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A REVIEW ON RNA THERAPEUTICS BEYOND mRNA VACCINES: CURRENT ADVANCES AND FUTURE ASSESSMENT

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Abstract:

The development of messenger RNA vaccines against diseases has shown that RNA is a great tool for biomedical applications. RNA can be used to make treatments quickly and in a controlled way. Now people are looking into using RNA for things, including cancer immunotherapy, replacing proteins, treating rare diseases, regenerative medicine, and gene regulation or editing. One way RNA is used is through RNA interference, which has been proven to work. There are already medicines like patisiran on the market that use this method. People are also working on using mRNA to replace proteins and create cancer treatments. New kinds of RNA like saRNA and circRNA are being studied to make RNA therapy better. These new kinds of RNA could make treatments last longer, be more stable, and require less medicine. To get RNA into the body, scientists are looking at using particles like lipid nanoparticles, polymeric nanoparticles, and exosomes. These particles can help deliver RNA to the tissues and cells. Computers and machine learning are being used to pick the RNA sequences and design personalised treatments. However, there are still some problems to solve. It is hard to get RNA to go to tissues and cells without causing side effects. Also, people may need to take RNA treatments multiple times, and making these treatments can be difficult. This article talks about the developments in RNA therapy beyond just vaccines. It looks at what's coming next and how new technologies will help create RNA treatments in the next few years, such as 2026 and 2027.

Keywords: *RNA Therapeutics, mRNA, siRNA, Self-Amplifying RNA, Circular RNA, Lipid Nanoparticles.*

1. Introduction

RNA therapeutics are an exciting area of research that uses RNA to control how genes work and make proteins for a short time. The success of COVID-19 vaccines that use messenger RNA has made scientists more interested in the possibilities of RNA technology for research and treating diseases. RNA-based therapies have a lot of potential

to help with diseases, such as cancer, rare diseases, and regenerative medicine. There are other types of RNA molecules besides the traditional messenger RNA that can help control specific genes. For example, interfering RNA molecules can stop or reduce the activity of certain genes, and antisense oligonucleotides can change how RNA is processed or help break it down. Other types of RNA like self-amplifying RNA and circular RNA, are also being studied for their potential to make proteins for a time. These different types of RNA give us options for developing new RNA-based treatments (1).

There are many challenges to using RNA therapeutics in the clinic. RNA molecules are not very strong. Can be broken down easily by the immune system, which limits their use. So we need to find ways to deliver RNA molecules into cells safely and effectively. This can be done using vehicles like lipid nanoparticles and extracellular vesicles. However, we still need to make progress in areas like targeting tissues, getting RNA out of cells, and making sure RNA therapeutics are stable and can be stored properly (2)(3).

Recently, there have been advances in RNA therapeutics that have shown a lot of promise. For example, we can engineer RNA molecules to make them stronger and more effective by changing their nucleotide composition and other features. Self-amplifying RNA technology can also increase the amount of RNA produced inside cells, which can lead to protein being made. Circular RNA is another type of RNA that is being studied for its potential to make proteins for a time. Finally, artificial intelligence is being used to help design better RNA molecules and predict how they will work (4).

Combining RNA technology with areas of research like gene editing and artificial intelligence could lead to even more exciting developments in the field. For example, we could use CRISPR technologies with RNA therapeutics to control when genes are turned on and off and make gene editing more precise. Artificial intelligence could also help us design RNA molecules, and new technologies for delivering RNA therapeutics could expand their use to more diseases and ways of delivering them. Overall, these advances could turn RNA therapeutics into tools that can be used in many different clinical settings.

2. Major RNA therapeutic platforms

2.1 mRNA as therapeutic

mRNA is delivered to the cytoplasm, and the cell's own machinery reads it to make a protein. mRNA that is properly designed does not need to integrate into the genome, which makes it a good option for replacing proteins for medicine for immunotherapy and for making therapeutic factors that are only needed for a short time. The research that is provided includes modified mRNA that makes VEGF-A for heart tissue recovery and modified mRNA biomaterials that help heal wounds in people with diabetes, showing that mRNA has uses beyond vaccines (1).

