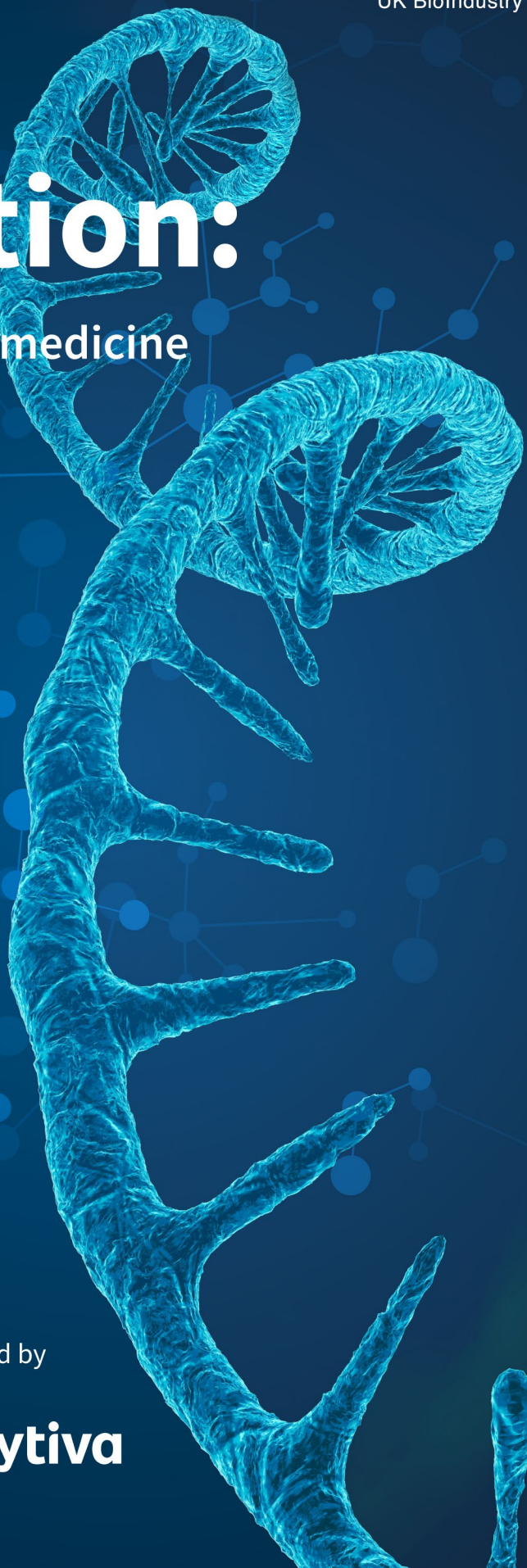
UK BioIndustry Association

mRNA Revolution:

A new generation of medicine

Updated for 2024



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Contents

Forewords New 3

Introduction New 6

Why RNA? 6
What is mRNA? 6
Types of RNA 8
saRNA: A new frontier in RNA therapeutics? 8
mRNA timeline 9

RNA therapies 12

mRNA therapies 12
Impact of mRNA 13

Manufacturing mRNA 14

Encapsulating RNA 15

Landscape New 16

Map of mRNA companies 17
Skills 18

Case studies New 22

Moderna 22
SiSaf 23
CPI 26
eXmoor 28
Touchlight 30
New England Biolabs 31
TriLink 35

Conclusion New 38

About BIA 39

About Centre for Process Innovation (CPI) 40

About Cytiva 40

Forewords



mRNA technology is a rapidly growing field with the potential to revolutionise the way we treat diseases. mRNA is a single-stranded molecule of RNA that carries genetic instructions from DNA to the ribosomes, where it is translated into proteins. In recent years, mRNA has been used to develop vaccines against COVID-19 and other diseases.

Steve Bagshaw CBE,
Chair of High Value Manufacturing Catapult

The BIA is committed to supporting the development and manufacturing of mRNA technology in the UK. We believe that the UK has the potential to be a world leader in this field, thanks to our strong research base, skilled workforce, and supportive regulatory environment.

This report provides an overview of the state of mRNA technology in the UK. It highlights the progress that has been made in recent years and identifies the challenges that still need to be overcome. The report also makes recommendations for how the UK can further support the development and manufacturing of mRNA technology.

We hope that this report will help to raise awareness of the potential of mRNA technology and encourage more companies and organizations to invest in this field. We believe that by working together, we can make the UK a leading destination for mRNA research and development.

The BIA can maximise the impact of mRNA in a number of ways, including:

- Promoting the UK as a leading destination for mRNA research and development by highlighting the strengths of the UK bioscience sector, such as the availability of skilled talent, the strong research base, and the supportive regulatory environment.
- Advocating for favourable policies, supportive taxation environment and streamlined regulatory approval processes.
- Supporting the development of education and training programs in mRNA technology which will help to ensure that there is a skilled workforce available to support the development and manufacturing of mRNA-based products.

- Fostering collaboration between companies and organisations working in mRNA technology which will help to accelerate the development of new mRNA-based products.
- Raising awareness of the potential of mRNA technology among the public, government, and investors, which will help to create a favourable environment for the development of mRNA-based products.

These are just some of the ways that the BIA can maximise the impact of mRNA. The BIA is committed to supporting the development of the UK bioscience sector, and will continue to work with its members and partners to ensure that the UK remains at the forefront of mRNA research and development.

New



At CPI, we help companies develop, scale up and commercialise innovative technologies to deliver novel products and processes. We offer world-leading facilities and expertise in nucleic acid therapeutics and vaccines, small molecules, biologics, oligonucleotides, and complex medicines to accelerate drug development and scale-up.

Louise Taylor,
RNA Training Academy Lead, CPI

Through our role in the UK Government's Vaccine Taskforce, we've built the infrastructure, skills and knowledge and networks to support RNA- LNP vaccine and therapeutic development and manufacture. Our RNA Centre of Excellence is a multi-million-pound GMP facility that is currently the only UK-based open-access facility with the capability to develop and manufacture lipid nanoparticle encapsulated messenger and self-amplifying RNA vaccines and therapies ready for use in early-phase clinical trials. We also deliver CPD-certified industry-focused learning courses within RNA manufacturing, scale-up, and analytics.

Our work is advancing next-generation therapeutic modalities, expanding vaccine production capacity, and reducing the risks around developing advanced vaccines and therapeutics to accelerate time to market. We're also involved in oligonucleotides, developing new manufacturing processes to get these promising drugs to market faster. This therapeutic approach allows the targeting of molecules that conventional drug modalities cannot tackle, with the potential to treat underlying genetic drivers of disease.

New



At TriLink, we partner with drug developers to help bring transformative nucleic acid medicines from research to patients.

Victoria Smith,
Application Scientist, Technical Design, TriLink

We offer innovative nucleic acid tools and services, leading-edge manufacturing facilities, and technical expertise from concept through commercialisation. With over a decade of mRNA manufacturing experience, TriLink is determined to deliver so our partners can confidently bring mRNA-based therapies to patients.

Introduction

Why RNA?

We are experiencing what has been described as an "RNAaissance" since the COVID-19 pandemic in 2020. RNA therapeutics rose to prominence with mRNA/LNP COVID-19 Vaccines from Moderna and Pfizer-BioNTech. However, there is more to RNA therapies than just prophylactic vaccines; RNA-based therapeutics can target diverse cellular molecules, including those deemed "undruggable" pathways or molecules that are not amenable to targeting by conventional drugs. Here, we are focussing on mRNA-based therapeutics.

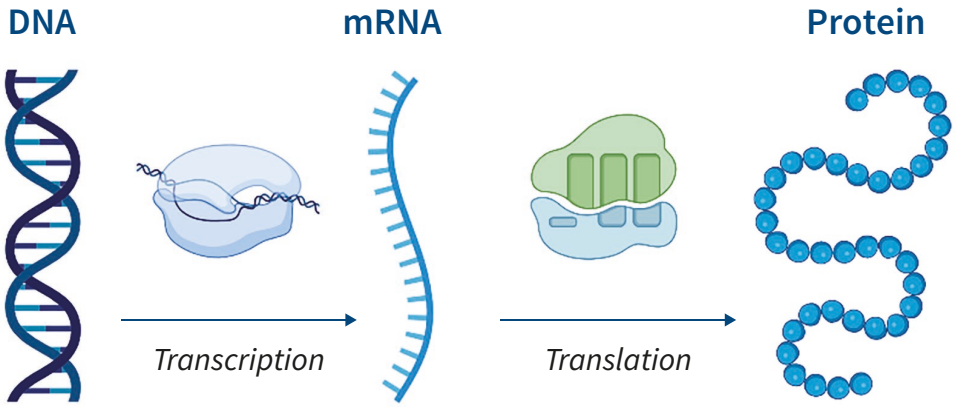
There are several advantages to using mRNA as a therapeutic – mRNA is simpler to synthesise than conventional therapies, making it both faster and cheaper to produce. It is also more widely adaptable than conventional therapies and can be used to treat a variety of diseases and conditions, ranging from infectious diseases, to cancer and rare genetic disorders. mRNA is also an alternative to protein therapy, and able to overcome some of the limitations and challenges of delivering proteins directly into the body, such as stability, immunogenicity, and bioavailability. Finally, mRNA is transient and non-integrating, hence it does not alter the genome of the cells and only expresses the desired protein for a limited time, reducing the risk of unwanted side effects or long-term consequences.

However, there are also some challenges to using mRNA as a therapeutic. mRNA is susceptible to degradation and unable to cross the cell membrane, therefore it needs to be delivered in a way that protects it from the body's natural defences and helps deliver it into cells. mRNA can also trigger an immune response, which can limit its therapeutic potential. Despite these challenges, mRNA is a promising new drug platform with the potential to revolutionize the way we treat diseases. This explainer will define mRNA, discuss its role in medicines manufacturing, and explore its potential as a next-generation treatment.

What is mRNA?

