Sustained viral resilience by strengthening innate immunity

Programme Thesis

v1.0

Brian Wang, Programme Director

CONTEXT

This document presents the core thesis underpinning a programme that is currently in development at ARIA. We share an early formulation and invite you to provide feedback to help us refine our thinking.

This is not a funding opportunity, but in most cases will lead to one – sign up **here** to learn about any funding opportunities derived or adapted from this programme formulation.

An ARIA programme seeks to unlock a scientific or technical capability that

+ changes the perception of what's possible or valuable
+ has the potential to catalyse massive social and economic returns
+ is unlikely to be achieved without ARIA's intervention.

This programme thesis is the starting point for a potential ARIA programme. It is the foundation around which the programme team will build a full programme.

We aim to launch the programme funding call in late 2025, pending approval.

PROGRAMME THESIS, SIMPLY STATED

An overview of the programme thesis, accessible & simply stated

Humanity first started to engineer the immune system by inventing vaccines, which revolutionised 20th-century medicine by nearly eliminating many once-common viral diseases, including polio, measles, and smallpox. While vaccines are highly effective at directing the **adaptive immune system** toward a single, unchanging target, rapidly mutating and highly diverse viruses such as influenza, HIV, and coronaviruses comprise the majority of viral disease burden today and have eluded "universal" vaccine development thus far. In addition, novel pandemic viruses continue to punctuate the human story with periods of major societal and economic disruption in the months or years before specific vaccines can be developed. Until we create medical interventions that are more resilient to the spectrum of viral diversity, disease from both common and pandemic viruses will remain a constant feature of the human experience.

In contrast to the adaptive immune system, the **innate immune system** consists of a diverse toolkit of molecular defences evolved to provide wide-ranging protection against viruses. Engineering the innate immune system therefore offers abundant opportunities to develop new medicines that could provide resilience to common and pandemic viruses alike.

This programme aims to create medicines that confer broad-spectrum prophylactic protection against respiratory viruses by engineering the innate immune system, integrating advances from synthetic biology, AI, materials chemistry, and systems immunology to maximise **precision**, **accuracy**, and **durability**. We plan to support direct research and development as well as the creation and provision of shared resources, tools, and services that support the advancement of these medicines. If successful, this programme will demonstrate a step change in our ability to combat rapidly mutating, diverse, and unknown viruses, building on the legacy of vaccines to continue humanity's march against infectious disease.

This programme thesis is derived from the ARIA Opportunity Space: Sculpting Innate Immunity.

PROGRAMME THESIS, EXPLAINED

A detailed description of the programme thesis, presented for constructive feedback

Why this programme?

Vaccines have dramatically cut the toll of viral diseases over the past century, largely removing from daily life illnesses such as polio, measles, and smallpox that were once taken for granted as routine features of human existence. Yet it is clear the job is far from complete: viral infections still impose a substantial health and economic burden in the UK and worldwide. The COVID-19 pandemic is estimated to have claimed upwards of 15 million lives[1] and to have cost the global economy upwards of £10tn[2]. Seasonal influenza continues to infect one billion people and hospitalise millions annually[3]. Forty million people worldwide are living with HIV, with no effective vaccine in sight[4]. Beyond direct health costs, respiratory infections cost UK employers tens of billions of pounds annually in lost productivity[5]. Finally, viral infections often contribute to pernicious long-term health consequences: millions in the UK are living with long COVID[6], and viral infections have been variously associated with an increased risk of developing autoimmune, neurological, or cardiovascular complications[7–13].

Looking ahead, these challenges are likely to intensify. An ageing global population will be more vulnerable to severe outcomes from viral infections, while other global trends—such as climate change, urbanisation, increasing global travel, and agricultural expansion—elevate the risk of new pandemic viruses emerging[14]. Additionally, rapid advances in AI—including both general-purpose large language models and narrower biological design tools—are raising the spectre of an engineered pandemic by lowering barriers to the development of biological weapons[15]. Building humanity's resilience to the spectrum of both common and pandemic viruses will therefore be of increasing societal importance over the decades to come.

