RNA-targeting Therapy: A Promising Approach to Reach Non-Druggable Targets

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https://dx.doi.org/10.13005/bpj/2277

(Received: 18 September 2021; accepted: 05 November 2021)

The term "non-druggable" refers to a protein that cannot be targeted pharmacologically; recently, significant efforts have been made to convert these proteins into targets that are reachable or "druggable." Pharmacologically targeting these difficult proteins has emerged as a major challenge in modern drug development, necessitating the innovation and development of new technologies. The idea of using RNA-targeting therapeutics as a platform to reach unreachable targets is very appealing. Antisense oligonucleotides, nucleic acid or aptamers, RNA interference therapeutics, microRNA, and synthetic RNA are examples of RNA-targeting therapeutics. Many of these agents were FDA-approved for the treatment of rare or genetic diseases, as well as molecular markers for disease diagnosis. As a promising type of therapeutic, many studies are being conducted in order for more and more of them to be approved and used in different disease treatments and to shift them from treating rare diseases only to being used as more specific targeting agents in the treatment of various common diseases. This article will look at some of the most recent technological and pharmaceutical advances that have contributed to the erosion of the concept of undruggability.

Keywords: Antisense Oligonucleotides; Aptamers; Interference Therapeutics; MicroRNA; Synthetic RNA.

Recently using RNA-targeting therapeutics as drugs to control disease-relevant gene expression as a treatment is very promising. These RNA targeting drugs include antisense oligonucleotides (ASOs), nucleic acid or peptide aptamers, RNA interference therapeutics (RNAi), microRNA therapeutics, and synthetic mRNAs. These drugs can engage several “difficult to drug” targets, including enzymes, ion channels, receptors, kinases, or transporters, giving hope for treating uncontrollable diseases. Some of these therapeutics are already in clinical practice and approved by the FDA, such as Nusinersen1, which is splicing switching ASOs used to treat spinal muscular atrophy. Patisiran is an RNAi drug approved by the FDA for treating hereditary transthyretin amyloidosis2. A number of RNA targeting drug candidates can be directed towards liver conjugation, GalNac, an amino sugar that can be added to siRNA, and ASO drugs to help better cellular uptake of the liver due to its unusually high expression on the hepatocyte’s surface. Inclisiran is a GalNac-conjugated siRNA drug that decreases LDL cholesterol expression through
the downregulation of PCSK9. This drug is now being studied in different studies in order to treat several cardiovascular patients with elevated LDL levels. If successful, RNA-targeting therapies can be used in the treatment of diseases that affect a large proportion of the population beyond rare diseases. Additional RNA therapeutics had to be explored, approved, and used in life-saving applications from various rare, aggressive diseases which did not yet have an effective treatment. Currently, hundreds of RNA-targeted research drugs for different indications of diseases are under clinical development, including neurodegeneration, metabolism, cardiovascular, and various cancers.

RNA-targeting therapeutics may be promising in treating several central nervous system diseases, especially genetic ones. It has been a challenge to deliver such drugs into their proper target tissues. Several experimental trials used different methods of delivery. Dahman and colleagues tried to use nanoparticles for RNA targeting drug delivery with promising results. Sugo and colleagues revealed that siRNAs conjugation with antibodies could ease recognizing different specific surface receptors and consequently direct the drugs to muscle tissue or cancer cells, as reported by Bäumer and colleagues. In addition, Kamerkar and colleagues reported that siRNAs could be delivered against KRAS in their pancreatic cancer experimental model using exosomes. In this review, the authors discussed and reviewed some of these promising drugs, their effect, expected mechanism of action, and adverse reactions. Table 1 lists different studies of RNA targeting therapies on the human, cell line, or animal and their type and role (Table 1.)