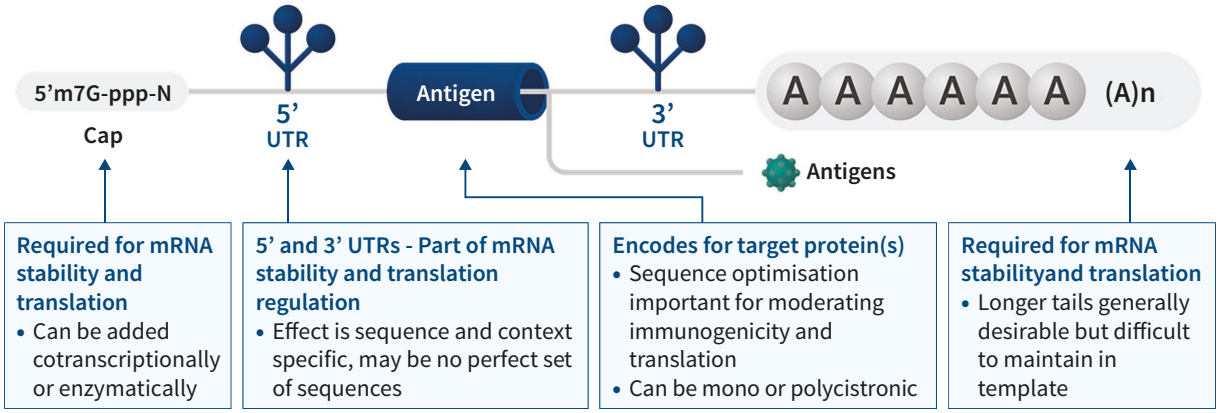
Simply, mRNA is a molecule that carries instructions from DNA to the ribosomes, where proteins are made. Proteins are the building blocks of life and are responsible for a wide range of functions, including cell structure, metabolism, and signalling.

Deoxyribonucleic acid (DNA) is a molecule that contains our genetic code, the blueprint of life. This essential molecule is the foundation for the "central dogma of biology", or the sequence of events necessary for life to function. DNA is a long, double-stranded molecule made up of bases, located in the cell's nucleus. The order of these bases determines the genetic blueprint. To 'read' these blueprints, the double-helical DNA is unzipped to expose the individual strands and an enzyme translates them into a mobile, intermediate message, called ribonucleic acid (RNA). This intermediate message is called messenger RNA (mRNA), and it carries the instructions for making proteins.



The main use of mRNA so far is as a vaccine. RNA vaccines harness our own cells to act as the factory to make the protein that triggers an immune response. However, the RNA encodes for only a small and harmless part of the virus, such as the spike protein with COVID-19. It does not actually contain the virus itself. This then triggers our adaptive immune response to create antibodies to destroy the spike proteins. After the protein pieces are made, our cells break down the RNA and remove it. So, the RNAs are merely temporary messages to evoke the immune response.

There are many design options when working with RNA. The conventional RNA-based vaccines are shown in the figure below. The mRNA encodes the cap, 5', and 3' untranslated regions (UTRs), the gene of interest for the target protein, and a polyadenylated tail. In the case of COVID-19 vaccines, the code is for the spike protein found on the outer shell of the Sars-CoV-2 virus, which causes the disease.



Chemical modifications of RNA, for example, modified nucleosides, have been utilised to increase protein expression. Compared to conventional mRNA, self-amplifying RNAs or saRNA is another kind of mRNA with a different structure. saRNA encodes not only for the gene of interest but also for viral replication machinery that enables intracellular RNA amplification and abundant protein expression. As the self-amplifying RNA self-replicates, the required dose is smaller. saRNA can be delivered as two separate transcripts (trans-amplifying saRNA) which helps reduce the RNA's overall size. Circular RNAs are single stranded, covalently closed RNA molecules that are an alternative to linear RNA constructs. They have the advantage of being more resistant to exonuclease activity, extending longevity and avoiding the need for the costly 5' cap as there's no poly A tail.

New

Types of RNA

There are multiple types of RNA, some of therapeutic relevance include:

- Messenger RNA (mRNA) is the most common type of RNA. It carries genetic information from DNA to the ribosomes, where it is translated into proteins.
- MicroRNA (miRNA) regulates gene expression by binding to mRNA and preventing it from being translated into protein.
- Small interfering RNA (siRNA) prevents gene expression, a process called RNA interference, which is a vital part of the immune response.
- Piwi-interacting RNA (piRNA) is involved in the silencing of transposons, which are mobile genetic elements that can cause mutations.
- Transfer RNA (tRNA) transports amino acids to the ribosomes, where they are assembled into proteins.
- Ribosomal RNA (rRNA) is a component of ribosomes, where proteins are assembled.

The different types of RNA play different roles in the cell, but they all have one thing in common: they are essential for life.

New

saRNA: A new frontier in RNA therapeutics

saRNA, or self-amplifying RNA, represents a significant advancement in RNA technology. Unlike traditional mRNA vaccines that require a relatively high dose, saRNA can replicate within the cell, leading to sustained production of the desired protein. This self-amplification characteristic has the potential to enhance vaccine efficacy and duration of protection, as well as reduce manufacturing burdens.

While saRNA offers promising advantages, it also presents challenges. The larger size of saRNA molecules compared to mRNA can complicate delivery, as well as the manufacturing process and there's a potential for increased innate and adaptive immune responses. Despite these hurdles, ongoing research and development efforts are focused on optimising saRNA technology for therapeutic applications, while also addressing potential challenges.

The future of saRNA is bright, with the potential to revolutionise vaccine development and treatment of various diseases. However, further clinical trials and real-world data are necessary to fully understand its impact.

New

mRNA timeline

1961: mRNA discovered

In the summer of 1961, both the discovery of mRNA and the cracking of the genetic code was announced

This was a monumental discovery for mRNA manufacturing; the five prime Cap is responsible for reducing degradation and promoting translation

1975: Discovery of 5' Cap modification

1978: Lipid-based mRNA delivery developed

For in vivo functionality, mRNA needs safe, effective, and stable delivery systems that protect it from degradation and facilitate both cellular uptake and release of the mRNA

T7 Polymerase catalyses the formation of RNA in the correct direction

1985: First commercialisation of T7 polymerases

1990: Discovery of the mechanism of action

Naked RNA was injected into mice which proved direct gene transfer in vivo

Researchers entered a multimillion-dollar research collaboration and licensing pact with Merck, evaluating mRNA in mice with the aim of creating an influenza vaccine. The collaboration was abandoned due to the cost and feasibility of manufacturing

1991: Merck collaboration

1993: Injection of influenza mRNA

Mice were injected to induce an immune response. Here the mechanism of action was discovered

The very first mRNA vaccine was designed for cancer treatment in mice

1995: Mice cancer vaccine

1997: First mRNA company founded

Merix Biosciences, now Argos Therapeutics

Antisense RNA (RNA complementary to a protein coding messenger) drug approved for the first time

1998: First antisense RNA drug approved

2002: RNA interference in mice

RNAi was first used to destruct Hepatitis C in mice

Pegaptanib was the first RNA aptamer drug designed to treat age-related macular degeneration

2004: The first RNA aptamer drug approved

2005: Nucleoside-modified mRNA found to be non-immunogenic

Therefore less non-specific immune responses will occur. Kariko and Wiessman won the 2023 medicine Nobel Prize for their work in this area and its contribution towards the COVID-19 vaccines

Stability is particularly important in mRNA vaccines. Uradine is replaced with the modified pseudouradine in some mRNA vaccines.

2008: Nucleoside modifications found to improve stability and translation approved

2009: First use of mRNA for human cancer immunotherapy Human tissue with metastatic melanoma underwent trials

In which mRNA was used to induce immune response against the melanoma associated antigens

mRNA vaccine for Flu and RSV protection

2012: Preclinical study

2013: Use of CRISPR-Cas9 mRNA as gene-editing tool

2017: The first human proof of concept for personalized neo-epitope mRNA cancer vaccines

2018: Regulatory advancements

NIH's response to the Ebola epidemic in the Democratic Republic of Congo helped to establish pathways to streamline and speed up regulatory review and emergency use of treatments during outbreaks

First report of SARS-Cov-2 outbreak in China

31 December 2019: First signs

10 January 2020: SARS-Cov-2 Sequenced

Chinese scientists share the first genetic sequence of SARS-Cov-2 with the NIH database GenBank

Moderna initiated GMP production

14 January 2020: Moderna process reaches GMP

2 February 2020: Moderna RNA proof of concept

Moderna validates in-vitro expression of mRNA-1273

Moderna vials clinical batch drug product

4 February 2020: First Covid Vaccine Fill Finished

18 February 2020: Moderna animal study

During a study on mice, Immunogenicity was confirmed post mRNA vaccine

Clinical Trial begins

16 March 2020: Moderna Phase 1

30 April 2020: UK Government's Vaccine Taskforce established

A collaboration between government, academia and industry to help rapidly find a vaccine against COVID-19. The BIA Industry-led vaccine manufacturing group aimed to create a UK capability that could deliver 25 Million doses in 24 weeks by 2023

Clinical Trial begins

29 May 2020: Moderna Phase 2

27 July 2020: Moderna Phase 3

Clinical Trial begins

Moderna Phase 3 study met statistical criteria with a vaccine efficacy of 94.5%

16 November 2020: Moderna clinical success

November 2020: Pfizer and BioNTech success

Vaccine candidate BNT162b2 proven to have a 95% efficacy post phase 3 clinical study

FDA grants emergency use authorization to the Pfizer-BioNTech mRNA vaccine for over 16 year olds

11 December 2020: BioNTech vaccine use

18 December 2020: Moderna vaccine use

FDA grants emergency use agreement to the Moderna mRNA vaccine for people over 18

CPI support vaccine development with a 1L scale up production of saRNA

December 2020: CPI proof of concept

March 2021: AstraZeneca Clinical success

Vaccine candidate AZD1222 proven to have 76% vaccine efficacy against symptomatic Covid

CPI creates platform process for RNA-LNP vaccines

July 2022: Platform development

October 2022: CPI RNA-LNP GMP build complete and validated

"UK cements 10-year-partnership with Moderna in major boost for vaccines and research". The new Innovation and Technology centre will offer NHS patients access to Moderna's multi-variant COVID-19 vaccines, allowing for rapid scaling and production in the event of future public health emergencies

December 2022: UK-made respiratory disease vaccine deal finalised

February 2024: CPI obtain MHRA licence for RNA-LNP facility

Researchers at the University of Oxford, the Francis Crick Institute and University College London have been granted £1.7 million of funding from Cancer Research UK and the CRIS Cancer Foundation to develop a lung cancer vaccine