To do so, we need new tools that match the challenges we face. While many of the major causes of viral disease in the 20th century were individual viruses that could be effectively targeted by specific vaccines, the major viruses we face today are either rapidly mutating (e.g., new strains of influenza and COVID-19 arising on a regular basis), highly diverse (e.g., respiratory viral infection being caused by any of hundreds of distinct viral strains), or unknown (e.g., the next pandemic virus). Such viruses have posed an immense challenge to vaccine developers: despite intensive research efforts, we still do not have universal vaccines against influenza, HIV, coronaviruses, or even the common cold, and pandemic viruses consistently cause significant societal damage in the months or years before a vaccine can be developed and distributed.

Because vaccines stimulate the **adaptive immune system** to produce highly specific antibodies and T cells toward particular viral antigens, it is difficult to design vaccines that

cover the "surface area" of diversity required by today's major viral threats. On the other hand, the **innate immune system** has evolved to maximise the surface area of pathogens it responds to, with its role being to broadly detect foreign substances rather than to recognise specific targets. As such, the innate immune system is a fit-for-purpose tool for providing broad-spectrum antiviral protection. Just as we've learned to engineer the adaptive immune system using vaccines to address specific viruses in the 20th century, we believe that learning to engineer the innate immune system is the key to addressing the major viral challenges of today.

What we hope to achieve

Current medicines that engineer the innate immune system against viral infection—such as recombinant interferon or pattern recognition receptor agonists—remain limited by **precision**, **accuracy**, and **durability** (see Box 1 for definitions). We hypothesise that each of these features is required for new medicines that engineer the innate immune system to have maximal impact: they must be effective against viral infection in as few doses as possible while minimising side effects. Vaccines have been so impactful because they score high along these dimensions. How might we re-create the success of vaccines within the paradigm of engineered innate immunity?

Box 1 – Key definitions

Innate immune system – We take an expansive view of what constitutes the "innate immune system." In addition to conventional cellular (e.g., macrophages, dendritic cells, neutrophils, NK cells) and humoral (e.g., complement, interferon, antimicrobial peptides) mediators of innate immunity, we also include physical and chemical barriers, innate-like B and T cells, non-immune sentinel cells, and cellular stress and defence responses.

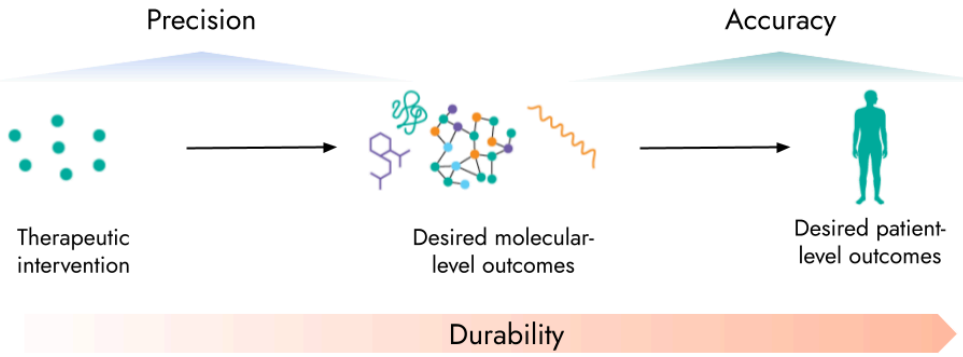
Engineering the innate immune system – includes stimulating, dampening, or redirecting pre-existing innate immunity, as well as introducing additional natural or synthetic components of innate immunity.

Precision – the ability to map therapeutic intervention to desired molecular-level outcomes, and not others. Involves biological control, spatial control, and/or temporal control (e.g., drug A will cause a certain amount of upregulation of gene B within tissue C and at time D, with minimal other molecular-level effects).

- Biological control: control over the *nature* and *magnitude* of biological effects that are induced by a therapeutic intervention
- Spatial control: control over *where* the biological effects occur
- Temporal control: control over *when* the biological effects occur

Accuracy – the ability to map molecular-level outcomes to desired patient-level outcomes, and not others (e.g., a certain amount of upregulation of gene B within tissue C and at time D will effectively prevent viral infection with minimal patient-level side effects).

