SUBMISSION

Submission to the Department of Industry, Science and Resources

Submission to the Understanding our RNA Potential consultation

16 October 2023

The Australian Academy of Technological Sciences and Engineering (ATSE) is a Learned Academy of independent, non-political experts helping Australians understand and use technology to solve complex problems. Bringing together Australia's leading thinkers in applied science, technology and engineering, ATSE provides impartial, practical and evidence-based advice on how to achieve sustainable solutions and advance prosperity.

Australia has a notable opportunity in biotechnology, with ribonucleic acid (RNA) therapies and technologies primarily in the research phase, focusing on vaccines, protein therapies, cancer treatment and biopesticides. However, our nation faces several critical challenges in harnessing its potential. These include limited funding for research and innovation, a need for enhanced collaboration among research institutions and industry, and insufficient support for domestic RNA technology start-ups in expanding into global markets. To address these challenges, it is essential to establish a comprehensive national RNA initiative with stable government funding, focusing on research excellence, manufacturing, and driving more effective translation and collaboration. Strategic supporting initiatives can help local RNA technology start-ups thrive in international markets, fostering innovation, economic growth, and global competitiveness for Australia in the RNA technology sector.

ATSE makes the following recommendations:

Recommendation 1: Establish a comprehensive national RNA therapeutics and technology strategy with a strong focus on collaboration, research excellence, developing state-of-the-art infrastructure, and manufacturing.
Recommendation 2: Include One Health within the national RNA strategy for enhanced research translation and innovation.
Recommendation 3: Assist domestic RNA technology start-ups in global markets through export promotion initiatives, attracting talent, investment, and multinationals.
Recommendation 4: Allocate stable funding and resources to support RNA research and innovation, in line with the national strategy.
Recommendation 5: Invest in education and training programs to address skills shortages in the RNA sector.
Recommendation 6: Implement regulatory frameworks to facilitate swift development, approval and market access for RNA technologies.

Overcoming challenges in RNA technology development

RNA technologies hold promising applications, including vaccine development for infectious diseases in both humans (Bloom et al., 2020) and animals (Hoelzer et al., 2018). mRNA technology has been applied in COVID-19 vaccine development (Fang et al., 2022), while RNA-based treatments hold potential for conditions including breast and lung cancer (Zhao et al., 2023), and Alzheimer's (Riscado et al., 2021). Exploiting the different types of RNAs offers new opportunities for developing medicines, even for genes and gene products that were previously considered difficult to target. Some of the main types of RNA include (Santosh et al., 2015; Wang & Farhana, 2023):

Messenger RNA (mRNA)	Coding RNA[1] molecule that is translated into proteins within cells and has therapeutic implications such as vaccines.
Transfer RNA (tRNA)	Non-coding RNA[2] that plays a crucial role in protein synthesis and has been essential for synthetic biology and protein engineering.
Micro RNA (miRNA) and small interfering RNA (siRNAs)	Non-coding RNAs that regulate gene expression and have therapeutic implications such as cancers and infections .
Circular RNA (circRNA)	A closed loop structure, held together by strong chemical bonds. Plays a crucial role in controlling cells and is linked to health problems such as cancer, cardiovascular disorders and neurological conditions.
Ribosomal RNA (rRNA)	Non-coding RNA responsible for protein synthesis. Even though not a therapeutic RNA type, its understanding is essential for designing therapies that aim to stop protein production such as in acute myeloid leukemia.
Double-stranded RNA (dsRNA)	Non-coding RNAs that are the precursor to siRNAs and have been widely used to manage pests and pathogens including viruses, trait modifications and enhanced stress responses in agriculture.

Developing RNA-based technologies comes with many challenges. RNA is an inherently unstable molecule prone to degradation, potentially reducing its effectiveness. It can trigger immune responses when introduced to the body, which may lead to side effects or limit its therapeutical potential. Efficiently delivering RNA to target cells within the body often requires the use of specialised carriers or vehicles. Without such vehicles, RNA molecules may not reach their destination or may be destroyed before they can apply their intended effects. Over the past few decades, researchers have explored various delivery systems to overcome these challenges and enhance the efficacy of RNA products such as mRNA vaccines (Zhang et al., 2023).

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Another major challenge with mRNA vaccines has been the requirement to store them at extremely low temperatures, which limits their application in areas where this is not available or affordable. Recent progress has led to the development of vaccines that can be stored at +5°C (Kis, 2022). With the advancement of synthetic RNA treatments that can control genes, modify proteins, or edit the genome, the United States Food and Drug Administration (FDA) has approved twelve RNA-derived therapies and two mRNA vaccines authorised for emergency use to prevent COVID-19, and dsRNAs are being used to target specific genes in pests.