March 2024 : Lung cancer vaccine

July 2024 : CPI in production

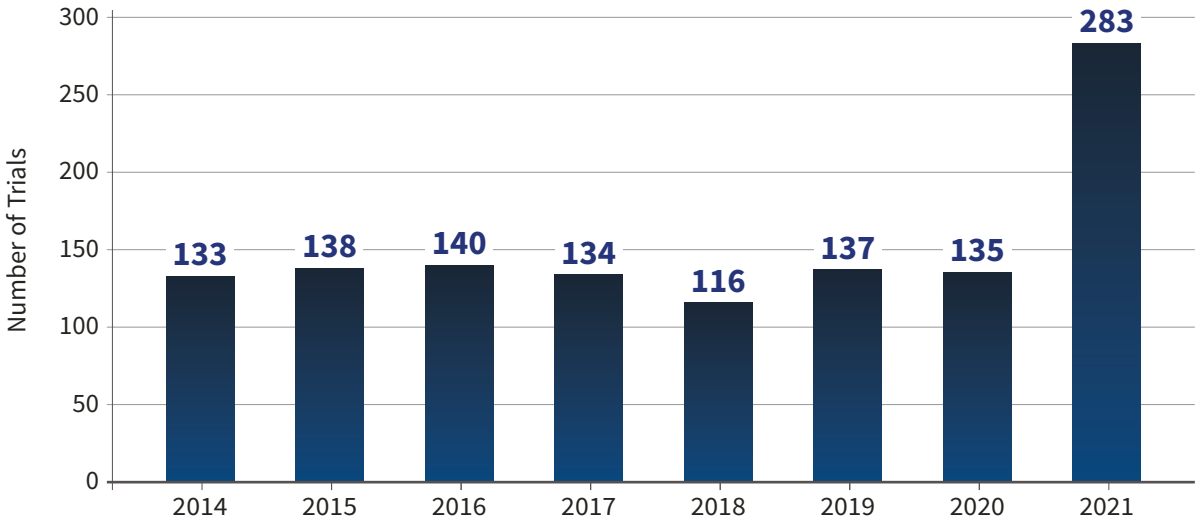
First GMP RNA-LNP batch complete

mRNA therapies

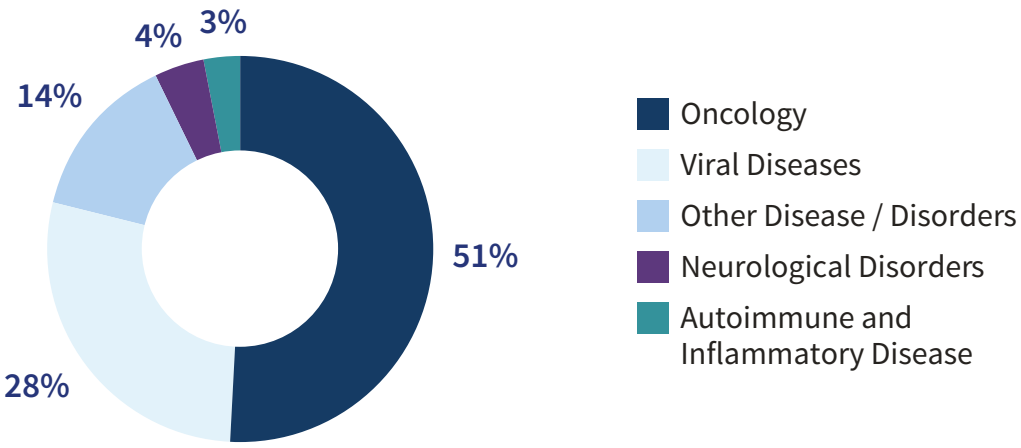
mRNA therapies work well as vaccines. Immunisation requires only a minimal amount of protein production, as the immune system can amplify the antigenic signal through cell-mediated and antibody-mediated immunity. mRNA therapeutics require as much as a 1,000-fold higher level of protein to reach a therapeutic threshold. The challenge for the next generation of therapeutics involves better targeting, better expression and different delivery mechanisms. The different approaches to improving protein expression through modification of the mRNA bases and the use of saRNA was covered above. Improved delivery mechanisms for mRNA are being explored using a variety of approaches, including cell based, extracellular vesicles, biomimetic vesicles, polymeric delivery and optimised LNPs which are targeted. To reach their full potential, RNA therapies require more targeted delivery to reach organs other than the liver. Administration routes other than intravenous delivery include intranasal, inhalation and injection into the target organ.

Currently, varying types of general and personalised mRNA vaccines are being developed against both viral diseases and cancer in tandem with work in optimising mRNA synthesis, delivery, stability, efficacy and safety standards. Clinical trials with RNA doubled in 2021. Trials cover oncology, viral diseases, neurological disorders and autoimmune and inflammatory diseases.

Total number of clinical trials with mRNA across UK and USA



UK and US mRNA Clinical Trials (2014–2022)

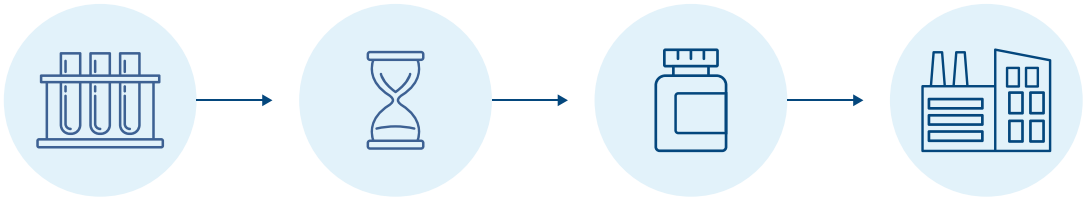


Impact of mRNA

Traditional vaccine platforms struggle with the costs of manufacturing, scale capability and lengthy development times. RNA vaccines harness our own body to make a small protein to teach the body's immune system to recognise it as foreign. The use of a genetic code lends itself to a "plug-and-play" vaccine approach with rapid development times, lowering the overall costs.

The processing time is also a lot shorter than traditional biologics production where a host cell line or egg-based platform are used to create the proteins of interest.

Another advantage to the technology is that only small doses are required for vaccines and as such they can be produced at smaller scales allowing the use of smaller manufacturing facilities.



Platform process
Easy to integrate new products

Short processing time

Small dose required
Low volume production

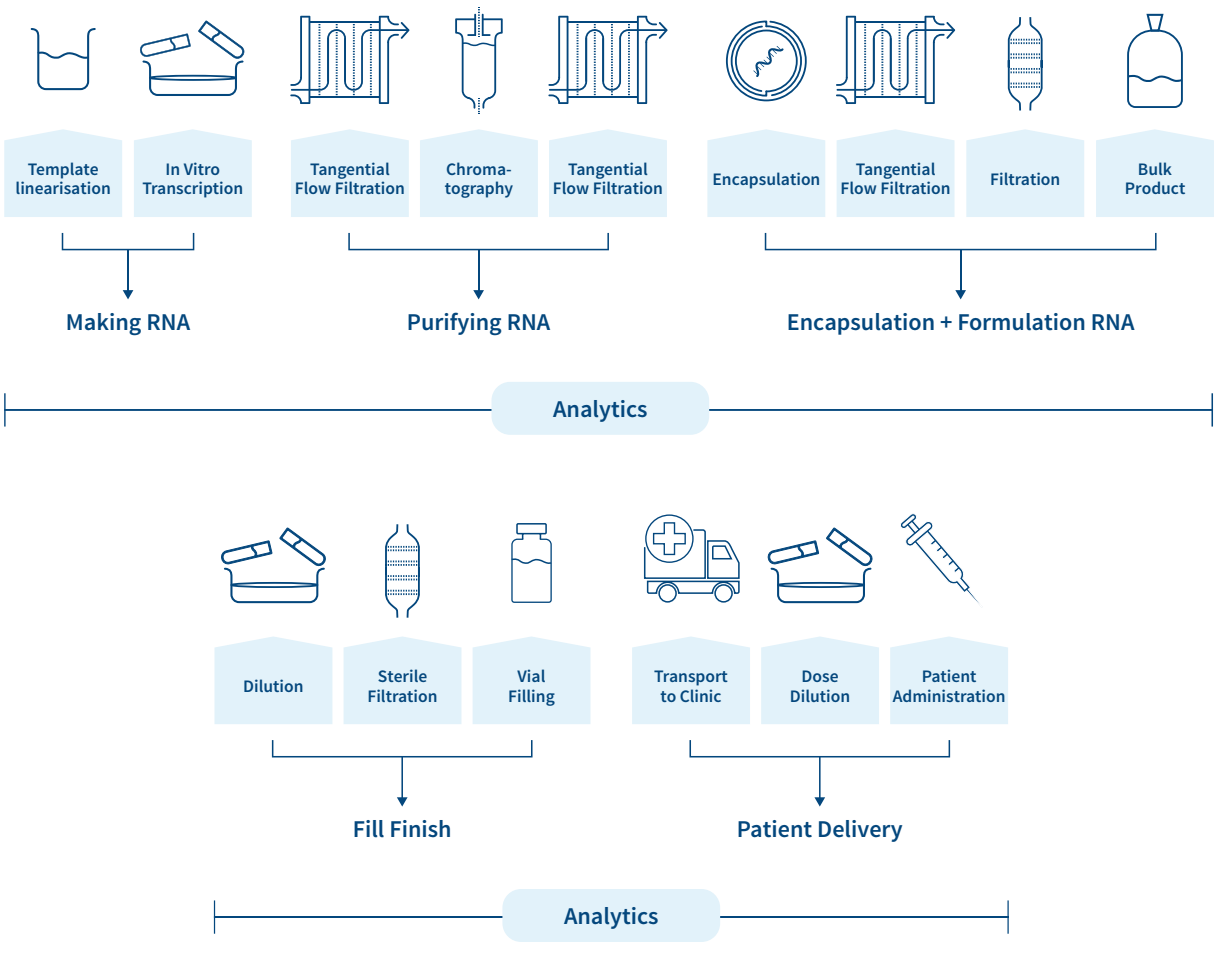
Small manufacturing footprint
Smaller scale equipment needed

Manufacturing mRNA

Manufacturing in mRNA is essential for the development and production of mRNA vaccines and therapeutics. mRNA is a delicate molecule that is easily degraded, so it is important to develop manufacturing processes that are efficient, scalable, and produce high-quality mRNA.

Manufacturing mRNA on a large scale is challenging, but it is essential for meeting the global demand for mRNA vaccines and therapeutics. mRNA vaccines have been shown to be highly effective against COVID-19 and other infectious diseases, and mRNA therapeutics are being investigated for the treatment of a variety of diseases, including cancer, heart disease, and rare genetic disorders.

In terms of costs, the major cost drivers for mRNA therapeutics production are the raw materials. The figure below shows a typical process flow for mRNA manufacture. mRNA synthesis uses cell-free, in vitro transcription (IVT)-based platforms, where a DNA template encoding the desired sequence is transcribed. During the IVT, multiple components are mixed to synthesise mRNA and include the DNA template, a polymerase enzyme to start the synthesis, nucleotides to make the mRNA, and a capping agent and other additional enzymes and buffer components.