Durability – the length of time for which the therapeutic intervention yields the desired patient-level outcome.



The goal of this programme is to **unlock the potential of engineered innate immunity for broad-spectrum antiviral protection by achieving a step change in precision, accuracy, and durability over the current state-of-the-art (Figure 1).** As a "north star"

to guide Creators toward the necessary innovations, the programme will target the development of innate immunity-engineering interventions that can provide safe and effective >3-month-long prophylactic protection against respiratory viruses across at least 3 separate viral families with a single course of administration—a capability that is not possible with either current medicines that engineer innate immunity nor with current vaccines (see the Appendix for rationale on the target specification)

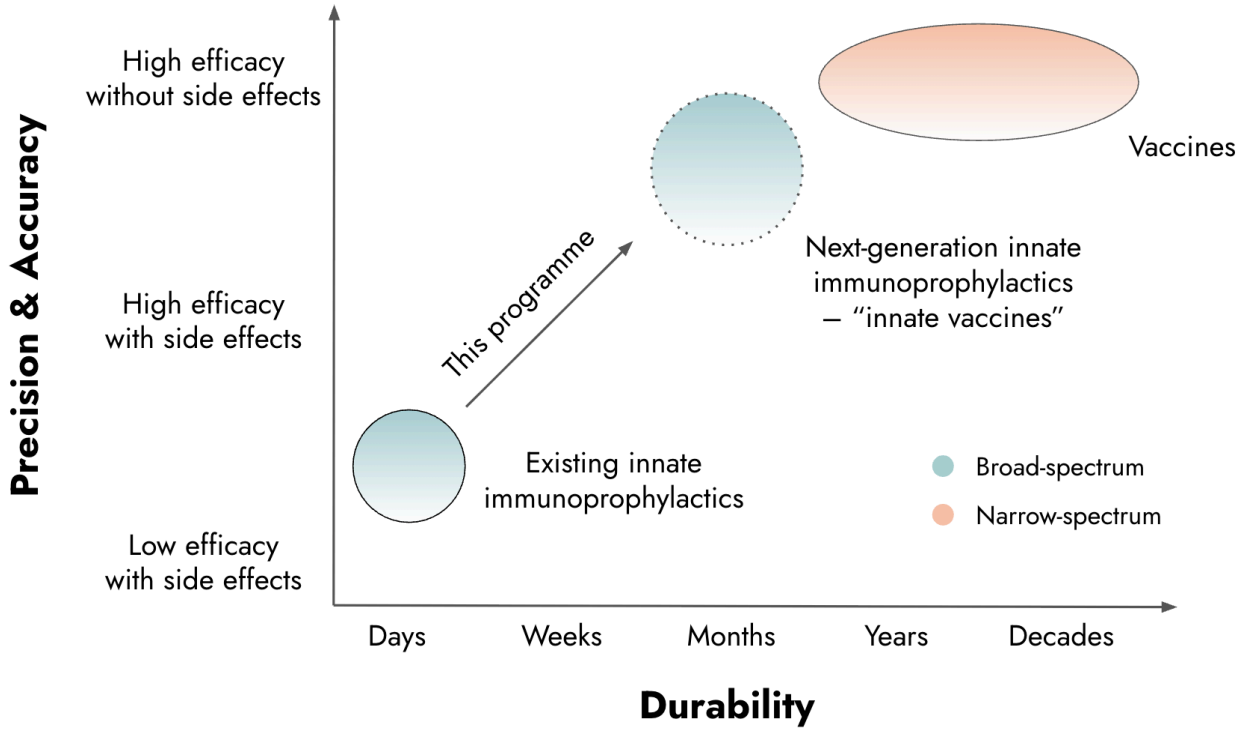


Figure 1: What we hope to achieve – combining the precision, accuracy, and durability that have made vaccines so successful with the broad-spectrum antiviral protection enabled by innate immune engineering.

Why now?