### Nucleic acid or peptide aptamers

The word ‘Aptamer’ is the Latin word ‘aptare’ for ‘to fit or join,’ and the Greek word ‘mero’ means ‘to part.’ A nucleic acid Aptamer is a short chain of single-stranded DNA or artificial oligonucleotides RNA with nucleotide bases that vary between 40 and 100 nucleotide bases. Aptamers are small single-stranded DNAs or RNAs that link with high affinity and selectivity their specific targets. Aptamers can also function as an intracellular supply vehicle. Aptamers may also be crosslinked to small iRNA or miRNA to improve virulence, drug resistance, or pathogenesis through their drug delivery. They have a unique, flexible 3D structure, high affinity, and high specificity, strongly related to their ligand sequence. These critical features allow them to distinguish between objectives. In addition, aptamers can bind to their cognate target protein’s functional domains, such as allosteric sites. Small ions, large proteins, whole cells, viruses, and tissues can be their targets. Various medicines, such as ampicillin aptamer conjugate, can easily be linked to aptamers and offer a better effect. One aptamer conjugates for photodynamic therapy (PDT) is (Apt@Au NRs), an aptamer-functionalized gold nanorods. Aptamers are produced by systematic ligand evolution by the exponential method of enrichment (SELEX) or other modified SELEX strategies. Without prior knowledge of the objective, SELEX has the advantage of selecting aptamers. Lately, aptamers have been considered for a wide range of human disorders in several clinical evaluations. They are flexible and efficient instruments for therapeutic objectives. Aptamers offer several benefits, making them preferable to the traditional drug used containing antibodies, since aptamers are not immunogenic and have a high cell/tissue selectivity, penetration, and many potential objectives. Aptamers are not immunogenic. They are thermally stable, have fewer lots of batch variability, short production time, and low expense.

Aptamers are excreted renally with a short half-life in vivo, challenging for therapeutic aptamers development. In furthermore, RNA-based aptamers are susceptible to hydrolytic nuclease breakdowns and several changes have been made to prevent and improve pharmacokinetics, including 2-fluoro pyrimidine changes, 2-O-methyl nucleotides and introduction of cholesterol or polyethylene glycol as the anchor group (Figure 1).

Macugen®, a VEGF165 aptamer or pegaptanib, is a 2004 FDA-approved aptamer-based drug. It strongly impedes angiogenesis by hindering the extracellular form of the endothelial growth factor and by treating adults with age-related wet form macular degeneration. This aptamer-based drug is a 22 fluoropyrimidine aptamer-based modified RNA that contains 22 O-methyl purine modifications to improve its stability against endonucleases, in addition to
introducing a 52-PEG moiety and a 32 dT link to improve its pharmacokinetic profile and protect it from exonuclease\textsuperscript{17,18}.

Aptamers based on RNA are more structurally different from DNA-based aptamers and are also focused on medical applications. They are used for molecular in vivo imaging\textsuperscript{19}. Aptamers can be employed as carriers of polymeric NPs, such as polylactides, and antiproliferative conjugating drugs, like taxol\textsuperscript{20}. Aptamers may also be able to deliver cisplatin to prostate tumor cells from aptamer-functionalized Pt (IV) prodrug-PLGA-PEG nanoparticles\textsuperscript{21}. It’s of particular interest that aptamers can be used as a specific carrier of therapeutic oligonucleotides for diagnosis, precision medicine, and personalized medicine, such as small-interfering (si)RNAs, miRNAs, short hairpin (sh)RNAs and antisense oligonucleotides (ASOs)\textsuperscript{22}.

### Antisense Therapeutics

The transcription of Antisense was regarded as a transcriptional noise. This is a generalized phenomenon in both eukaryotic and human transcriptomes, which depends in two ways on the functioning of the antisense RNA in cis or trans. This process can create the long, non-coding RNAs (LncRNAs), one of the most diversified cell transcript groups, that demonstrated multiple function roles, including embryonic pluripotency, differentiation, and growth, in fundamental biological processes\textsuperscript{23}.

The antisense RNA molecule is a unique DNA transcript type with 19-23 nucleotides and an mRNA supplement. In controlling gene expression, antisense RNAs play an essential role in multiple stages including replication, transcription, and translation. Furthermore, the expression of associated genes in host cells can be effectively regulated by artificial antisense RNAs. The research into antisense RNA functions has emerged as a hot study area in the development of antisense RNA\textsuperscript{24}.

Cardiomyopathy of TTR is a disease that may be caused by a transthyretin inherited mutation (ATTRm) or by natural transthyretin deposition in older people (ATTRWT). Antisense oligonucleotide (ASO) downregulates both wild and mutant hepatic TTR synthesis\textsuperscript{25}. Inotersen, a transthyretin-specific oligonucleotide, was initially shown to suppress TTR for transgenic mice carrying the human TTR Ile84Ser gene causing decreased immunoglobulin (Ig) and amyloid serum A proteins that restrict or stop the progression of the disease\textsuperscript{26}.