The way mRNA works depends on the 5′ and 3′ untranslated regions, on how the coding sequence is set up, on the poly(A) tail, on the cap structure, on the changes made to the nucleotides, and on how it is cleaned up. N1-methylpseudouridine and similar changes can help with making protein while also reducing unwanted reactions from the immune system (5,6).

2.2 siRNA and antisense oligonucleotides

siRNA and ASOs mostly work by controlling the way the body's own genes work or by making up for a missing protein. siRNA is used by the RNA-silencing complex (RISC), which helps find and break down target mRNA that

matches the sequence. ASOs can help break down RNA, stop it from making proteins, or change how the RNA is put together, depending on how they're made and what they are designed to do.

The proof that RNA interference works in people showed that it is possible to stop genes from working in humans. A major step in the clinic was the approval of patisiran, an siRNA treatment for a disease called transthyretin amyloidosis. However, delivering the RNA and the problem of effects on the genes still cause problems, especially for parts of the body that are hard to reach using current methods, like conjugates or nanoparticles. siRNA and ASOs mostly work by controlling the way the body's own genes work or by making up for a missing protein. siRNA is used by the RNA-silencing complex (RISC), which helps find and break down target mRNA that matches the sequence. ASOs can help break down RNA, stop it from making proteins, or change how the RNA is put together, depending on how they're made and what they are designed to do.

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2.3 Self-amplifying RNA (saRNA)

saRNA takes the idea of mRNA and expands it by including both a therapeutic or antigenic part and a replicase system. This replicase system is usually taken from alphavirus replicons. Once it gets inside the cytoplasm, the replicase makes copies of the RNA. This increases the amount of RNA inside the cell for making proteins. This can lead to protein production even when a much smaller amount of RNA is given compared to regular mRNA (7).

The main benefit of saRNA is that it uses RNA. saRNA is bigger and more complicated than regular mRNA. This makes it harder to make, keep intact, clean up, deliver, and manage the body's response. Recent studies on kinds of nucleotides show that changing the chemical parts can lower the body's interferon response and make the RNA work better. (8) (9)

2.4 Circular RNA (circRNA)

Unlike linear RNA, circRNAs form a loop. They are closed in a circle. Don't have free ends at the 5' or 3' positions. This shape makes them less likely to be broken down by enzymes that attack RNA. This can help them stay in the cell longer. Engineered circRNAs can be used to make proteins if the right parts for starting the process are added. Wesselhoeft et al. Showed that engineered circRNA can make proteins strongly and steadily. This was a step forward for using circRNA in treatments (10). Recent studies looked at making proteins for a long time and creating specific peptides. The advantage of being more stable doesn't mean circRNA is always better than mRNA. How well it works depends on how it is made into a circle, how it is cleaned up, how the sequence is designed, what parts help with making proteins, how it is delivered, and how the body's immune system reacts (11). So the latest studies suggest that comparing circRNA and mRNA directly is important.

2.5 Regulatory non-coding RNAs

miRNA acts like a broad regulator – a single one can knock down many different mRNAs at once. IncRNAs work more behind the scenes, shaping things like transcription, chromatin structure, RNA stability, and even how proteins interact with and target each other. These mechanisms may be useful in cancer and complex diseases. However, broad regulatory activity can create specificity-validation challenges. Emerging work on snoRNAs and tRNA-derived fragments further expands the therapeutic RNA repertoire.