Once produced, the mRNA product is purified from the rest of the reaction mixture. The reaction mixture contains not only the desired product but also a number of impurities, which include enzymes, DNA template and any residual buffer components along with any aberrant mRNA that is not single full-length mRNA product. Purification involves the addition of DNase for DNA template removal, chromatography and tangential flow filtration (TFF) steps to remove the other impurities. Following purification, the drug substance requires safe, effective and stable delivery systems that protect it from degradation and allow cellular uptake and release. Therefore, the next step is the encapsulation process whereby the mRNA is packaged into lipid nanoparticles to make the drug product. Analytics run across all these steps to ensure the quality, safety and efficacy of both the drug substance and product. The bulk product is further diluted and sterile filtered before being dispensed into vials. This is referred to as fill and finish. The product is then ready for patient use.

The vials are sent to the clinic where they have a final dilution before patient administration.

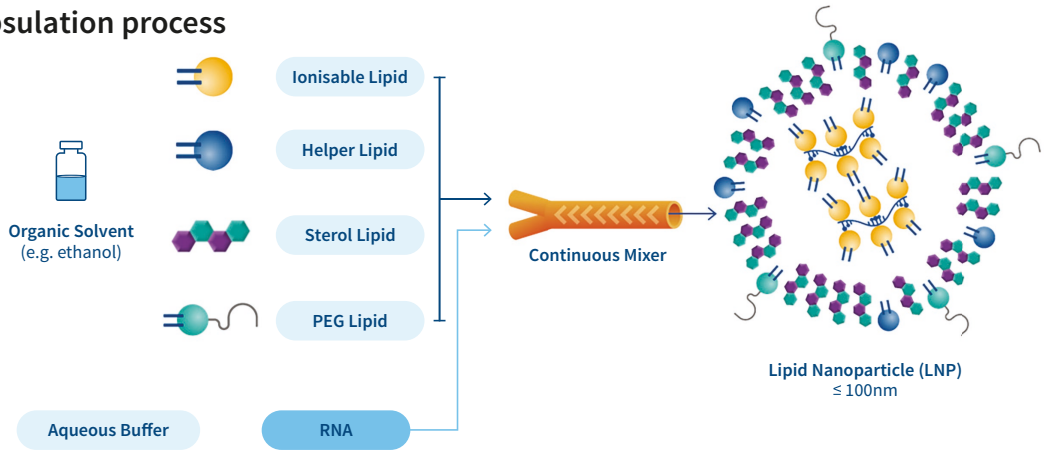
Encapsulating RNA

The main reason for encapsulating mRNA is that naked RNA is degraded by enzymes such as nucleases which are present in the body and the environment and would render the RNA inactive. In addition, RNA cannot easily cross the outer cell membrane, so it needs help to enter cells if it is to be used therapeutically. Many materials can be used to protect and deliver RNA to its desired target, such as polymers and nanoparticle carriers, but one of the most common materials used today are lipids, which are water insoluble fatty materials. They both protect the RNA from degradation and also help it to cross the cell membrane and release it at the right place inside the cell. Typically, the lipids that are used consist of a hydrophilic (water loving) head and two hydrophobic (fatty, therefore oil loving) tails. Once the RNA is encapsulated inside a lipid shell, the resulting complex is known as an RNA-LNP.

A modern RNA-LNP is made up of 5 components. mRNA is negatively charged and so it can be protected and coated by positively charged lipids. This complex is further stabilised by helper and PEG lipids and sterols to form a lipid shell encapsulating the mRNA.

To encapsulate RNA, the lipids are dissolved in an organic solvent, such as ethanol, while the RNA is dissolved in an aqueous buffer. Both solutions are then passed through a continuous mixer where the lipids and RNA self-associate and an RNA-LNP complex is formed which flows out of the other end of the mixer.

Encapsulation process



Landscape

What does funding, skills and innovation in mRNA look like in the UK?

As RNA therapeutics become a focus for many new therapies, there is a need to ensure industry has a robust workforce trained to support this pipeline of new products, both in development and manufacture. Following work with the Vaccine Taskforce, CPI is now home to the largest concentration of RNA manufacturing experts in the UK. This RNA expertise is being shared with the pharma industry through the CPI RNA training academy. This is helping to seed the industry with skills in next-generation RNA technologies, crucial for pandemic preparedness as well as developing other therapies.

The UK is a leading country in the development of mRNA technology. There is a strong foundation of research and development in the UK, and there are several companies that are developing mRNA-based products. In terms of funding, the UK government has provided significant funding for mRNA research. In 2020, the government announced £200 million in funding for mRNA research and development. This funding is being used to support a range of projects, including the development of new mRNA vaccines, the development of mRNA-based treatments for cancer, and the development of new delivery methods for mRNA.

Here are some of the key organisations involved in funding, skills, and innovation in mRNA in the UK:

The Wellcome Trust

The Wellcome Trust is a charitable foundation that supports biomedical research. The Wellcome Trust has funded several projects in mRNA research and development.

The Medical Research Council (MRC)

The MRC is a government agency that funds biomedical research. The MRC has funded several projects in mRNA research and development.

The University of Oxford

The University of Oxford has a strong research base in mRNA technology. The University of Oxford has several research groups working on mRNA technology.

Imperial College London

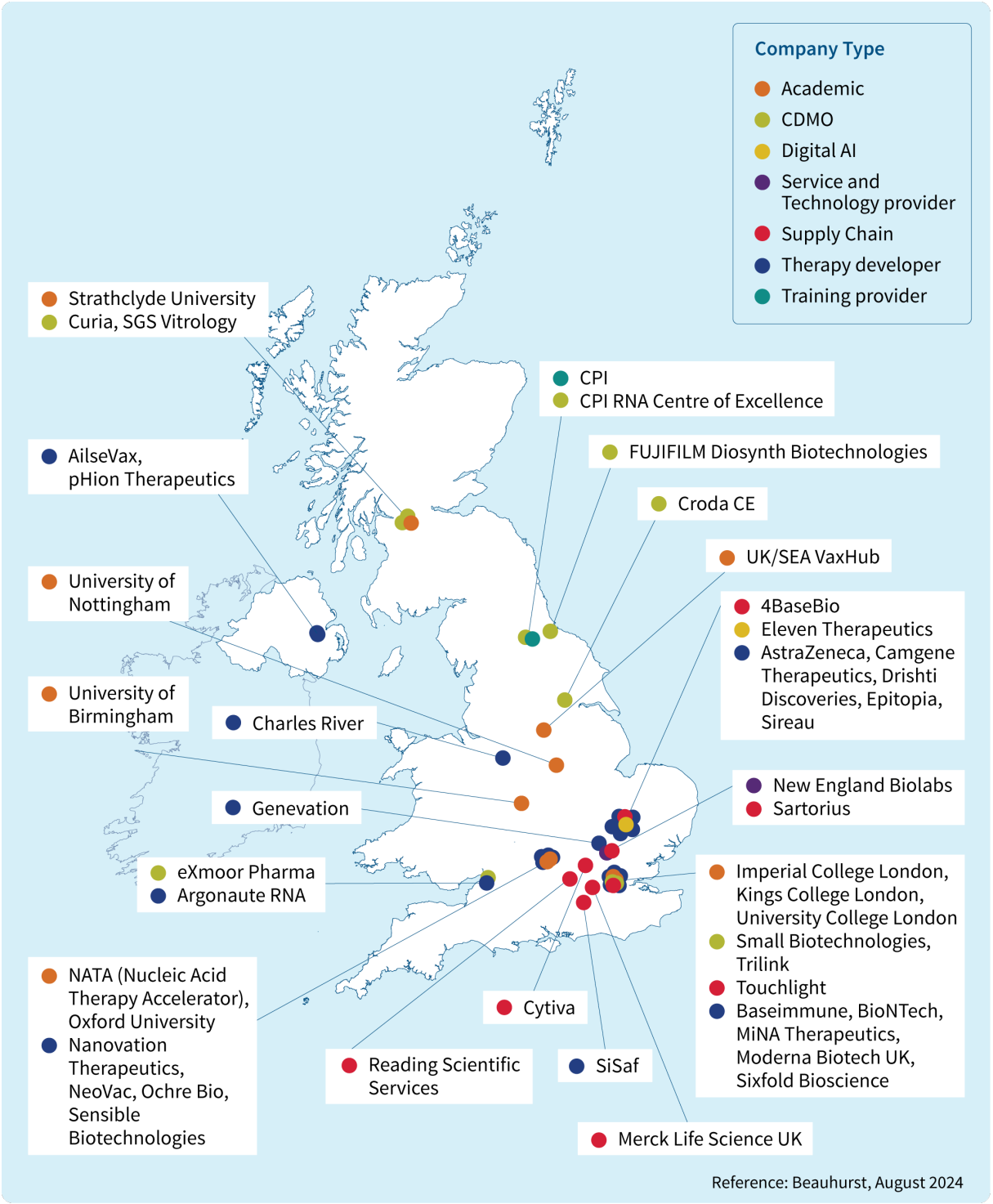
Imperial College London has a strong research base in mRNA technology. Imperial College London has a number ofresearch groups working on mRNA technology.

Innovate UK

Innovate UK is a government agency that provides funding and support for innovation. Innovate UK has a few funding programs that support mRNA research and development.

New

Map of mRNA companies



The UK has emerged as a global leader in the rapidly expanding field of mRNA technology. This map provides a snapshot of the diverse range of companies contributing to the UK's mRNA ecosystem. From pioneering therapy developers to essential supply chain providers, the UK boasts a rich tapestry of organisations at the forefront of this revolutionary field.

This map highlights the geographic distribution of key players across the country, showcasing the UK's commitment to advancing mRNA research, development, and manufacturing. By understanding the breadth and depth of the UK's mRNA landscape, one can appreciate the nation's pivotal role in shaping the future of medicine.

New

Skills

Preparing the UK workforce for an increase in RNA therapeutic manufacturing.



Karen Burgess,
Learning and Development Specialist
CPI

The rise of RNA therapeutics and manufacturing challenges

Due to the speed of development, safety, and broad application, RNA therapeutics are set to have an incredible impact on the treatment of a wide range of infectious diseases.

After rising to prominence in 2020 during the COVID-19 pandemic, they are now potentially able to play a huge role in addressing how we treat life-threatening and contagious diseases. Over the next few years, there is likely to be a significant increase in the manufacturing output of RNA therapeutics.

For the UK to remain at the forefront of this technology and market opportunity, the development of an appropriately skilled workforce is essential.

Workforce Foresighting: A collaborative approach

In response to this challenge, CPI, working with FUJIFILM Diosynth Biotechnologies, have created a workforce foresighting report to highlight the future capabilities and skills required to deliver an intensification of manufacturing of RNA therapeutics.