Dasgupta and Benson reported Inotersen’s tolerability and safety profile. During their research, there were no deaths, and it was well tolerated. The drug-related side effects included minor reactions to the injection site and minor flu-like symptoms post-injection. There was no observation of serious thrombocytopenia or drug-related adverse renal effects. Important negative events included hyperkalemia, heart failure aggravation, urinary retention, atrial fibrillation, bacteremia, lower limb cellulite, anemia, heart pacemaker placement, and decubitus ulcers\textsuperscript{25}.

The progressive degenerative disease, Duchenne muscular dystrophy (DMD), is a recessively linked X-like, evenly lethal neuromuscular disease caused by a lack of dystrophins, resulting in early adolescents losing outpatient ambulation and addiction to wheelchairs\textsuperscript{27}. Eteplirsen is the first FDA-approved DMD therapy which is also prescribed for individuals with genetically confirmed DMD genetic mutation, who are responsive to exon 51 skippings\textsuperscript{28,29}. Contrary to the previously mentioned successful antisense drugs, the addition of apatorsen, which is a non-squamous, non-small-cell lung cancer (NSCLC) anticytoveted oligonucleotide targeted at a heat shock protein (Hsp) of 27 mRNA, did not add any value compared to the original doublet protocol as reported in the recent study\textsuperscript{30}.

Another antisense oligonucleotide is Nusinersen which is capable of modifying the SMN2 gene expression and, subsequently, increase the synthesis of SMN protein and enhance the motor function. The FDA and the European Medicines Agency (EMA) have approved Nusinersen as the first option for 5q spinal musculoskeletal atrophy treatment for patients of different ages and stages\textsuperscript{1,31}.

### RNA interference therapy

RNA Interference (RNAi) is a biological process that occurs in several eukaryotic cells; it is a gene silence mechanism after transcription. It is a two-strand RNA (dsRNA) that induces a homologous mRNA sequence-specific degradation. A gradual cleavage of dsRNAs (siRNAs) into 21-23 nucleotides (nt) begins. These native SiRNA
duplexes are integrated into a complex of proteins called the RNA-induced silences complex (RISC). The ATP-dependent disassembly of the siRNA duplex creates an active RISC complex that recognizes and cleaves the respective siRNA by guiding the antisense strand of siRNA to protect the genome from retro-transposition by silence or gene expression. In eukaryotes, RNAi is a mechanism where ncRNAs (non-coding RNA) control the post-transcriptional expression of the target gene. This genetic intervention strategy can be clinically implemented using a double-stranded gene RNA (dsRNAs), a small synthetic RNA (siRNA) derived from the genome, and exogenous nucleic acids such as (sh)RNA. siRNAs have also become a robust genetic function study tool32,33. Silencing any protein with RNAi by selecting the effective target is theoretically applicable. RNAi is also involved in various cellular processes such as viral infection defense, cell transformation, and disease development34.

The detection of the RNAi mechanism and its participation in human diseases allows researchers to develop various forms of RNA molecules and use the RNAi process to target gene expression, as well as to control cellular processes and conditions34. A regular biomedical research laboratory can manufacture RNAi agents similarly to producing various recombinant/bioengineered DNA and protein macromolecules in living organisms.

In 2002 McCaffrey and RNAi colleagues targeted a hepatitis C virus sequence for destruction in mice5 to demonstrate this therapeutic potential35.
### Table 1.

Shows different studies of RNA-targeted therapeutics, types of studies, types of RNA agent used and its role concluded from the study.