2.6 RNA-guided CRISPR and RNA editing

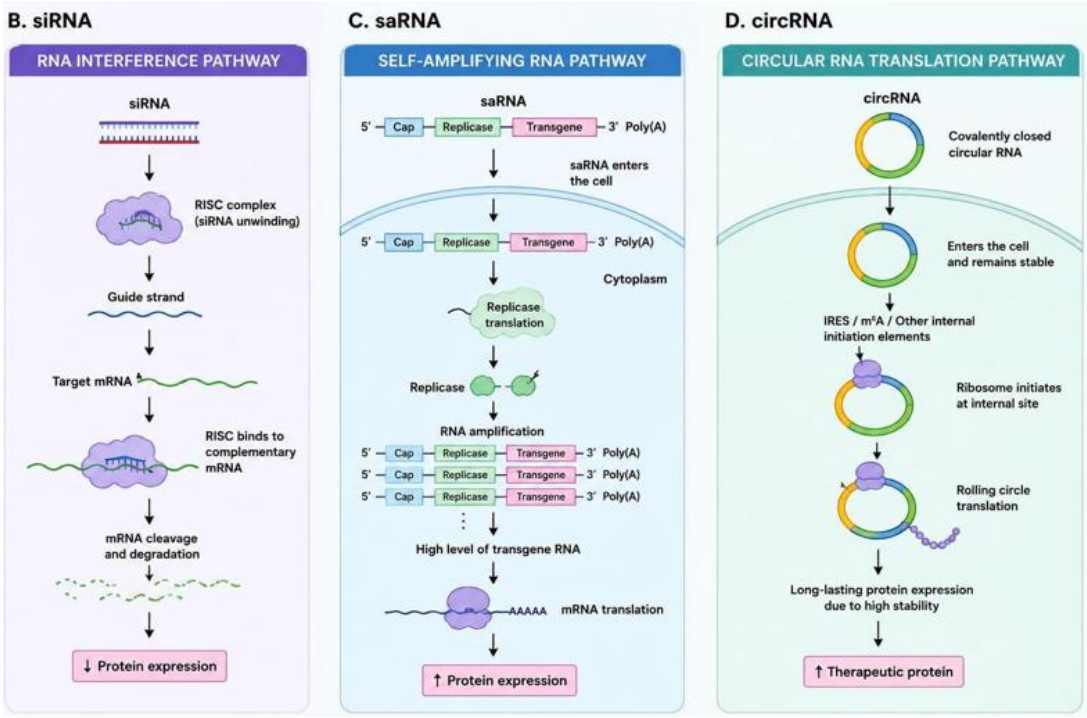

Figure 1: Structure and mechanism of siRNA, saRNA, circRNA (4)