Vaccines have transformed medicine for over a century, and yet their innate immunity counterparts—long-acting, broad-spectrum antiviral prophylactics, which here we term "innate vaccines"—remain virtually non-existent. What explains the divergence, and why might opportunities to develop the latter be particularly ripe today?

We believe three main factors are at play. First, an understanding of the components and functional mechanisms of the adaptive immune system preceded that of the innate immune system, which has enabled more sophisticated vaccine designs earlier. Second, the innate immune system typically mediates broader biological effects than the highly target-specific responses of the adaptive immune system, raising the requirements for precision and accuracy to safely and effectively engineer innate immunity. Third, stimulating the adaptive immune system naturally results in durable responses due to the maintenance of long-lived

plasma cells and memory B and T cell populations, while the innate immune system has long been thought to lack analogous memory functions.

Recent advances across multiple fields, however, have created new opportunities. First, we have gained an increasingly comprehensive understanding in recent decades of the components and mechanisms of innate immunity, from the initial discoveries of pattern recognition receptors to the elucidation of downstream signalling pathways[16,17]. Second, new tools from synthetic biology (e.g., genetic and protein circuits[18,19]), materials chemistry/drug delivery (e.g., smart materials[20], tissue-specific drug delivery[21]), and AI (e.g., *de novo* protein design[22], biomolecular complex structure prediction[23]) are enabling us to engineer biological systems with increasing precision along the axes of biological, spatial, and temporal control. Third, the rise of single-cell omics technologies[24] combined with better models for respiratory viral infection (including nasal and lung tissue models[25] and human challenge models[26]) now facilitates the characterisation of innate immune signatures of protective responses with increased depth and fidelity. Finally, a wide array of developments now allows us to engineer more durable innate immune responses, including a greater understanding of innate immune memory processes (i.e., trained immunity[27]), the characterisation of long-lived tissue-resident innate immune cells[28], and the rise of long-acting drug modalities (e.g., sustained-release formulations[29], Fc conjugates[30,31], lipidated peptides[32], GalNAc-siRNA conjugates[33], non-viral DNA delivery[34], genetic and epigenetic editing[35,36]).

Simply put, the design requirements for precision, accuracy, and durability are more stringent for innate vaccines than for standard vaccines—but we believe the pieces are now in place to meet the challenge, if they can be put together (Figure 2). By integrating the above advances in a coordinated community effort, we can bring an important new class of medicines into being and set down a course toward increased collective resilience to viral infection.