| Serial | Author | Year | Type of Study | Subject | RNA | Role |
|--------|--------|------|---------------|---------|-----|------|
| 1      | Gragoudas et al (1) | 2004 | prospective | human  | VEGF 165 aptamer (pegaptanib) | Inhibit angiogenesis |
| 2      | Gragoudas (2) | 2004 | prospective | human  | VEGF 165 aptamer (pegaptanib) | Inhibit angiogenesis |
| 3      | Tong et al (3) | 2010 | prospective | cell line | Aptamer | conjugation with antiproliferative drugs like Taxol |
| 4      | Dhar et al (4) | 2008 | prospective | cell line | Aptamer | deliver cisplatin nanoparticles to prostate tumor cells |
| 5      | Hagenacker et al (5) | 2020 | prospective | Human  | Anti-sense (Nusinersen) | safe and effective in treating adults with 5q spinal muscular |
| 6      | Dasgupta & Benson (6) | 2019 | prospective | human  | Anti-sense (Inotersen) | supress progression of transhyretin cardiomyopathy |
| 7      | Ackermann et al (7) | 2016 | prospective | human  | Anti-sense (Inotersen) | supress the progression of transhyretin cardiomyopathy |
| 8      | Charlestone et al (8) | 2018 | prospective | human  | Anti-sense (Eteplirsen) | Therapy for Duchenne muscular dystrophy (DMD) |
| 9      | McCaffrey et al (9) | 2002 | prospective | mice   | RNAi | destruction sequence of hepatitis C virus in mice |
| 10     | Song et al (10) | 2003 | prospective | human  | RNAi (CCR5,P25) | Supress HIV replication in macrophages |
| 11     | Davis et al (11) | 2010 | prospective | human  | RNAi | Therapy for skin cancer melanoma |
| 12     | Yuen et al (12) | 2020 | prospective | human  | RNAi (ARC520) | reduction in HBsAg and HBeAg positive |
| 13     | Thi et al (13) | 2019 | prospective | cell line | RNAi (ARB-1740) | degredation of HBV viral replication in hepatocytes |
| 14     | Adams et al (14) | 2017 | prospective | human  | RNAi (Patisiran) | supress progression of transhyretin cardiomyopathy |
| 15     | Zimmernmann et al (15) | 2017 | prospective | human  | RNAi (Revusiran) | supress progression of transhyretin cardiomyopathy |
| 16     | Varghese et al (16) | 2020 | prospective | human  | RNAi (siG12D-LODER) | in combination with gemcitabine for better efficacy in pancreatic cancer |
| 17     | Pipe et al (17) | 2019 | prospective | human  | RNAi (Fituiran) | Antithrombin in treating hemophilia A or B |
| 18     | Wang et al (18) | 2020 | prospective | human  | miRNA(miR-93) | Molecular marker in prostate cancer |
| 19     | Li et al (19) | 2015 | prospective | human  | miRNA(miR-93) | Molecular marker in Head and neck squamous cell carcinoma |
| 20     | Smith et al (20) | 2012 | prospective | cell line | miRNA(miR-93) | Molecular marker in breast cancer |
| Reference | Year | Design | Type | Treatment/Target | Effect |
|-----------|------|--------|------|-----------------|--------|
| Zaafar et al. (15) | 2021 | Randomized | Human | miRNA(miR-93) | Cardiomyopathy, in combination with gemcitabine for better efficacy in pancreatic cancer |
| Varghese et al. (16) | 2020 | Prospective | Human | siRNA (siG12D-LODER) | Antithrombin in treating hemophilia A or B |
| Wang et al. (17) | 2020 | Prospective | Human | miRNA(miR-93) | Molecular marker in prostate cancer |
| Li et al. (18) | 2015 | Prospective | Human | miRNA(miR-93) | Molecular marker in Head and neck squamous cell carcinoma |
| Pipe et al. (19) | 2019 | Prospective | Human | Fituiran | Molecular marker in breast cancer |
| Smith et al. (20) | 2012 | Prospective | Human | miRNA(miR-93) | Molecular marker in lung cancer |
| Fang et al. (21) | 2011 | Prospective | Human | miRNA(miR-93) | Molecular marker in glioblastoma |
| Wang et al. (22) | 2020 | Prospective | Human | miRNA(hsa-miR-155-5p and has-miR-532-5p) | Potential pharmacogenomic predictors of ICS response in asthma |
| Li et al. (23) | 2020 | Prospective | Human | miRNA(hsa-miR-221, hsa-miR-628-3p and has-miR-654-5p) | Play a significant role in development and regulation of atrophic bone non-union |
| Wei et al. (24) | 2020 | Prospective | Human | miRNA(miR-30a-5p) | Increase beclatuzumab sensitivity in lung cancer |
| Xu et al. (25) | 2017 | Prospective | Cell line | miRNA(miR-30a-5p) | Role in cisplatin resistance in ovarian cancer |
| Liu et al. (26) | 2016 | Prospective | Cell line | miRNA(miR-30a-5p) | |

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**RNAi Process Mechanism**

RNAi-mediated gene expression suppression and protein production using synthetically prepared siRNAs specifically designed to silence specific genetic sequences of a gene that causes disease. The mechanism is as follows:

1. **RNAi:** RNAi is a process by which a cell decreases the expression of a particular gene, leading to a decrease in the expression of the corresponding protein. This process is achieved through the production of short interfering RNAs (siRNAs) that are designed to target specific sequences in the genome.