Developing of key areas for sovereign capability in RNA technology supply chain

Numerous opportunities exist within the RNA field, both in Australia and on a global scale, with research and trials in the medical and agricultural sectors underway. mRNA, along with its derivatives circRNA and siRNA technologies, have gained significant attention in recent research and investment due to their distinct advantages. CRISPR[3]-based RNA editing systems are also poised for a similar surge in research and development.

RNA technology and therapeutic research can be categorised into three overarching phases: research, development, and in-market manufacturing (pre-clinical, clinical, and post-market approval). During the development phase, efforts are directed towards scaling up for clinical trials, while the in-market phase is focused on large-scale human deployment, pest control, animal disease treatment or diagnosis, and increased crop yields. Australia excels primarily at the research stage and, to some extent, in the development of therapeutics, due to its collaborations between universities and biotechnology companies. However, there is a notable scarcity of activity at the in-market stage, which needs substantial investment and industrial manufacturing capabilities on a large scale.

In Australia, RNA therapies and technologies are predominantly situated at the research stage, with specific emphasis on prophylactic vaccines, protein replacement therapies, and cancer treatment. There are also ongoing initiatives to manufacture mRNA products at a laboratory scale. Key research strengths that align with promising emerging RNA technologies encompass personalised cancer therapeutics, siRNA drugs for rare genetic disorders, the utilisation of non-coding RNAs[2] for diseases such as neurodegenerative disorders, and applications spanning agriculture and aquaculture, including animal vaccines and RNA-based pesticides. To fully harness the potential of RNA technologies and therapeutics, fostering strong collaboration between academia, industry, and government entities is critical. This collaborative approach can facilitate the seamless transition of promising research findings into practical applications and drive innovation in the field.

State-of-the-art infrastructure will be required to fully realise Australia's potential to be an RNA leader. Australia's currently operating and planned facilities are:

BioCina manufacturing facility	Translational Science Hub	Moderna manufacturing facility	Myeloid RNA research and pilot manufacturing facility
• Commenced operation in Adelaide in 2021 • Collaboration with the University of Adelaide and the South Australian Health and Medical Research Institute	• mRNA research facility in Brisbane in 2022 • Will connect with Sanofi researchers in France and the United States	• Facility in Melbourne expected to be completed in 2024	• Housed at Macquarie University, due for completion in 2025 • Partnership between New South Wales Government and Myeloid

Acknowledging the significance of these recent developments in RNA technology and vaccine production in Australia, continuous investment, guided by a strategy, is needed to ensure their long-term viability. Additionally, expanding and establishing more advanced facilities across the nation is important to enhance

[2] Non-coding RNAs: act as cellular regulators without encoding proteins.
[3] CRISPR: short for "clustered regularly interspaced short palindromic repeats". It is a technology research scientists use to selectively modify the DNA of living organisms. For example, REPAIR and RESCUE are cutting-edge genetic tools that utilise CRISPR technology to edit RNA (Lo et al., 2022). The use of CRISPR/Cas13 by bacteria to degrade viral RNA is currently being adapted for use in mammalian species (Xu et al., 2021).

Australia's capacity in RNA research, manufacturing, and therapeutic development, thus fortifying our standing in the global biotech landscape.

Recommendation 1: Establish a comprehensive national RNA therapeutics and technology strategy with a strong focus on collaboration, research excellence, developing state-of-the-art infrastructure and manufacturing.

Applying RNA technologies within a One Health framework

The use of RNA has become a promising addition to small molecules, proteins/antibodies, and cell-based therapies to improve both public health and the broader One Health framework (that considers the interdependencies of human, animal and environmental health). The projected global population is 10 billion by 2050; this will require a 70% increase in food production, making crop and animal protection critical. RNA-based strategies for plant disease management present an appealing alternative to agrochemicals which can have adverse effects on human health and the environment, deteriorate the nutrient availability and fertility of soil, and contribute to pathogen resistance. Around 30% of global crop loss is due to pathogen-related factors (Savary et al., 2019). Mycoviruses, which are small viruses often with RNA genetic material, and RNA interference (RNAi) are among the promising methods to help protect plants from disease. RNA-based technologies including mRNA, dsRNA and siRNAs for both crop protection and animal health represent effective and sustainable future technologies. mRNA-based therapies can also be used to address infectious diseases, genetic diseases and cancer within the livestock and aquaculture industries. For example, Meat & Livestock Australia (MLA) has recently funded a project to begin testing mRNA vaccines that can be mass-produced in Australia in the event of a lumpy skin disease outbreak (Meat & Livestock Australia, 2023).