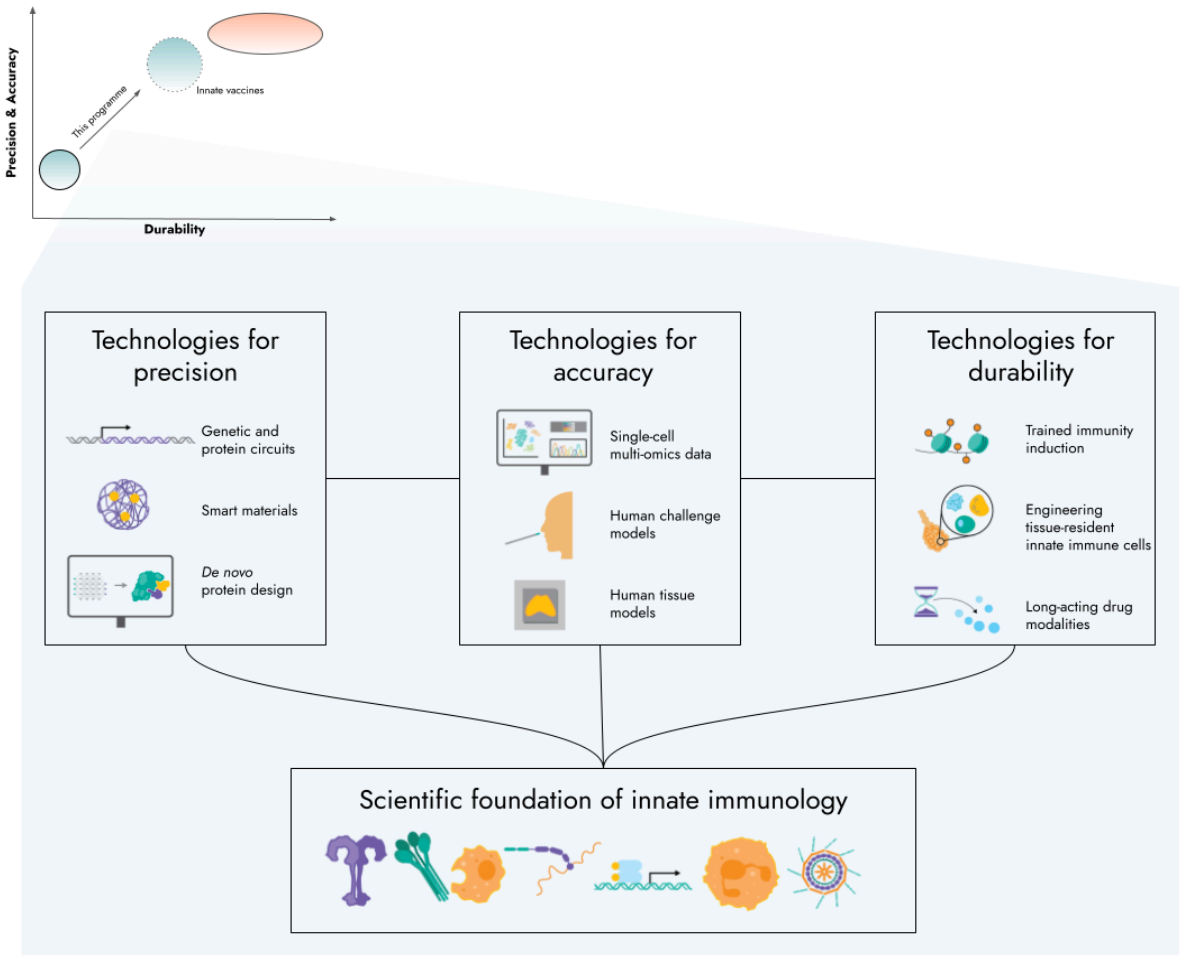


Figure 2: We expect the road to impactful innate vaccines to be paved by the integrated application of new technologies for precision, accuracy, and durability on top of a scientific foundational understanding of the innate immune system.

Toward broader horizons

While vaccines against infectious disease were the first medical fruits of leveraging the adaptive immune system as a tool, they were far from the last. Monoclonal antibodies have proved transformative across disease classes—from autoimmunity to cancer to infectious disease—and engineered T cell therapies have revolutionised cancer treatment. Cancer vaccines may be on the horizon, having recently achieved significant clinical validation[37]. Vaccines against infectious disease have consistently catalysed progress across this broader class of adaptive immunotherapy. In the 20th century, they were a driving force to produce fundamental immunological insights and techniques; in recent years, the success of mRNA

vaccines against COVID-19 has given momentum to RNA-encoded antibodies, in vivo CAR-T cell therapy, and personalised cancer vaccines.

Similarly, while innate vaccines against viruses have high intrinsic value, we envision they'd also serve as a launchpad for the broader project of leveraging the innate immune system as a *tool*. To date, the innate immune system has mostly been viewed as a *target* instead, with the most successful innate immunomodulatory medicines being anti-inflammatory treatments that inhibit key mediators of innate immunity. Given the protective role that innate immunity plays across a wide range of disease areas, this represents an enormous missed opportunity. If we can learn to strengthen innate immunity's protective functions how, when, and where it is needed, we may unlock a tremendous number of transformative new innate immunotherapies for cancer, neurodegenerative diseases, metabolic disorders, and more.

In particular, we expect that the innovations developed during this programme would have spillover effects into therapeutic areas beyond viral infection prophylaxis, as the fundamental challenges of engineering precision, accuracy, and durability are universal across disease areas. We anticipate the development of new platforms for measuring perturbations to innate immunity and new strategies for modulating innate immunity for maximal therapeutic benefit, both of which should be generalisable.