The report was generated in partnership with The Workforce Foresighting Hub programme, which works with the Catapult Network to convene industry employers, educators, and technology specialists to assess capability needs and identify the skills required to drive future growth.

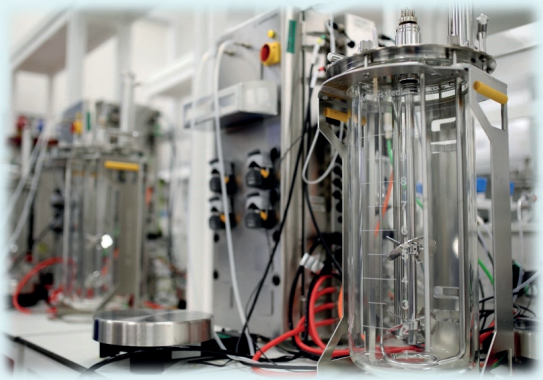
The workforce foresighting process brings together industry experts to establish Future Occupational Profiles (FOPs) which inform what skills will be needed in the future. They are then measured against existing IfATE standards and provision to identify if these standards are suitable to deliver the capabilities required.

Critical skills and capabilities: Report insights and findings

The report found that:

- New capabilities are required within the workforce, to design and develop novel equipment and reagents to increase efficiencies within RNA therapeutics manufacturing. The report also highlights the need to enhance technical and digital capabilities so companies can scale-up manufacturing.

- These capabilities will be delivered through particular roles within the workforce (FOPs) including technician scientist, process leader, automation engineer and development scientists within the supply chain.
- The majority of workforce changes are required within Biopharmaceutical manufacturers and CDMOs. Although the Future Occupational Profiles (FOPs) or roles identified are likely to sit across several parts of the supply chain
- The existing education provision provides a solid foundation for the future skills, however further development is required to deliver an appropriately skilled workforce. To enable this, a collaborative approach between educators and employers is required to prepare the future workforce to allow the UK to fully exploit the potential of this technology.
- Upskilling and reskilling of the current workforce should be considered to meet the demands of emerging technologies in the short term.





Building a future-proof workforce

The report urges the industry to plan for the future roles, novel equipment, and capabilities needed to develop and deliver innovative treatments and medicines. Then establish partnerships with education institutions to develop and implement appropriate education and training provision to help address the skills gap.

Without a skilled workforce to fully exploit the intensification of RNA therapeutic manufacturing, there is a risk of deterring inward investment and consequently making it harder for the UK to compete on a global scale.

CPI working in partnership with FUJIFILM Diosynth Biotechnologies and the BIA have convened a working group to translate the report recommendations into action.

Any interested parties who would like to join this collaboration or find out more about how Workforce Foresighting can help their industry should contact learning.development@uk-cpi.com

Discover more

To understand more about the unique challenge of the intensification of RNA therapeutics manufacturing, and what CPI can do to address this challenge, you can read the report.

Innovate UK case study

What is the role of Innovate UK in supporting the development of mRNA manufacturing in the UK?

Innovate UK is the UK government's innovation agency supporting business-led innovation across all sectors, all technologies and across the UK regions. Innovate UK are a key delivery body of the government's innovation strategy. The life sciences vision identifies a number of areas where the UK government would like to see UK development and manufacturing strengths grow to tackle various healthcare priorities. One of those areas is mRNA manufacturing. Innovate UK's role is to stimulate the development of innovative manufacturing technologies in the broadest sense that will enable the UK to grow a strong if not world-leading position in mRNA therapeutics manufacturing.

Why have Innovate UK made this a funding priority?

As part of the Transforming Medicines Manufacturing Programme, which is the current Innovate UK programme for supporting the new medicines manufacturing sector in the UK, they have run three competitions to cover the broad remit of RNA therapeutic manufacturing innovation.

The origin of those competitions goes back to an agreement between Novartis and the Department of Health around inclisiran, which is an oligonucleotide therapy for high cholesterol. This therapy is an alternative to statins and offers the benefits of being an injection taken twice a year rather than a tablet taken daily. It has the potential to save significant cost in the NHS by reducing the number of deaths related to heart disease associated with high cholesterol.

Currently those types of therapies cannot be manufactured effectively at large scale, certainly not sustainably at large scale with the established process. With a number of company pipelines looking increasingly at RNA therapeutics and mRNA therapeutics in particular, Innovate UK saw a growing need and, through the Medicines Manufacturing Challenge Fund, supported a project to look at a next generation manufacturing process for oligonucleotides.

Through COVID-19, where mRNA vaccines came to the fore and the UK had a very successful programme in the development of the Oxford AstraZeneca vaccine there was a recognition that it would be valuable to invest in parallel in technologies enabling mRNA process development, therapeutics development, vaccines development and delivery technology development.

Innovate UK realised that for the UK to adopt this world-leading position, much could be learnt from the Cell and Gene Therapy Catapult (CGTC) in terms of the position that has provided Innovate UK in cell and gene therapy expertise. This would be a good opportunity to start to make investments and adopt a leading position in mRNA type technologies as well, for global benefit, but developing manufacturing capability and expertise in the UK.

What grants have already been awarded?

CPI's Intracellular Drug Delivery Centre will help predict the stability, efficacy, performance and any potential adverse reactions of RNA vaccines and therapeutics. This will help unlock the potential of RNA-based medicines, creating greater access to cost-effective vaccines and therapeutics. This is a £10 million investment over three years.

Innovate UK have funded projects that are focused on a broad section of RNA therapeutics and vaccines including a number of mRNA technologies but also other RNA and oligonucleotide based technologies.

Case studies

Moderna case study

What does the company do?

Moderna creates medicines that aim to deliver the greatest possible impact to people by using mRNA technology. The COVID-19 pandemic proved that mRNA was the fastest route to developing highly effective vaccines and since 2010, Moderna have been using this technology to develop and test a wide range of medicines that span a variety of therapeutic areas, such as infectious diseases, immuno-oncology and rare diseases. The speed, scale and flexibility of mRNA allows us to accelerate the discovery of new medicines, and get them to those who need them, faster.

Tell us about Government facilities in the UK and supplier agreement.

The strategic partnership between Moderna and the UK Government, signed in December 2022, will boost the country's research and development capabilities with the construction of the Moderna Innovation and Technology Centre (MITC) in Harwell, Oxfordshire. This state-of-the-art R&D and manufacturing centre will be at the heart of the partnership to develop and manufacture innovative vaccines for respiratory diseases. Production capacity at the centre can be scaled up in the event of a pandemic, offering the potential to develop up to 250 million vaccines per year, thus massively enhancing the UK's ability to cope with and respond to future public health threats.

Why set up in the UK?

Moderna is excited to be making a significant investment in the UK and is working together with a range of partners, to support the UK to unleash its full potential and cement itself as a life sciences superpower. Thanks to the UK's thriving biomedical sector, Moderna believes that it is an excellent location to carry out research and development. Moderna are looking forward to working with leading scientists on the next generation of treatments and are committed to upstream collaboration, co-creating with partners, staying attentive to their needs, and maintaining a seamless partnership in clinical research.

The work Moderna are doing in the UK would not be possible without the UK Government who recognise the importance and value of life sciences, the efforts of the NHS, world-leading scientific research institutions, a progressive regulator in the form of the MHRA (Medicines and Healthcare Products Regulatory Agency) and many others. Moderna have already built close relationships with Merit, for example, a construction specialist based in Cramlington, Northumberland who are partnering

with Moderna to develop a biomarker lab that will form part of the MITC. They are onshoring their supply chain in the UK as much as possible and look forward to more partnerships in the coming years.

What are the challenges?

The strategic partnership will operate at the intersection of the public and private sector and its success will hinge on the seamless collaboration between numerous partners, each bringing unique expertise and perspectives.

The skills shortage in the life sciences sector poses a challenge, particularly given the specialised nature of mRNA technology. However, this also presents a unique opportunity for Moderna to invest in the development of the UK's talent pool, fostering the next generation of a highly skilled workforce.

The scale and complexity of Moderna's pipeline of clinical trials will also demand careful planning with system partners. Moderna are committed to working with the UK Government to implement the recommendations of Lord O'Shaughnessy's report on commercial clinical trials and to create a more innovative, inclusive, and digitally enabled clinical trial ecosystem.

UK-MRNA-2300072 Date of preparation: August 2023

SiSaf case study

What does the company do?

SiSaf is an RNA delivery and therapeutics company. Its proprietary Bio-Courier® technology addresses the limitations of other nucleic acid delivery technologies through the hybridisation of organic materials with inorganic bioabsorbable silicon. The company's business model is to maximise the potential of its technology by licensing to industry partners and by developing an in-house pipeline of RNA therapeutics. SiSaf's most advanced programmes are RNA treatments for rare genetic disorders, but the company has the strategic ambition to expand its focus to other therapeutic areas, including oncology.

How does the technology work?

Lipid nanoparticles (LNP) have become the standard delivery system for mRNA. Bio-Courier® silicon stabilised lipid nanoparticles (sshLNP) are the next generation of lipid nanoparticles combining organic material – lipids – with inorganic material – bioabsorbable silicon. The silicon matrix stabilises both the lipid components and the RNA payload, reducing the need for ionisable or cationic lipids, PEGylated lipids, and cholesterol. This improves safety, targeting, and transfection. Unlike conventional lipid nanoparticles, sshLNP can be manufactured empty and loaded with the RNA later, at the desired point and time of use.

How is this an improvement on existing delivery technologies?

The stabilisation of both lipid components and RNA payload through silicon, as well as the ability to manufacture the carrier without RNA, overcome the key limitations of conventional LNP delivery systems for nucleic acid.

In conventional LNPs, the nucleic acid payload must be introduced early in the production process during the initial formation of LNPs prior to subsequent purification and fill/finish steps. This restricts batch sizes in commercial manufacturing due to the chemical lability of RNA, it affects the quality of the product that ultimately reaches the patient, and requires an ultra-cold chain for storage and shipping. In Bio-Courier sshLNPs, the nucleic acid can be introduced after the manufacture of the sshLNP particles. As a result, RNA encapsulation and fill/finish operations can be separated from carrier manufacture by considerable time and distance, readily permitting on-demand preparation of customised RNA-loaded LNPs on any scale.

In addition, Bio-Courier technology offers significant advantages over conventional LNP technology regarding stability, safety, targeting, and transfection.

Stability

The use of the positively charged silicon matrix to bind and stabilise the RNA payload reduces the need for cationic/ionisable lipids, avoiding the risk of premature leakage of RNA from the nanoparticles as the positive charge from the lipids decays. The improved physical stability also translates into improved transfection efficiency.