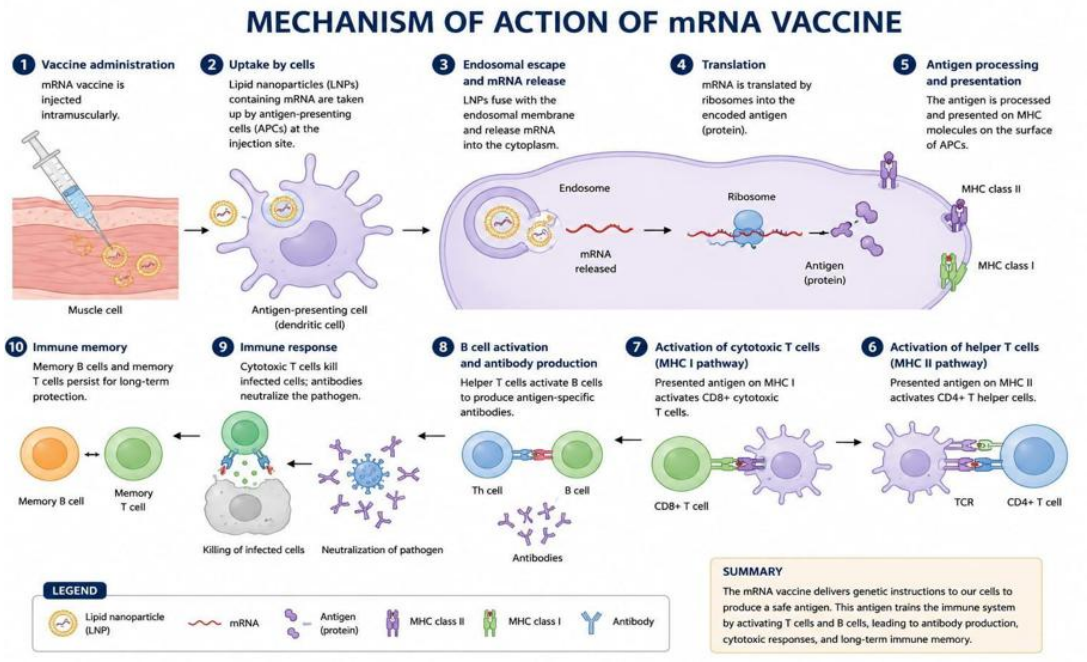

Figure 2: Mechanism of action of mRNA vaccine (12)

RNA-guided CRISPR systems use programmable guide RNAs to direct molecular machinery to selected nucleic acid sequences. Unlike conventional mRNA therapy, CRISPR-based approaches can modify DNA or RNA targets and may provide durable correction or regulation. In vivo genome editing studies have demonstrated the feasibility of delivering CRISPR components using viral and non-viral systems (9), while clinical genome-editing studies have established important proof of concept (10).

The main advantages are programmability and target specificity; the main concerns are off-target editing, unintended biological effects, tissue distribution, and long-term safety.

3. Molecular mechanisms of action

RNA therapeutics work in ways inside our cells. Some RNA therapeutics like mRNA and circRNA are used to make proteins. They do this by acting as templates for protein production. SaRNA works a bit differently. First, it increases the amount of RNA inside our cells. Then it helps our cells translate this RNA into proteins. SiRNA works by reducing the amount of target mRNA. It does this with the help of a thing called RISC-mediated cleavage. ASOs change how RNA is processed or help break it down. CRISPR-associated guide RNAs are like guides that help target parts of our cells.(12)

4. RNA delivery technologies

Getting RNA into our cells is a problem. If we just use RNA on its own, it gets broken down quickly and has trouble getting into our cells. That is why we use things like LNPs. LNPs are like shields that protect RNA from getting broken down. They also help RNA get into our cells. Make sure it does not get destroyed. This is why LNPs are used for mRNA and siRNA drugs. Now people are also using them for other types of RNA.

Compared to LNPs, polymeric nanoparticles are better because we can control their properties easily. Exosomes are different because they come from living things. They might be good at targeting parts of our body. We can also combine materials to make hybrid systems. The next step in delivery research is to make sure RNA gets to the place in our body. We want to be able to control where it goes when it is released and which cells it targets. We also want to make sure it is safe to use more than once. One big problem with getting RNA into our body is that it usually goes to the liver. This is okay if we are trying to treat liver diseases. It is not good if we want to treat other parts of our body, like the brain, muscles or lungs. So we need to make delivery systems that can target specific organs. We can do this by using lipids, nanoparticles that are guided by specific molecules, or exosomes that are engineered to target specific parts of our body. We might also need to use ways of giving RNA to our body.(13)

Table 1: RNA delivery systems

Delivery system	RNA compatibility	Advantages	Limitations	Potential applications
Lipid nanoparticles (LNPs)	mRNA, siRNA, saRNA, circRNA	High delivery efficiency; clinically established	Tissue targeting; repeat-dose issues	Vaccines, cancer, genetic diseases
Polymeric nanoparticles	mRNA, siRNA	Tunable properties	Potential toxicity	Gene silencing, protein replacement
Exosomes	Various RNA types	Natural biological carriers	Isolation and scalability	Targeted RNA delivery
Lipid–polymer hybrids	Multiple RNA types	Combines material advantages	Formulation complexity	Advanced targeted delivery
Targeted nanoparticles	Multiple RNA types	Potential tissue specificity	Targeting efficiency	Cancer, extrahepatic delivery

5. Therapeutic applications

5.1 Cancer

RNA platforms can have an effect on cancer in several ways. MRNA can make tumor antigens or things that help the system; siRNA and ASOs can stop the bad parts of genes; and saRNA/circRNA can help keep antigens or proteins around for longer. Personalized neoantigen mRNA vaccines show how treatment can be made for each patient.

