Gbur, E.F., Patil, P., Colazo, J.M., Michell, D.L., et al. (2024). Structural optimization of siRNA conjugates for albumin binding achieves effective MCL1-directed cancer therapy. Nat. Commun. 15, 1581.