2. **Targeting:** The siRNAs are designed to target specific sequences in the genome. This targeting allows the siRNAs to bind to the messenger RNA (mRNA) of the gene of interest, leading to the destruction of the mRNA and the subsequent reduction in the production of the corresponding protein.

3. **Function:** The reduction in the production of the corresponding protein can have a wide range of effects, depending on the specific gene that is targeted. For example, siRNAs can be used to inhibit the production of proteins that are involved in cancer, leading to a reduction in the growth and spread of cancer cells.

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**ARC-520**

ARC-520 is one of the RNAi therapeutics designed to decrease viral and hepatitis B virus (HBV) DNA transcript derived from covalently closed circular DNA. ARC-520 was active both in HBV patients experienced by E-neg (Early Antigen HBeAg negatively) and E-pos (HBeAg positive). The absolute reduction in HBsAg (surface antigen) was moderate, possibly as a result of the HBsAg expression of integrated HBV DNA, indicating the need for RNAi treatments capable of targeting viral transcripts, regardless of origin. New therapies are needed to achieve functional cures that can lead to a decline in the serum levels of the surface antigen (HBsAg)³⁹. The ARB-1740 is a clinical-stage agent consisting of three Lipid Nanoparticles (LNPs), which protect siRNAs against nuclear plasma degeneration, allowing for the effective intracellular uptake into hepatocytes of the HBV targeting siRNA, a primary site of HBV infection. Once endocytosed, LNPs have been seen to dependently mixed with the endosomal membrane, leading to the release of the encapsulated siRNA into the cytoplasm.
It can then bind to the cellular complex (RISC) to detect, cleavage, and subsequently degrade viral transcripts. The function of this agent is to mediate viral transcript degradation, control viral replication, and reduce viral proteins in several HBV cell and animal models.

Patisiran has also been shown to alter the progression of cardiac manifestations of hereditary amyloidosis by FDA-approved RNAi therapy in Phase III trials. Amyloidosis-media-hereditary transthyretin disease is a rare, inherited, life-threatening neurodegenerative (hATTR) disease caused by TTR deposition in the peripheral nervous system, in the heart and gastro-intestinal tract. Revusiran is another medicine that has been tested to treat hATTR. The GalNAc-siRNA conjugate is the first metabolically stabilized to enter clinical trials and targets TTR mRNA targeted like Patisiran. siG12D-LODER is a small interfering RNA specifically targeted to the KRAS G12D mRNA mutant, frequent in pancreatic cancers. A phase I clinical trial highlighted the well-tolerated and targeted therapy combination of siG12D-LODER and gemcitabine in patients with locally advanced pancreatic cancer. 

Fituiran is an anti-thrombin-target SiRNA administered once-monthly subcutaneously and has shown a dose-dependent reduction in antithrombin level and increased thrombin production among participants who have no inhibitory effect alloantibodies with A or B hemophilia. Fitusiran has been clinically tested for hemophilia A and B in Phase III.

Lumasiran is an RNAi medicine that is used to treat primary hyperoxaluria type 1 of rare genetic disease (PH1). The disease is caused by the overproduction of hepatic oxalate that results in the formation of stones in the kidney that can progress towards kidney failure and systemic oxalosis. This therapeutic agent reduces the production of hepatic oxalate by inhibiting glycolate oxidase. Most lumasiran patients achieved low levels of urinary oxalate excretion. The most common side effect with lumasiran is the injection sitting reaction.

**Micro RNA Therapeutics**

Micro RNA is a small non-coding RNA molecule that induces cleavage or inhibits translation at specific sites with target mRNAs. These miRNAs play an important role in the expression of genes and in a number of other biological processes, including cell death. Results showed that miRNAs play an essential role in almost all biochemical processes such as proliferation, differentiation, metabolism and autophagy. In cancer, miRNAs impact many different types of biological processes, including the occurrence of tumors, metastases, invasion, microenvironment, and autophagy.

A lot of miRNAs are involved in prostate cancer development and progression. In prostate cancer tissues, the expression of miR-93 shows a significant increase compared to non-cancer prostate tissue. miR-93 is highly expressed in T-classification, lymph node metastasis, clinical stage, and poor prognosis in HNSCC squamous cell head and neck patients. MIR-93 may be a key molecular marker for both the metastasis and prognosis of the lymph node in HNSCC patients.

