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Zacks Small-Cap Research (NOTE)

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RNAZ: Introducing RNA Therapeutics

Research Note

RNA Oncology

Ribonucleic acid (RNA) oncology is a specialized field in the cancer space that focuses on using RNA-based molecules to diagnose, monitor, and treat cancer. This class of therapeutics was pioneered with the development of antisense oligonucleotides (ASOs) in the late 1970s[1] and the discovery of RNA interference (RNAi) in the 1990s, which revealed the ability of RNA to regulate gene expression at the post-transcriptional level.[2]

RNA is the messenger that translates genetic code into proteins. Traditional oncology often targets DNA or proteins while RNA oncology targets the instruction layer in between. MicroRNA (miRNA) therapeutics are distinct from but often grouped alongside other RNA oncology modalities like siRNA (RNAi), messenger RNA (mRNA) therapeutics, ASOs and aptamers. TransCode's TTX-MC138 is technically delivered as an ASO/antagomir but functionally operates through miRNA inhibition; thus, it bridges the ASO and miRNA therapeutic categories.

Therapeutic RNA works by either introducing new instructions to the body or by blocking unwanted instructions that drive cancer growth. One category of RNA therapeutics is mRNA vaccines. Similar to the technology used in Pfizer's and Moderna's COVID-19 vaccines, cancer mRNA vaccines instruct the immune system to recognize specific proteins (neoantigens) on the surface of a patient's tumor. The goal is to trigger a targeted immune response to destroy the cancer cells. Another approach is RNA Interference (RNAi). This uses small RNA molecules, such as siRNA, to silence specific genes. If a cancer cell is overproducing a protein that helps it survive or resist chemotherapy, RNAi can be used to deactivate that instruction. Yet another therapeutic RNA class is Antisense Oligonucleotides (ASOs). These are synthetic, single-stranded RNA or DNA strings that bind to a specific mRNA. The binding can physically block the translation of harmful proteins or cause the target mRNA to be degraded.[3]

Most of our genome produces RNA that doesn't code for proteins. For a long time, it was considered junk DNA, but research shows that these non-coding RNAs (like miRNA and long non-coding RNA) act as master regulators of cell behavior. In many cancers, these regulators allow for uncontrolled cell growth. RNA oncology seeks to restore balance by inhibiting microRNAs that promote cancer or replacing tumor-suppressor RNAs that have been lost. RNA has a few distinct advantages over traditional drugs. It provides versatility that can target proteins previously considered undruggable because they lacked a traditional binding pocket for small-molecule drugs.

Once the genetic sequence of a tumor is known, RNA-based therapies can be designed and manufactured relatively quickly. Targeting RNA does not require genomic alteration which eliminates the risk of permanent genome alteration. Unlike gene therapy that edits DNA, RNA is transient. It does its job and then degrades, which reduces the risk of permanent, unintended genetic changes.

One of the limitations and future areas of focus is extrahepatic delivery of RNA therapeutics. In part, the difficulty arises from the use of common non-viral carriers such as lipid nanoparticles and GalNAc (N-acetylgalactosamine)

[1] Zamecnik, P.C., Stephenson, M.L. Inhibition of Rous sarcoma virus replication and cell transformation by a specific oligodeoxynucleotide. Proceedings of the National Academy of Sciences (PNAS). January 1978.
[2] Fire, A., *et al*. Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. Nature. February 1998.
[3] Singh, A., *et al*. Advancements in RNA-based therapies from bench to bedside. Drug Discovery. February 2026.

conjugates as they exhibit strong hepatic tropism.[4] Targeting areas in the CNS, lung and tumors is inefficient and new delivery mechanisms are being developed to access these tissues and organs. These modalities include hybrid carriers, nanoparticle surface modifications and exploratory ligands targeting tumor associated antigens or other components of the tumor microenvironment.[5]