RNA technologies including tests and sequencing are also used for biosecurity purposes to safeguard against biological threats, including infectious diseases, bioterrorism, and the introduction of invasive species. These technologies leverage the advantages of RNA molecules for detection, surveillance, and response to potential biosecurity risks. Zoetis, a world-leading animal health company, has recently received a $53.3 million grant under the Modern Manufacturing Initiative to build a new vaccine research and manufacturing facility in Australia (Australian Government, 2023).

Recommendation 2: Include One Health within the national RNA strategy for enhanced research translation and innovation.

Fostering competitive industry opportunities for sustainable impact

Australia has taken a leading role in the field of RNA research, making discoveries that have had a profound impact on the lives of people globally. Notable among these achievements is the identification of the Shine-Dalgarno sequence, a crucial finding that has enabled the high-yield production of medicines like insulin and growth hormone. The innovative RNAi technology developed by CSIRO and Peter Waterhouse has allowed for the targeted regulation of genes, offering protection to plants and animals against various diseases. To build on these achievements, it is crucial to assist local RNA technology start-ups in expanding their research to global markets through robust support for export promotion initiatives. By nurturing this sector, we not only contribute to advances in medicine and other biotechnology sectors but also pave the way for sustainable economic prosperity.

In 2021, The United States maintained its position as the primary host country for Foreign Direct Investment (FDI) in DNA/RNA research (Karadima & Vaidya, 2022). Western Europe and North America saw a nearly twofold increase in the number of project figures compared to the levels recorded in 2019. In the Asia-Pacific region, the number of projects surged, surpassing threefold growth during the same period. Recognising the transformative potential of RNA technology in Australia, it is important to allocate stable funding and resources that align with the national strategy to support RNA research and innovation. A thriving RNA technology sector in Australia holds immense promise for our nation's economic growth, but it requires ongoing and consistent investment to prosper globally.

The development of a robust RNA technology sector with facilities as anchors can catalyse significant job creation across various domains, ranging from research and development to manufacturing and distribution. These new opportunities would help attract top talent, fostering skills development and knowledge transfer, which in turn enhances national competitiveness in the global biotech arena. A strong RNA technology sector can also stimulate investment in research and innovation, leading to ground-breaking discoveries and intellectual property generation, ultimately bolstering Australia's export potential and economic resilience.

Recommendation 3: Assist domestic RNA technology start-ups in global markets through export promotion initiatives, attracting talent, investment, and multinationals.
Recommendation 4: Allocate stable funding and resources to support RNA research and innovation, in line with the national strategy.

Building the skills and capabilities required to support growth in the RNA sector

Addressing the workforce challenges in the RNA sector is critical. The shortage of professionals trained in Good Manufacturing Practices (GMP), including engineers, technicians, and scientists, presents a significant hurdle. Roles in quality control and regulatory affairs also demand attention (ATSE, 2022). This could be addressed through the policy agenda set out by the Government's Employment White Paper, which articulates the need to fill skills needs and build the future workforce.

RNA technologies hold the potential to mitigate rising healthcare costs and establish a platform for rapid response and future preparedness. Australia possesses notable strengths in clinical trials, RNA diagnostics, and world-class research. While incentives like the Research and Development Tax Incentive exist, there is a need for more targeted investment and incentives to nurture this burgeoning sector. Leveraging our geographic location in the Asia-Pacific, Australia has the potential to become a centre of excellence for RNA technologies in the region.

Regulation is a critical aspect that requires attention, with a call for streamlined, harmonised, and transparent regulatory frameworks that are fit for purpose, enabling swift development, approval, and market access. Australia could take a leadership role in shaping policy and regulation in the region. For example, the Office of the Gene Technology Regulator has exempted topically applied dsRNA, used for crop protection, from GMO regulations.

To bolster the RNA sector, we must cultivate stronger international partnerships, fostering collaboration through conferences, information sharing, and resolving disputes related to intellectual property (IP). IP safeguards restrict who may benefit from or use these resources or innovations on an equal basis (Gaviria & Kilic, 2021). Furthermore, there is a pressing need to support the growth and innovation of RNA technologies in Australia.

Recommendation 5: Invest in education and training programs to address skills shortages in the RNA sector.
Recommendation 6: Implement regulatory frameworks to facilitate swift development, approval and market access for RNA technologies.

ATSE thanks the Department of Industry, Science and Resources for the opportunity to respond to the Understanding our RNA Potential consultation. For further information, please contact academypolicyteam@atse.org.au.

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