Current developments

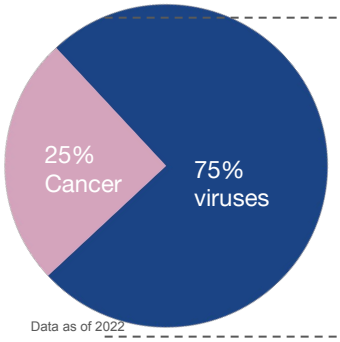
and outlook on mRNA vaccines

Discover the process of development, manufacturing, and mitigation of challenges associated with mRNA vaccines

mRNA vaccines “a promising alternative to traditional vaccines”

While the immunostimulatory effects of RNA have been known for decades, the use of *in vitro* transcribed mRNA for introducing genes expressing proteins was demonstrated in 1990 through direct injection of "naked" nucleic acids. mRNA vaccine development may have been delayed due to the instability of mRNA; The approval of the the Pfizer/Biontech and Moderna COVID-19 vaccines catapulted the interest in mRNA vaccines

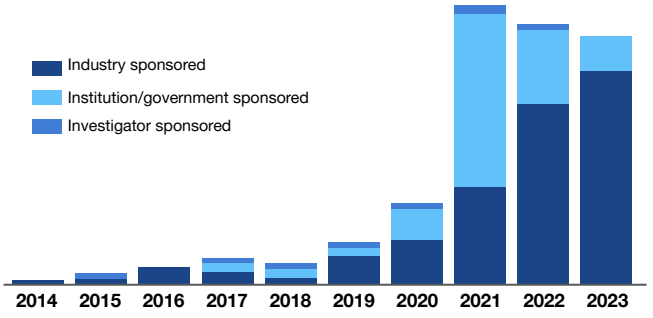
In the clinical setting, 75% of mRNA vaccines are being tested for the prevention of viral infections, while 25% are being investigated for cancer therapy

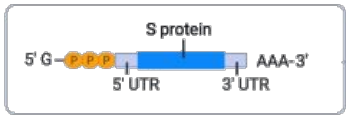


SARS-Co V-2 (35%)
RV (15%)
HIV (10%)
IFV (5%)
RSV (5%)
Zika (5%)

Following successful development, mRNA vaccines mRNA-1273 from Moderna and BNT162b2 (Comirnaty) from BioNTech/Pfizer have received global approval to target the COVID-19 virus's spike protein.

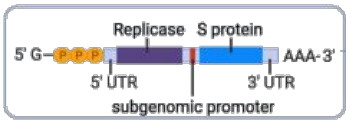
mRNA vaccine trials initiated as a percentage of vaccine trials each year, sorted by sponsor type





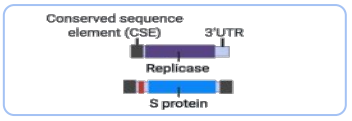
Non-replicating RNA

Deliver exclusively genetic information coding for the target antigen, thus containing the 5′-cap, 5′ untranslated region (UTR), 3′ UTR, and 3′-poly(A) tail regions
Approved mRNA vaccines are based on this technology



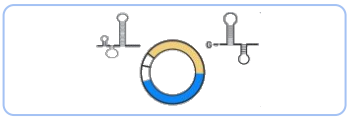
Self-amplifying RNA

saRNA vaccines can deliver genetic information encoding the target antigen and other genes, e.g., viral RNA polymerase, to enable mRNA to self-replicate.
A subgenomic promoter is also used to initiate transcription of the gene coding for the target antigen