Safety

Existing approved LNPs rely on PEGylated lipids to protect RNA against enzymatic degradation, however, PEGylated lipids can induce anti-PEG antibodies and provoke an immune response. Due to their silicon-stabilised design, Bio-Courier sshLNPs are less reliant on PEGylated lipids than conventional LNPs, to the extent that some formulations are entirely free of PEGylation.

Targeting

LNPs have a strong tendency to accumulate in the liver. Biodistribution studies with Bio-Courier sshLNPs have demonstrated minimal accumulation in the liver and Bio-Courier formulations can be customised to provide controlled release and targeting of specific cells and tissues.

What are the challenges?

Opportunities for RNA medicines have advanced hugely in recent years. That being said, RNA remains a new modality with all of the associated development, manufacturing and regulatory challenges. SiSaf believe delivery technology helps move the field forward positively.

The patent landscape in RNA therapeutics including delivery platforms is complicated. However, SiSaf are confident of the strength of our IP (Intellectual Property) portfolio and both our freedom to operate and our ability to license our technology to others.

As a small but ambitious company, SiSaf needs to focus its resources on demonstrating the power of its technology and to attract external partnerships and investment to progress clinical programmes. We are proud that our lead programme SIS-101-ADO, an siRNA therapeutic for patients with Autosomal Dominant Osteopetrosis Type 2 (ADO2), has been granted both Orphan Drug Designation and Rare Pediatric Disease Designation by the U.S. FDA (Food and Drug Administration). There are currently no approved treatments for Osteopetrosis ADO2 and no other treatments currently in clinical trials. If approved, SiSaf's SIS-101-ADO would thus be the first treatment for Osteopetrosis ADO2 and could provide life-altering benefits for those who suffer from this debilitating disease. Their fast follower programme, SIS-102-ACH, would offer the first treatment of Achondroplasia that targets the genetic root cause of the condition. SiSaf also have partnered programmes to treat Type II Corneal Dystrophy and an undisclosed programme using Bio-Courier for topical delivery.
SiSaf have raised significant funding to date. They are committed to take their lead programmes through early clinical development, and thus anticipate a series C in due course.

SiSaf have raised significant funding to date. They are committed to take their lead programmes through early clinical development, and thus anticipate a series C in due course.



RNA-based medicines are an incredibly exciting and promising new field of drug development. But the inherent instability of RNA means that delivery systems are key to the success or failure of RNA drugs.

Dr Suzanne Saffie-Siebert, Founder and CEO, SiSaf Ltd
Inventor of Bio-Courier® technology

At SiSaf, we have been developing and optimising Bio-Courier technology for 15 years. We have generated a large body of in vitro and in vivo data that show the safety and efficacy of our technology and we have created a strong IP portfolio that gives us extensive freedom to operate. I believe our innovative technology can play a key role in translating RNA-based medicines into clinical reality on a global scale."

CPI case study

What does the company do?

CPI is a technology innovation catalyst. They catalyse the adoption of advanced technologies and manufacturing solutions that benefit people, places and planet. CPI is a social enterprise, partnering with industry, academia, government and the investment community to deliver healthcare and sustainability innovations.

Within pharmaceuticals, CPI offer world-leading facilities and expertise in small molecules, biologics, oligonucleotides, and complex medicines to accelerate drug development and scale-up. They host the largest pool of RNA biomanufacturing experts in the UK and offer complementary drug delivery systems like lipid nanoparticles.

CPI supported the UK Vaccines Task Force's COVID-19 response with their world-leading expertise in the development of mRNA vaccines, working with partners such as Imperial College London to support the drive to develop, scale up, manufacture and supply vaccine candidates.

As part of this, CPI developed and built a new facility, The RNA Centre of Excellence, next to their National Biologics Manufacturing Centre in Darlington. This was designed to be a key part of the ongoing battle against COVID-19, a place where they could develop multiple vaccine candidates, ready to be rapidly manufactured in response to new variants.

What were the challenges you were seeing for RNA therapeutic manufacturers and how are you helping to address some of these?

Access to mRNA-LNP R&D and GMP manufacturing expertise with the people and facilities in a single location to support early-stage product development is a challenge for SME's and academics developing breakthrough medicines in this space.

Post-pandemic, as life starts to return to normal, CPI now has a multi-million-pound facility, one of the largest pools of RNA knowledge in the UK, and the equipment needed to deliver this new technology.

Now known as the RNA Centre of Excellence, we have a facility that forms the backbone of the UK's innovation infrastructure in RNA vaccines and therapies. This is the only open-access UK-based centre currently able to develop and manufacture lipid nanoparticle encapsulated messenger and self-amplifying RNA vaccines and therapies ready for use in early-phase clinical trials. It is this legacy that can be exploited in many ways for the benefit of people around the world.

How does RNA work?

Essentially the principle of mRNA vaccines is, that by providing the gene of a pathogenic protein, the antigen if you like, in the form of messenger RNA to human cells, the cells themselves can then synthesise that antigenic protein to generate the immune response that protects the individual from the actual pathogen.

The antigenic protein is then released or is both displayed on the surface cell and acts as the antigen to stimulate the immune response and provide the vaccination and the protective effect.

So, mRNA vaccines work not by injecting the antigen itself, but by supplying the mRNA that codes for the antigen allowing the cells to do the hard work of making it themselves.

How will RNA be used?

There are several key drivers for that explosion of activity and interest in RNA vaccines.

- Firstly, it is that they can be produced very quickly, so ideal for healthcare emergencies. They are also easy to make in high yields using platform processes. This means we can do a rapid response and respond to new or mutating viruses.
- We use the body to create the antigen itself so very small doses are required of mRNA compared to other vaccines.
- The relatively low immunogenicity as no viral vector to elicit an immune response.
- RNA vaccines do their work in the cytoplasm so there is no need for them to enter the nucleus like DNA vaccines. This also means that they are non-integrating; so they will not be integrated into the host genome; so there is no risk of infection or mutagenesis. RNA will be degraded by the normal cellular processes in cytoplasm so there is no long-lasting effects.
- Finally, variation in structure and delivery methods chosen can impact the half-life of mRNA which might be important for specific indications.

In summary there a lot of good reasons why people are considering mRNA as a treatment modality.

What are the challenges?

Companies are facing challenges around:

- Joined up manufacturing of mRNA vaccines in a single location – including mRNA production but also the lipid nanoparticle encapsulation.
- Access to GMP manufacturing for clinical trial evaluation – at the right scale (often small scale) and at fast pace.
- Access to R&D expertise to evaluate, develop, scale-up, and fully develop commercial processes for mRNA-LNP products.
- Access to R&D expertise for biophysical and biochemical characterisation and quality control of mRNA-LNP products.
- Access to a trained and experienced workforce that can work in both the R&D and GMP manufacturing environments.

eXmoor case study

What does the company do?

eXmoor is a one-stop cell and gene therapy CDMO (contract development and manufacturing organisation), accelerating the manufacturing journey from research to patients. The company has grown over the last 19 years from supporting clients through consultancy for capital and technical projects and now offers in-house process development and GMP manufacturing. Phase 1 of eXmoor's new purpose-built 65,000 ft2 facility includes four clean rooms, a fill and finish suite and a range of laboratories for process development, analytical development and quality control.



In August 2023 eXmoor formed a global partnership with Kincell Bio, a US-based CDMO that seamlessly brings together both companies' capabilities, giving customers the opportunity to access a global development and manufacturing footprint in combination with a boutique customer-focused offering.

How will RNA be used?

The COVID-19 pandemic highlighted the significant benefits of mRNA-based vaccines, helping to accelerate the applications of this technology beyond just infectious diseases to other areas such as enzyme replacement and oncology. This has resulted in increased demand for mRNA manufacturing capacity.

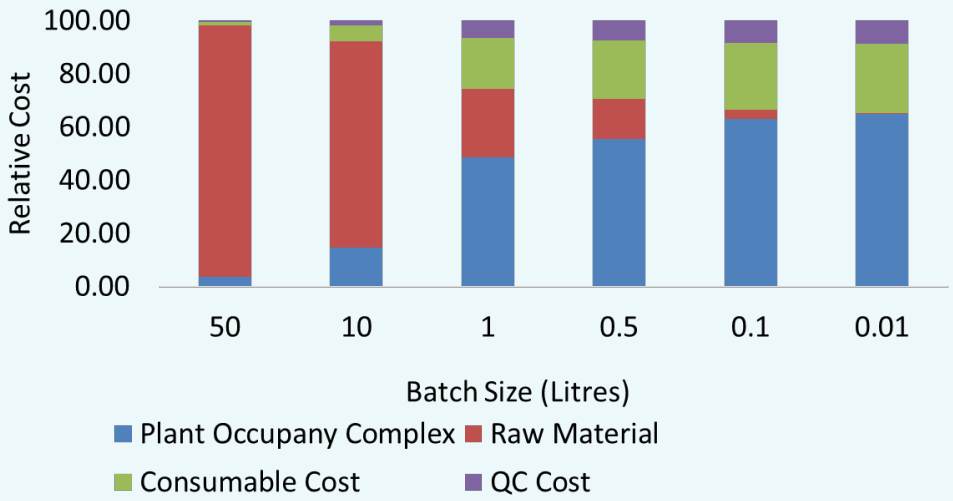
What are the challenges?

mRNA manufacture has unique challenges, and some learning is better transferred from skills developed in cell and gene therapy manufacture rather than classic biologics. eXmoor is uniquely positioned to help with additional capacity and specialist expertise.

Normally, as the scale of a biomanufacturing process increases the price per dose is reduced. But with RNA, driven by the high raw material costs, scale-up results in

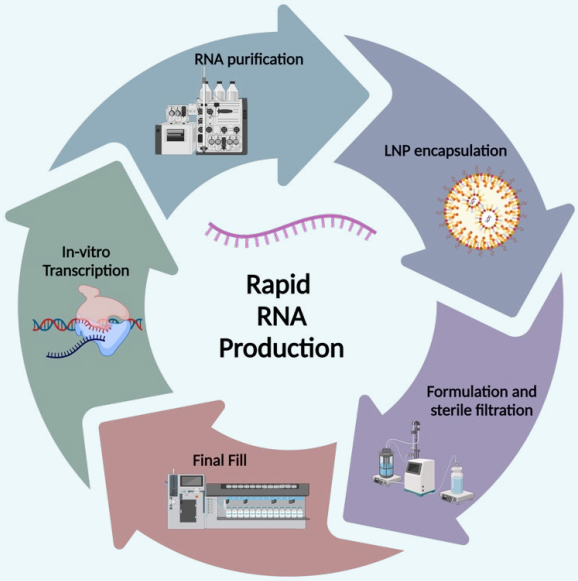
significant financial risk but only a limited reduction in the price per dose. Vaccine manufacture requires larger batch sizes so process development is likely to focus on efficient use and cost reduction of raw material, as this will have the biggest impact on the price per dose. But not all applications of mRNA need large-scale manufacture and are more sensitive to price per batch than price per dose.