The mechanism of miRNA oncogenicity can be explained in several cancer types, since the miR-93 has been found to regulate cancer metastases by controlling multiple metastasis genes and pathways. In breast cancer, miR-93 participated by inhibiting Smad7 expression and activating the TGF-α signaling pathways in the epithelial-mesenchymal transition (EMT).

During lung cancer, miR-93 suppressed LATS2 in vitro. It increased in vivo angiogenesis and lung metastases to promote the development of endothelial cell tubes miR-93 helped endothelial cells to grow, relocate and tube by suppressing the expression of ITGB8, which is the primary receptor in the extracellular matrix proteins and regulates cell-to-ECM adhesion in glioblastomas. These research results show that miR-93 contributes to invasion and metastases by controlling several related metastases, including induction of the transition between epithelial and mesenchymal syndrome, stimulation of angiogenesis, and interference with cell-to-ECM adhesion.

Jiang and colleagues had a clear association between the long-term responsiveness of ICS (inhaled corticosteroid) and circulating miRNAs. They have shown that miRNAs are potential ICS pharmacogenomic predictors. In particular, 15 miRNAs with a significant change in the ICS treatment effect. Two miRNAs were significantly interlinked with cortisol-dependent NF-kB-ICS (hsa-miR-155-5p and hsa-miR-532-5p). Hsa-miR-
155-5p had a good impact on pulmonary function over time, while hsamiR-532-5p had a negative effect on pulmonary function.

A recent experimental study found upregulated miRNAs (hsa-miR-149, hsa-miR-221, hsa-miR-628-3p, and hsa-miR-654-5p), by suppressing numerous specific osteogenic genes, may play a significant role in the development and regulation of atrophic bone nonunion.

Potential functional target genes for differentially expressed miRNAs have comprised osteogenic and associated regulatory factor genes involved in fracture repair initiatives. Multifunctional growth and differentiation factors forming part of the transforming growth factor-beta (TGF-b) superfamily, are bone morphogenetic proteins (BMPs). TGF-b was suggested to play a role in bone remodeling by influencing the differentiation and function of osteoblasts forming from bone and osteoclasts absorbing the bones. BMP-2 is the prominent bone morphogenetic protein used for osteoblast differentiation and function in preclinical and clinical trials. It can also be employed in treating bone abnormalities, nonunion fractures, spinal fusion, osteoporosis, and root canal operations. Liver/bone/kidney alkaline phosphatases and bone gamma-carboxyglutamate proteins indicate mature osteoblasts, and their expression is linked to bone formation and calcification.

Type 1 spinal muscle atrophy (SMA) is a rare progressive neuromuscular disease due to low motor neuron functional (SMN) protein levels. Risdiplam is an oral medicinal product administered for treating the SMA type 1 infants at a dose of 0.2mg/kg, increasing the functional SMN protein that leads to mRNA shifting to SMN2mRNA exorption.

MiR-30a over-expression has been shown to increase the sensitivity of paclitaxel by decreasing the expression of the cell apoptosis promoter BCL-2; in the same way, over-expression of BCL-2 increases tolerance of paclitaxel, reducing the expression of MiR-30a. This data shows that miR-30a controls paclitaxel’s vulnerability by BCL-2 downregulation.

In cisplatin resistant ovarian cancer patients, MiRNA was found upregulated in drug-resistant cells; homo sapiens (hsa)-miR-30a-5p and hsa-miR-34c-5p. The expression of has- miR- 30a-5p was highly upregulated in two forms of resistant ovarian cancer cell lines compared to those of chemotherapy-responsive lines. The resistance mechanism can be attributed to the increased miRNA 30a 5p expression, which could enhance the cellular growth and colony development potential and improve both cellular migration and invasion. Therefore, miRNA 30a 5p is projected to become an essential promising target for treatment that will be resistant to ovary cancer.

CONCLUSION

It is clear now that more RNA targeting agents need to be discovered. They are promising agents that target a specific enzyme or protein to treat a particular disease or can be used as a molecular marker for a particular disease. Scientists are now working hard to enable RNA targeting agents for different common cardiovascular and hepatic disorders. More studies needed to be held to investigate other drugs and help for FDA approvals.

Declaration of competing interest

The authors declare no competing financial interests or personal relationships could have influenced the work reported in this review article.

Financial support

None.

Ethics statement

None.

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