Trans-amplifying RNA

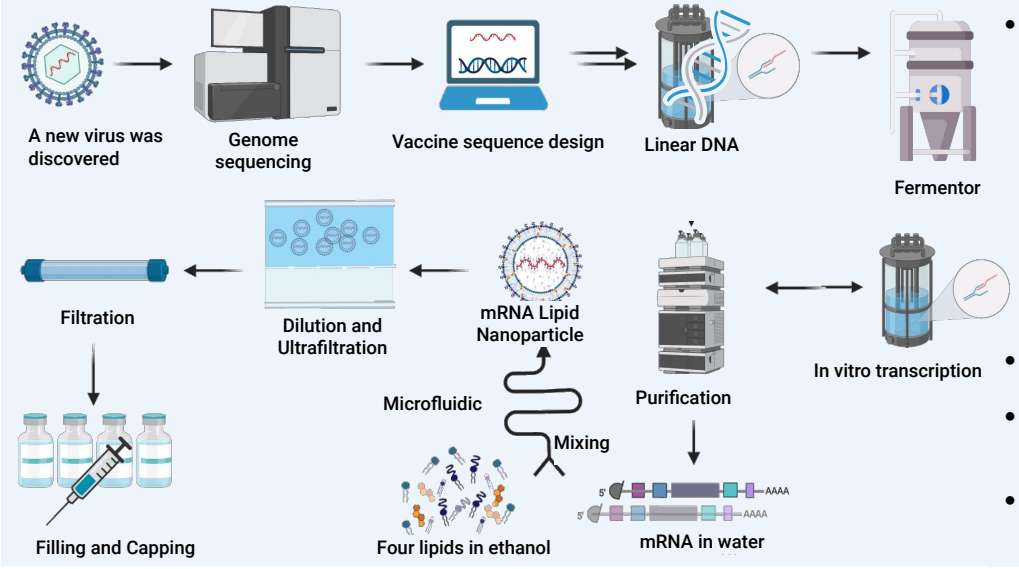
taRNA is a self-amplified RNA composed of two separate RNA molecules developed to circumvent the problems caused by large and complex sequences of saRNA



Circular RNA

CircRNA is a highly stable RNA with a covalently closed loop structure, including a large category of non-coding RNAs generated by back splicing in eukaryotic cells
Despite the lack of essential elements for cap-dependent translation, circRNA can be translated by adding the IRES element or m6A modification incorporated to its 5′ UTR region

Currently only non-replicating mRNA vaccines are approved; saRNA vaccines are in preclinical and clinical trial stage



Manufacturing of mRNA vaccine

- The production process of mRNA vaccine mainly involves the following steps:
  - target antigen sequence design
  - plasmid construction
  - DNA template preparation
  - *In vitro* transcription (IVT) of mRNA
  - mRNA purification
  - Lipid nanoparticles (LNP) formulation and encapsulation
  - mRNA-LNP complex dilution
  - mRNA-LNP complex concentration
  - sterile filtration and filling
- The production of mRNA vaccines starts with the synthesis of the target antigen sequence
- To improve the safety, efficacy, and stability of mRNA vaccines, researchers usually perform codon optimization
- Optimization of mRNA secondary structure and stability can be achieved by increasing the GC content of the coding sequence

Challenges	**Lack of stability:** mRNA was highly unstable and the free floating RNA would get destroyed by ribonucleases	**Immune recognition:** The immune system can rapidly detect and destroy pathogenic mRNA before eliciting an immune response	**Delivery:** Enzymes would quickly destroy the naked mRNA before it could “deliver” its message
Solution	**Capping and Tailing:** Adding specific gene sequences to the beginning and end of the mRNA strand to make it stable	**Nucleoside modifications:** Karikó *et al.* found, mRNA modified with uridine could avoid recognition & degradation by immune system	**LNP technology:** Encapsulating the RNA in lipid nanoparticles helps protect the mRna

“Unlocking the potential of mRNA technology beyond COVID-19 vaccines will require robust research to address limitations head-on. To improve mRNA vaccine technology, future research should seek to develop more temperature-stable vaccines, increase how long protection lasts, and ensure effectiveness against a diverse range of strains and variants.”- **Prof Harold Varmus, Chair of the WHO Science Council & former Director of the U.S. National Institutes of Health**

Note: This report is generated based on publicly available data