The high raw material cost used to manufacture mRNA significantly impacts the distribution of costs when working at larger IVT volume as shown below.



What does the future look like for eXmoor?

To support the additional mRNA manufacturing requirements, eXmoor is expanding its portfolio to include an end-to-end service for the manufacture of early-stage mRNA products and therapeutics focusing on flexible scale, rapid turn around and responsive material supply.



eXmoor's approach is designed to meet the needs of customers requiring smaller batch sizes and will target IVT scales of up to 0.5l.

Touchlight case study

What does the company do?

Touchlight is a UK-based contract development and manufacturing organisation (CDMO) and has developed a novel, enzymatically produced DNA vector, known as doggybone DNA or dbDNA™, which is disrupting the decades-old technology of fermentation-based DNA manufacture. With Touchlight's established low-footprint manufacturing facilities, they produce GMP-grade DNA API and starting materials for viral therapies and RNA therapeutics from the milligram to multigram scale. Extensive investment in facilities has positioned Touchlight as one of the world's largest DNA manufacturers by capacity, making Touchlight the ideal provider to meet the demands of the rapidly growing advanced therapy market.

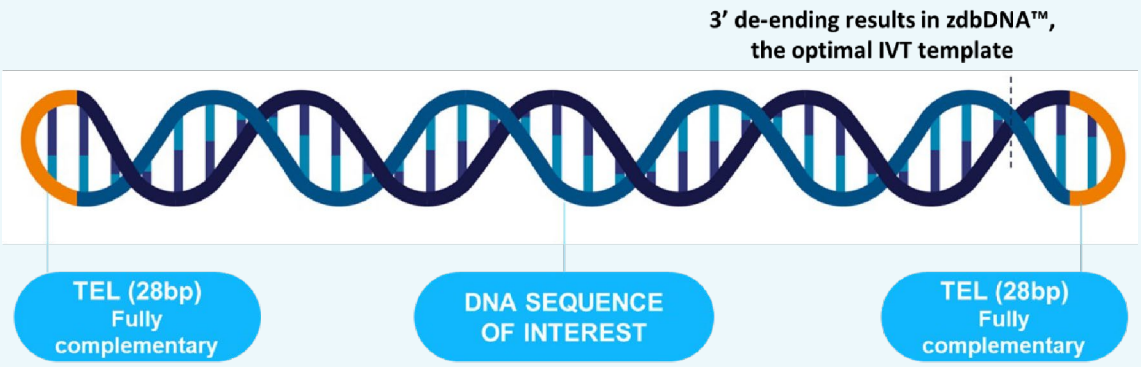
From discovery to GMP, they can offer up to 5 g dbDNA™ per batch in 5 to 6 weeks. Today, dbDNA™ is being implemented by Touchlight's clients across the genetic medicine spectrum. Within the mRNA space, dbDNA is being used as a critical starting material in multiple clinical trials in the UK.

How does the technology work?

dbDNA™ is an enzymatically produced, linear, double stranded and covalently closed minimal DNA vector with no bacterial backbone sequences, and no origins of replication or antibiotic resistance genes. dbDNA™ is first amplified from minute amounts of DNA template by the high-fidelity Phi29 polymerase. The resulting concatemers are linearised and covalently closed at the ends by a proprietary TelN mediated procedure, allowing for removal of backbone and accessory sequences through concerted action of sequence-specific endonuclease and exonuclease. The dbDNA™ is then purified applying state-of-the-art chromatography and filtration methods and controlled for safety and purity before release with established quality control methods (QC). dbDNA™ can encode long, complex, and unstable DNA sequences such as structured regions, repeats or homopolymer stretches like polyA, which otherwise would cause toxicity in *E. coli* cultures, and rendering unpredictability to fermentation-based DNA manufacture.

How is dbDNA used for RNA manufacture?

De-ending dbDNA™ through restriction digestion results in zdbDNA™, which acts as starting material for run-off *in vitro* transcription (IVT). The minimal sequence and its enzymatic manufacturing enable consistent production of large quantities of highly pure sequences with the dbDNA™ technology. Together with the potential to use lower template amounts in IVT, dbDNA™ constitutes an optimal starting material for GMP manufacturing of diverse RNA modalities.



What does the future look like for eXmoor?

The recent pandemic has highlighted the need for rapid, scalable, and seamlessly transferable vaccine production. Although RNA vaccines have demonstrated potential to combat unprecedented infectious disease, rapid provision of clinical trial material, and subsequent commercial supply and resupply remain challenging. A critical bottleneck for rapid onset of clinical trials as well as for resilient supply of commercial RNA products is the production of plasmid DNA, which often fails to provide the starting material for manufacture of mRNA and the rising self-amplifying or circular RNA modalities reproducibly and consistently. Touchlight is alleviating that bottleneck through enzymatic production of dbDNA™, and delivers at unparalleled speed, reproducibility, scale, and purity. Touchlight relies on a highly skilled and experienced team of RnD, GMP, QC, regulatory and commercial experts to support customer-specific demands and to enable on-time provision of high-quality templates for diverse RNA modalities.

New

New England Biolabs case study

What does the company do?

Founded in 1974, New England Biolabs (NEB) is a leading company developing and manufacturing enzymes and reagents for life sciences research. They specialise in products crucial for mRNA production, offering solutions for both research and commercial-scale manufacturing. Their offerings span the entire workflow, ensuring consistent high-quality mRNA at all stages.

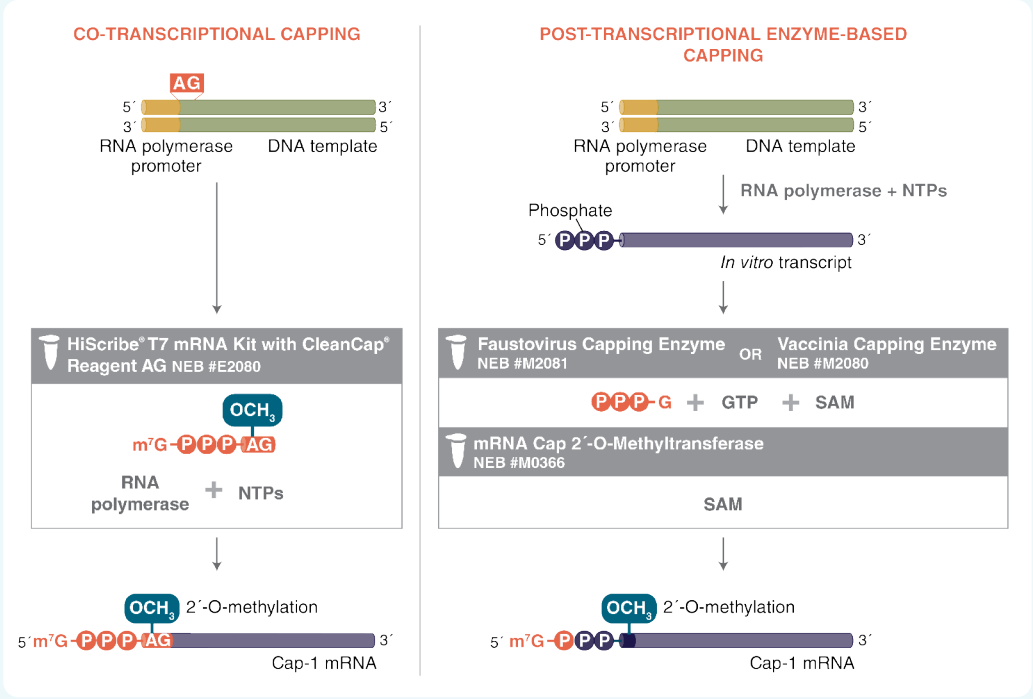
How does NEB's technology work?

NEB provides a comprehensive suite of enzymes and kits for in-vitro transcription (IVT), the process of creating mRNA from a DNA template. Their products include:

- T7 RNA polymerase: The workhorse enzyme for mRNA synthesis.
- NTPs: Building blocks for constructing the mRNA molecule.
- DNAse I: Eliminates the DNA template after transcription.

- Murine RNase inhibitor: Protects newly synthesised mRNA from degradation.
- Capping enzymes: Add a crucial modification (cap) to the mRNA for stability and translation efficiency.
- mRNA Cap 2'-O-Methyltransferase: Further refines the cap structure for optimal function.
- Restriction enzymes (optional): Linearize plasmids for efficient IVT.

NEB offers both research-use-only and GMP-grade enzymes, catering to various development stages. Additionally, they provide large-scale production capabilities to meet the growing demand for mRNA therapeutics.



What are the challenges?

NEB understands the challenges of scaling up mRNA production. They've addressed this by:

- Investing in infrastructure: Increased fermentation capacity allows them to produce enzymes in bulk quantities.
- Early client engagement: Working with clients early on ensures a smooth transition from research to large-scale manufacturing.
- Diverse product formats: Offering enzymes in various sizes caters to different research and production needs.

NEB emphasises the importance of choosing a reliable raw material supplier for mRNA production. They highlight their strengths in this area:

- Quality management: Certified facilities and rigorous quality control processes ensure consistent product performance.

- Technical expertise: NEB scientists are well-versed in mRNA workflows and can provide valuable support.
- Transparency: NEB encourages client visits to their facilities and welcomes audits, demonstrating confidence in their manufacturing practices.
- Future-proof compliance: NEB actively monitors regulatory changes and ensures their products remain compliant.

Questions therapy developers and manufacturers should ask their suppliers

In addition to the points mentioned above, here are some key questions therapy developers and manufacturers should ask their raw material suppliers:

- Can the supplier guarantee consistent batch-to-batch performance of their enzymes and reagents?
- Does the supplier offer a wide range of products to support the entire mRNA production workflow?
- Can the supplier scale up production to meet the demands of commercial-scale manufacturing?
- Does the supplier have a proven track record of supplying high-quality products to the mRNA therapeutics industry?
- Is the supplier willing to collaborate with clients to develop custom solutions?
- Does the supplier offer technical support to help clients troubleshoot issues?

By considering these questions, therapy developers and manufacturers can select a reliable raw material supplier that can help them bring their mRNA therapies to market.



What does the future look like for NEB?