Tumors are especially difficult to penetrate given their dense extracellular matrix, stromal barriers, high interstitial fluid pressure and convoluted vasculature. One approach to address this shortcoming includes encapsulating therapeutics in nanoparticles, which can extend the half-life of the drug and increase the likelihood of delivery. Another approach is to use polymer-based vectors and exosome-based delivery systems.[6,7] Many miRNA candidates have stalled in trials due to insufficient extrahepatic efficacy, even when using advanced carriers. In many cases, a low efficiency of delivery requires high doses which can have safety concerns such as immune activation and off-target gene silencing. TransCode has advanced a new approach to improve delivery which employs an iron oxide core that has been optimized to carry various payloads. It allows systemic delivery of nucleic acids to tumors and metastases outside the liver. The iron oxide core avoids ApoE-mediated hepatocyte uptake while the tumors are attracted to the sugars that comprise the nanoparticle's dextran coating. This promotes rapid, preferential internalization by malignant cells while sparing normal tissue. The small size and positive charge of the nanoparticle allow it to penetrate the tumor and be endocytosed into the cell. Once inside the cell, the disulfide linker cleaves, releasing the miRNA inhibitor. The oligonucleotide then finds and binds to miR-10b and silences the RNA molecule.

miRNA

MicroRNAs are short, 19–24 nucleotide, non-coding RNAs that act as the genome's master regulators. The nucleotides exert their influence on cells by binding and silencing target mRNAs. Unlike siRNA, which usually corresponds to a single gene, one miRNA can regulate hundreds of genes simultaneously, making them powerful tools for treating complex diseases like cancer. They play an important role as gene regulators and impact physiological processes associated with disease. miRNAs require only partial complementarity to recognize their targets and can bind to many different mRNAs with varying levels of affinity.

miRNAs are naturally transcribed from miRNA genes by the cell's transcription machinery. The machinery relies on RNA polymerase and the epigenetic control of DNA methylation and histone modifications. Anti-miRNAs, which are also known as anti-miRNA oligonucleotides, are synthetic molecules designed to inhibit the activity of miRNAs. The anti-miRNAs bind to their target and sequester it, thus preventing its interaction with the complementary mRNAs.[8,9]

miRNAs play a critical role in tumorigenesis. They regulate key cellular processes such as proliferation and apoptosis, making them promising targets for cancer therapeutics. miR-155 was among the first oncogenic miRNAs identified and is highly expressed across multiple cancer types. Similarly, miR-21 is frequently upregulated in a wide range of both hematologic and solid malignancies. In addition to their oncogenic functions, miRNAs can also act as tumor suppressors by preventing the malignant transformation of normal cells. For example, miR-15a/16-1 negatively regulates cell proliferation, promotes apoptosis and inhibits cell cycle progression in human cancer cell lines. Conversely, a 2013 study demonstrated that the absence of miR-155 impaired the accumulation of effector $CD8^+$ T cells, resulting in increased susceptibility to both acute and chronic viral infections, as well as diminished anti-tumor immune responses. The molecule's pleiotropic profile illustrates its complexity and broad implications.[10]

Anti-miRNA can be used to inhibit oncogenic miRNAs using antisense oligonucleotides, antagomiRs or miR-decoys. Delivery of these nucleotides is a challenge and attempts have been made to transport them using lipid nanoparticles, viral vectors, and exosomes among others.[11] miRNA can also improve the performance of other drugs in combination. For example, Cochrane, *et al*. pointed out that restoration of miR-200c substantially increases sensitivity to microtubule-targeting agents such as paclitaxel.[12]

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[4] Lee, J.W., *et al*. RNAi therapies: Expanding applications for extrahepatic diseases and overcoming delivery challenges. Advanced Drug Delivery Reviews. October 2023.
[5] Makkar, S.K. Advances in RNA-based therapeutics: current breakthroughs, clinical translation, and future perspectives. Frontiers in Genetics. October 2025.
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