5.2 Genetic and rare diseases

Genetic diseases are candidates for RNA treatments because they often involve not having a working protein or making a bad one. mRNA can give the missing protein; siRNA can stop the one; ASOs can fix the way genes work and editing tools might fix the real problem. The right type of treatment depends a lot on if the fix needs to be temporary or last a time.

5.3 Regenerative medicine

Having mRNA work for a time is good in regenerative medicine because it allows growth factors to be made for just the right time without changing the DNA. Modified mRNA that makes VEGF-A has been looked at for helping blood vessels grow after a heart injury, showing that RNA can act like a short-term message for the body (14).

5.4 Infectious diseases

RNA tools are being studied not only for vaccines to stop sickness but also for treatments that boost the immune system, make proteins that fight viruses, and change how the body reacts. SaRNA is good when you want to use less of a dose while circRNA might last longer in making antigens. Far more saRNA has more real-world use than circRNA .(15)(16)

6. Recent study

The research shows that there is no one RNA platform. How well the RNA works depends on how the RNA's shape, how it works in the body, how it gets delivered, and what kind of disease is being treated. Regular mRNA has a design and can be changed easily, but it does not last long. SaRNA makes copies inside the cell, which means it can work longer and with less material, but it is bigger and needs more complex tools to make. CircRNA is more stable because it is shaped like a circle. Making it and checking that it is good is very hard.

The best proof that saRNA works comes from studies showing that it can make proteins or antigens in measurable amounts. Vogel and others found that people were protected from the flu with less saRNA than with regular mRNA. McKay and others found that a saRNA-LNP version for SARS-CoV-2 worked well in mice by making antibodies. These results show that less is needed. They don't prove that saRNA is always better. How the RNA spreads in the body and how the body reacts to it. How hard it is to make can all change what is best.

The research on circRNA is similar. Wesselhoeft and others showed that engineered circRNA can make proteins for a time. Later studies looked at making proteins for a time and creating closed systems with peptides. Recent reviews say that just being circular does not mean it will work better. How clean it is, how much normal RNA is left, how well it becomes circular, how it is built, and how it is delivered can all affect how well it works.

Research into how to deliver RNA shows more challenges. Changing the RNA can help it last longer and work better. It may not help if it ends up in the wrong place or gets stuck. LNPs have helped solve some problems. They also cause some parts of the body to get more than others and can cause side effects at higher doses. So future work should look at the RNA. How it is delivered as one whole system.

Another trend is using intelligence with RNA treatments. Machine learning can help make parts of the RNA that don't code for proteins choose better building blocks and create better features for making proteins. AI can help find options and make treatments that fit each person, but what it predicts still needs to be tested for how well it works, how it makes proteins, how the body reacts, and how it is delivered.

The research also shows that there is a gap between what's possible and what is used in real life. MRNA and siRNA are already used in medicine. SaRNA is being tested in people. CircRNA is still early. RNA-guided editing has made steps in medicine but needs to be very safe because mistakes can last a long time. Choosing the platform should depend on what is being treated.