NEB is committed to supporting the advancement of mRNA technology. Their focus areas include:

- Developing new enzymes and reagents: Continuously improving tools for mRNA production.
- Personalised medicine: Providing solutions for small-scale batches tailored to specific needs.
- Workflow simplification: Streamlining processes to save time and resources for researchers.
- Lyophilisation technology: Offering enzymes and mixes stable at ambient temperature, simplifying logistics.

NEB is well-positioned to play a key role in the ongoing mRNA revolution by providing scientists with the tools and expertise needed to develop next-generation therapies.

Note: The branding term “GMP-grade” has been clarified to avoid confusion with official GMP regulations.



New

TriLink case study

TriLink BIOTECHNOLOGIES
part of Maravai LifeSciences



It is my great pleasure to provide a foreword to the introduction of TriLink Biotechnologies. As a proud Scot/Brit who received my degree and PhD from the University of Glasgow prior to moving to the States, the critical work that BIA does to connect developers in the US with innovation in the UK is vital.

Kate Broderick, Chief Innovation Officer, TriLink

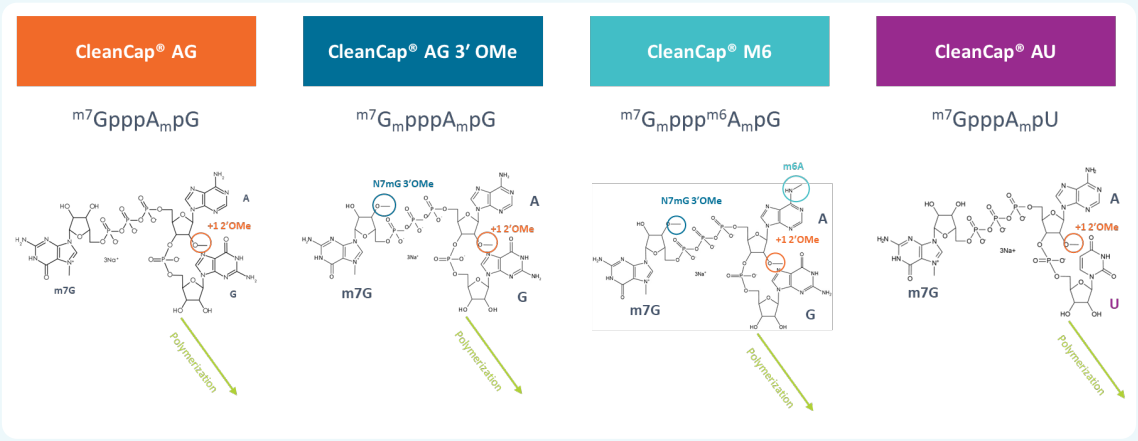
At TriLink, we believe that the future is RNA. The remarkable efficacy of the approved COVID-19 mRNA-based vaccines was only the start of the RNA-based medicine revolution. As an innovative CDMO, TriLink is honoured to support RNA developers as they bring their paradigm-shirting therapeutics and vaccines to patients. Our 20+ years of experience in the RNA field allow us to provide world-class expertise in the products and services critical for nucleic acid breakthroughs."

What does the company do?

TriLink BioTechnologies, part of Maravai LifeSciences, is a contract development and manufacturing organisation (CDMO) for the synthesis of nucleic acids, nucleotide triphosphates (NTPs), and mRNA capping analogs. TriLink has scale-up expertise and unique mRNA, oligonucleotide & template sourcing capabilities for companies focused on therapeutic, vaccine, diagnostic and biopharmaceutical breakthroughs. TriLink has been working in mRNA for over 20 years and was one of the first to provide GMP mRNA manufacturing. To date, TriLink has generated over 100 batches of GMP mRNA to be used in clinical trials. Our CleanCap® technology is in three of the four approved COVID-19 vaccines being used globally today. It was included in the capping technology used in the Pfizer BioNTech COVID-19 vaccine.

How does the technology work?

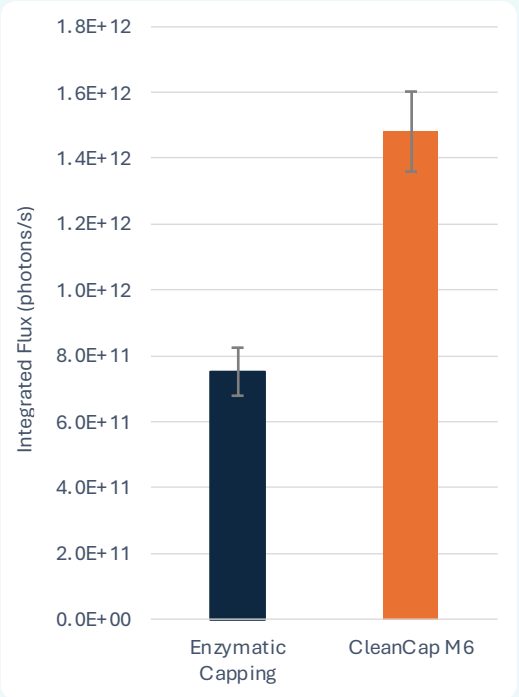
mRNA capping plays a critical role in the success of mRNA vaccines and therapeutics. The cap is a specialised structure placed at the beginning of the mRNA molecule that acts to prevent premature degradation, avoids triggering an unwanted immune response and ensures the mRNA reaches its intended destination and generates the desired protein product. CleanCap® mRNA capping technology offers a streamlined approach as the capping and mRNA synthesis occur in one step, referred to as co-transcriptional capping. The analog is extended by the RNA polymerase during In Vitro Transcription (IVT), enabling high capping efficiency of >95% in a one-pot reaction. Crude mRNA from the co-transcriptional CleanCap® reactions can be purified by industry standard methods including oligo dT affinity chromatography.



CleanCap® AG, AG 3′ OMe, M6, and CleanCap® AU reagents are shown above. All cap analogs result in Cap1 mRNA, the most abundant cap structure in eukaryotic cells. CleanCap® AU was developed for self-amplifying RNA to maintain the natural 5' UTR sequence of alphavirus vectors used in this technology, while the AG series of CleanCaps® are available for traditional linear mRNA. The +1 base, or what becomes the first base in the transcribed mRNA is an A, and the second base is a G (for 3 of the 4 analogs) for use on matched DNA templates. The +2 base is an important part of the cap analog as this allows for RNA polymerase extension from the 3' hydroxyl position of the unmodified ribose.

What advantages does CleanCap® technology offer?

There are different approaches to capping. Clean cap uses co-transcriptional capping as discussed above, whereas enzymatic capping utilises enzymes to add the cap after the mRNA has been made, resulting in more hands-on time to produce final desired mRNA. The CleanCap® M6 reagent is the newest cap analog available from TriLink. CleanCap® M6 offers a modified Cap 1 structure that is currently only achievable through cap analogs. The protein expression levels of M6 capped mRNA can be measured using an mRNA that encodes for a bioluminescent protein that emits light. The luciferase activity correlates with protein expression levels. The luciferase mRNA capped by the CleanCap® M6 reagent outperforms enzymatically capped Cap1 luciferase mRNA in mice as shown below. With the increased potency offered by this latest cap analog it may be possible to decrease mRNA doses in certain therapeutic applications.



*Performance of FLuc mRNA in an LNP-formulated, 1 mg/kg by tail vein delivery into mice. Luciferase activity (photons per second) was measured after luciferin injection from 3-48h for total AUC graphed here. *** p < 0.001, two-tailed T test. Error bars are standard error of mean. n = 9/group.*

How does TriLink support the community?

TriLink, through Maravai, is a member of the Alliance for mRNA Medicines (AMM), an organisation dedicated to advancing and advocating for mRNA and next-generation encoding RNA therapeutics and vaccines for the benefit of patients, public health, and society. AMM's mission is to propel the future of mRNA medicine, improve patients' lives, and advance scientific knowledge by convening and empowering mRNA industry leaders, innovators, scientists, and other key stakeholders.

TriLink has supported countless custom development and R&D collaboration projects. For example, during the height of the COVID-19 pandemic in 2020 the TriLink team pivoted resources to support a critical troubleshooting project for the manufacturing process of Imperial College London's saRNA vaccine prior to a tech transfer back to the UK. Additionally, the Science and Innovation Office led by Dr. Kate Broderick is always available to discuss novel academic collaborations (scan QR code if interested).

Conclusion

New

The BIA is committed to fostering a thriving mRNA ecosystem in the UK. To achieve this, we will:

- Provide a platform for companies to showcase their technologies more broadly, and explain the potential to investors and policymakers.
- Develop a community and provide networking opportunities for companies to meet with each other as well as policymakers, investors, and other stakeholders.
- Advocate for a supportive financial and regulatory environment to enable companies developing mRNA technologies to start and grow in the UK.
- With the community, identify and address challenges to the growth of the sector in the UK.
- Investigate and advance understanding of RNA regulation mechanisms to support the development of more effective mRNA-based therapies.

By taking these steps, the BIA aims to accelerate the development and availability of mRNA-based products, solidify the UK's position as a global leader in mRNA research, and ensure that patients worldwide benefit from these innovative treatments.

Find out more about the mRNA community

About BIA

The BioIndustry Association (BIA) is the voice of the innovative life sciences and biotech industry, enabling and connecting the UK ecosystem so that businesses can start, grow and deliver world-changing innovation. We are an award-winning trade association representing more than 600 member companies including:

- Start-ups, biotechnology and innovative life science companies
- Pharmaceutical and technological companies
- Universities, research centres, tech transfer offices, incubators and accelerators
- A wide range of life science service providers: investors, lawyers, IP consultants and IR agencies

Learn more at bioindustry.org

Our supporters

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About Centre for Process Innovation (CPI)

CPI's open innovation model enables clients to develop products and prove processes with minimal risk. They provide assets and expertise so their customers can demonstrate the process and prove it is feasible before investing substantial amounts of money in capital equipment and training. New products and processes can be proven; on paper, in the lab and in the plant before being manufactured at an industrial scale.

By utilising CPI's proven assets and expertise companies can take their products and processes to market faster. There is no down time in production as all of the process development is completed offsite and the technology transfer teams can help to transfer the product or process into full scale production.

www.uk-cpi.com

About Cytiva

Cytiva, a global provider of technologies and services that help advance and accelerate the development and manufacture of therapeutics. Previously GE Healthcare Life Sciences, Cytiva has nearly 7,000 employees and operations in 40 countries and is part of the Danaher Corporation Life Sciences platform.

www.cytivalifesciences.com/en/gb

UK BioIndustry Association

Explore opportunities to influence, connect and save with the BIA
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