Technology Networks

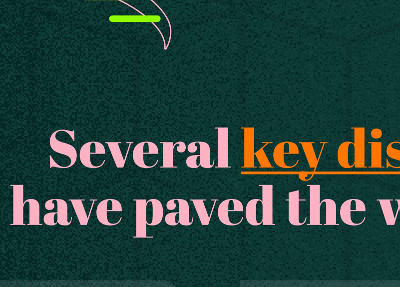
RNA Therapeutics

RNA therapeutics are a class of biopharmaceuticals that use RNA to treat or prevent human diseases, including infectious diseases, genetic conditions and cancer. This field of medicine is rapidly evolving and offers new avenues for targeting "the undruggable". In this infographic, we'll explore why.

Let's start by asking – what is RNA?

RNA
{ ribo·nucleic ac·id }

A biological molecule that is similar to DNA, but has only one helical strand of ribonucleotide bases:



DNA, trapped in a cell's nucleus, is transcribed to RNA that can then be translated to produce proteins within the cytoplasm. Proteins are the functional workhorses of the cell, conducting a myriad of important biological processes.

Several key discoveries in RNA biology have paved the way for RNA therapeutics:

1956 Rich and Davies demonstrate that two RNAs can form base-pairs with one another.

1961 Messenger RNA (mRNA) is discovered.

1962 RNA replicase is discovered.

1970 Reverse transcriptase is discovered.

1977 RNA splicing is discovered.

1993 Discovery of microRNA.

1998 Discovery of RNA interference.

RNA is a key player in the central dogma of molecular biology. Considering that many human diseases are caused by errors in this dogma, we can start to appreciate how useful RNA can be as a therapeutic modality.

RNA therapeutics are likely to change the standard of care for many diseases.

Targeting the undruggable
Only 0.05% of the human genome has been drugged by small molecule drugs and antibodies, as most of the genome does not encode protein. Some RNA molecules can target mRNAs and noncoding RNAs directly, meaning that RNA can hypothetically target any gene of interest, even if it does not encode a protein.

Fast development
RNA therapeutics can be designed and developed much faster than traditional small drugs or gene therapies. The design and synthesis of RNA molecules is also more adaptable, a critical feature for responding to public health emergencies.

Stimulating the immune system
RNA can be used to effectively stimulate the immune system, creating new opportunities for vaccine development. The BNT162b2 COVID-19 vaccine was the first mRNA-based vaccine to be approved for human use in history.

Short half-life
Some RNA molecules, like mRNA, have a short half-life. This can be beneficial, as it enables a controlled and reversible therapeutic effect.

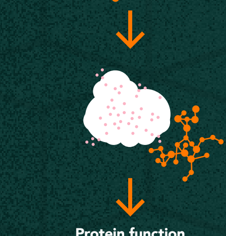
Personalized medicine
RNA therapeutics can be customized for individual patients.

Low risk of mutagenesis
Unlike gene therapies, RNA therapeutics do not integrate into the genome, and do not cause unintended mutations.

The different types of RNA

Scientists have discovered a variety of RNA molecules that have diverse roles, and many are still yet to be determined. RNA molecules can be used to modulate gene expression in various ways, such as by expressing therapeutic proteins, targeting RNA molecules to alter their function or silencing specific genes, for example.

Examples of RNA therapeutics



1 RNA aptamers

Pegaptanib was the first RNA therapeutic approved by the US Food and Drug Administration (FDA) for the treatment of age-related macular degeneration (AMD).

Pegaptanib interacts with vascular endothelial growth factor (VEGF), stopping it from interacting with its receptors.

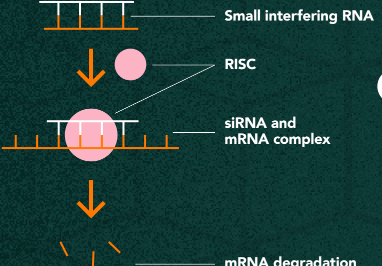
2 Antisense oligonucleotides (ASOs)

ASOs bind to target RNA and modulating gene expression either by:

- inhibiting translation
- promoting RNA degradation
- or altering splicing.

Nusinersen was approved by the US FDA in 2016 to treat spinal muscular atrophy (SMA), a genetic neuromuscular condition.

It corrects splicing errors in the *SMN2* gene, increasing production of the functional SMN protein and improving motor function.



3 RNA interference (RNAi)

Use small RNA molecules to silence target genes, halting the prevention of proteins by interfering with mRNA.

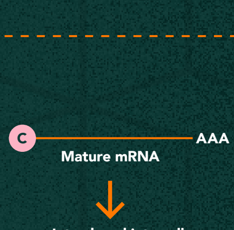
The two main forms of RNAi are genome-derived microRNAs (miRNAs) and small interfering RNAs (siRNAs).

Currently four siRNA therapeutics are approved by the FDA.

4 mRNA
(including mRNA vaccines, therapeutics and cell therapies)

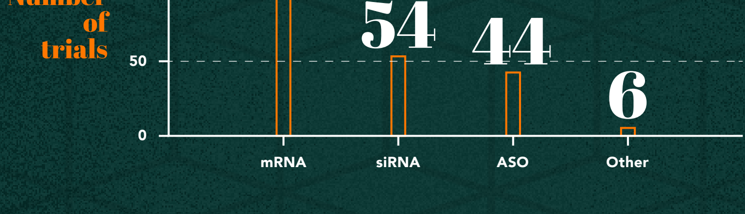
mRNA therapies work by introducing synthetic mRNA molecules into cells, which instruct the cell to produce a specific protein. This protein could be used to treat a disease or to trigger an immune response.

mRNA is being used to create flu, RSV and HIV vaccines, and therapies to treat conditions such as type I glycogen storage disease.



To date, the development of RNA therapies has focused largely on ASOs, RNAis and mRNA-based drugs or vaccines.

RNA theraputic type



Summary of RNA therapeutic ongoing clinical trial landscape.

Adapted from *Curreri et al*.

Manufacturing RNA therapies

Different methods and bioprocessing workflows are used to design and develop RNA therapeutics. Here's a "classic" example of a manufacturing process.

1. Obtain RNA sequence(s) for desired indication. Often gathered from a digital bank.

Once a workflow has been established, production facilities can typically "switch gears" quickly and adapt this workflow to produce other types of RNA drugs.

2. DNA template production
   - Clone
   - Expand
   - Linearize
3. Drug substance manufacturing
   - Cell-free transcription of mRNA
4. Drug product formulation
   - Self-assebly of RNA-lipid nanoparticles
5. Fill and finish
   - Purification
   - Sterilization
   - Packaging
6. Clinical trials to test efficacy and safety of the product.

   Despite many RNA therapeutics entering clinical trials, only a few have received FDA approval.
7. Subject to regulatory approval, global production and distribution may be the next step.

RNA therapies – the present and the future

Challenges associated with RNA-based therapeutics include:

Instability

Delivery

Making sure RNA molecules are stable and developing effective delivery methods to target specific cells without degradation is a challenge.

Immunogenicity

Addressing the potential of RNA molecules to activate the immune system, which can lead to adverse reactions or reduced therapeutic efficacy.

Clinical validation

Demonstrating safety and efficacy and gaining regulatory approval for RNA therapies can be a long and expensive process.

The swift expansion of RNA therapeutics can be attributed to the resolution of some of these challenges. Room for improvement remains, however the global RNA therapy clinical trials market is expected to reach

$3.5 billion

by 2030.

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