Table 2: Challenges and strategies

Challenge	Effect on RNA therapy	Current/proposed strategy
RNA degradation	Reduced therapeutic duration	Sequence/structural optimization
Innate immune activation	Reduced translation/tolerability	Modified nucleotides
Poor cellular uptake	Low therapeutic efficiency	Nanoparticle delivery
Endosomal trapping	Limited cytoplasmic release	Endosomal escape strategies
Liver-biased distribution	Poor delivery to other tissues	Targeted nanoparticles
Repeat-dose limitations	Reduced clinical applicability	Improved formulations and targeting
Manufacturing complexity	Increased production cost/time	Optimized synthesis and purification
Off-target effects	Safety concerns	Improved sequence/target design
Limited personalization	Variable patient response	AI-assisted and patient-specific design

7. Challenges and future perspectives

7.1 Stability and innate immune activation

Exogenous RNA can turn on immune receptors such as TLR3, TLR7, TLR8, RIG-I, and MDA5. Even though immune stimulation can help with vaccines, excessive activation can stop the process of making proteins and make the treatment harder to tolerate in protein-replacement or regenerative treatments. Nucleoside modification, cleaning, and changing the sequence are still ways to handle this (17).

7.2 Extrahepatic delivery and endosomal escape

The big step in delivery is getting the RNA to organs and cell types that are not in the liver. Getting the RNA out of the endosome is also needed because if the RNA is taken in but not released into the cytoplasm, it does not work well. Future nanoparticles will probably use targeting molecules with ionizable parts and ways to release the RNA at the right time.

7.3 Manufacturing and quality control

As RNA structures get more complicated, making them is more important. SaRNA needs control over the quality of RNA, while circRNA also needs good circularization and the removal of any linear or not fully circular parts. Tests that follow manufacturing practices must check the identity, purity, strength, and consistency of the RNA.

7.4 AI-assisted RNA design

Machine learning is expected to help with designing the sequence, improving the UTR, predicting the structure, making delivery better and grouping patients. The main benefit is cutting down the number of experiments needed. However, sequences made by AI still need to be tested for how they work, how they affect the immune system, how stable they are, and how safe they are (18).

7.5 Personalized and n-of-1 RNA therapeutics

RNA is an entirely new treatment. Personalized cancer vaccines and individualized antisense treatments show this. Future progress needs rules and ways to make batches or products made just for one; production works with personalized medicine because the sequence can be changed without making while still keeping safety and quality.(19))

7.6 Future direction

The exciting future might involve using different technologies together- for example, AI-designed RNA delivered by nanoparticles that target certain organs, or RNA editing parts used with systems that work for a short time. The field is heading toward making RNA structure, chemical parts, how it is delivered, and the type of cell it targets. How long it works, all better at the same time (20).

Table 3: Challenges and strategies

Challenge	Effect on RNA therapy	Current/proposed strategy
RNA degradation	Reduced therapeutic duration	Sequence/structural optimization
Innate immune activation	Reduced translation/tolerability	Modified nucleotides
Poor cellular uptake	Low therapeutic efficiency	Nanoparticle delivery
Endosomal trapping	Limited cytoplasmic release	Endosomal escape strategies
Liver-biased distribution	Poor delivery to other tissues	Targeted nanoparticles
Repeat-dose limitations	Reduced clinical applicability	Improved formulations and targeting
Manufacturing complexity	Increased production cost/time	Optimized synthesis and purification
Off-target effects	Safety concerns	Improved sequence/target design

8. Conclusion

RNA treatments have come a long way from just the idea of using mRNA for vaccinations. Now we have types of RNA treatments like mRNA that replaces proteins, siRNA and ASOs that silence genes, saRNA that helps with doses, circRNA that lasts a long time, and special RNAs that help regulate genes. Each of these RNAs solves a problem and has its own set of limitations. mRNA is very flexible; siRNA and ASOs are very good at controlling genes; saRNA helps make more of something inside cells; circRNA helps things last longer, and systems like CRISPR can target specific things. The big problems are still getting these RNAs to the place, making sure they do not cause bad reactions, avoiding unwanted effects, making them in large quantities, and dealing with regulations. To make progress, we need to design RNAs and their delivery systems, use computers to optimize them, make sure they are all of high quality, and tailor them to each person's needs. So the next step in RNA medicine will probably be about matching the RNA delivery system and disease rather than just finding a new type of RNA.

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