Given our relatively advanced understanding of the antiviral functions of innate immune components and the relative ease of testing candidates for viral infection prophylaxis compared to other disease areas, we see viral infectious disease as a suitable first proof point where progress can be made most quickly. If the programme is successful, we expect the demonstration of sustained broad-spectrum antiviral prophylaxis—a concrete, within-reach outcome with clear potential benefit to patients worldwide—to be a powerful signal to observers, shifting collective belief from one where harsh safety and efficacy tradeoffs are inherent to innate immunomodulation to one where navigating a complex landscape of innate immune profiles toward therapeutic peaks is now possible (Figure 3). Above all, we hope this programme will catalyse the formation of new communities directed toward unlocking the immense benefits of future innate immunotherapies, which would continue to drive progress well beyond the end of the programme.

Current view of innate immunomodulation

Future view of innate immunomodulation

Figure 3: How we expect views on therapeutic innate immunomodulation to change over time. Left: innate immunity is a single dial, and turning it up or down inextricably links safety risks with protective efficacy. Right: innate immunity is a complex multidimensional landscape, and navigating toward therapeutic peaks is challenging yet possible.

What we expect to fund

While pharmaceutical development is a competitive process, much of the early work required to enable innate vaccine development remains pre-competitive, and we believe that a spirit of collaboration will significantly contribute to the success of this programme. Thus, we aim to foster a diverse, interconnected, and dynamic ecosystem to facilitate the development of antiviral innate vaccines. We expect to fund across three key roles in this ecosystem – "Explorers", "Accelerators", and "Translators":

+ **Explorers:** Explore specific therapeutic hypotheses by directly designing and developing innate vaccine candidates
+ **Accelerators:** Develop tools, platforms, models, standards, and datasets to broadly accelerate innate vaccine development
+ **Translators:** Conduct research that broadly facilitates the clinical translation and future commercialisation of innate vaccines

These roles are not necessarily mutually exclusive – some Creator teams may bridge across roles, while others may exclusively fit within one. For example, we expect that some Explorer teams will heavily integrate elements of acceleration or translation into their proposed development activities, while others will focus only on candidate exploration. Nevertheless, we expect most Creator teams to identify primarily with one of the three roles.

Across all roles, we will first and foremost look to fund Creator teams who are fierce about achieving the programme goals and will offer flexibility if originally proposed plans change midstream, as new challenges or opportunities arise.

Explorers

Explorers are a central part of the ecosystem: by designing and testing innate vaccine candidates, they 1) generate valuable data to iterate on therapeutic hypotheses, 2) benchmark community progress toward the programme goals, and 3) create the most visible signals of success to external observers to attract follow-on funding and talent.

Explorers will most directly aim at the central programme target: demonstrating that innate vaccine candidates can provide safe and effective >3-month-long prophylactic protection against respiratory viruses across at least 3 separate viral families with a single course of administration. Given this target represents a step change over what is possible with existing technologies, we expect that this will require most Explorer teams to start by designing and

testing new candidates (including with novel and high-risk approaches) rather than advance existing candidates. We expect to fund a diversity of approaches spanning different therapeutic modalities and mechanistic hypotheses in order to maximise the chance that a Creator will meet the programme target. Approaches that could not plausibly meet this target even in principle will be considered out of scope.

Safety and efficacy are multifaceted concepts, and we do not wish to prescribe overly specific ways of assessing them. However, we offer the following as soft guidance on what might be considered as meeting the programme target:

+ **Safety**: A safe candidate has a well-understood mechanism of action and biodistribution pattern, does not induce clinically significant anti-drug antibodies, and is not associated with acute or chronic toxicity, including signs of autoimmunity or autoinflammation. Safety should be assessed a minimum of 3 months after innate vaccine candidate administration.

+ **Efficacy**: An effective candidate yields a >10-fold reduction of peak viral load in the lungs and/or a >50% increase in survival upon viral challenge compared to controls. Other parameters (weight loss, clinical signs, organ pathology, etc.) may also be measured to provide a fuller picture of candidate efficacy. Efficacy should be assessed 3 months after innate vaccine candidate administration, and should be assessed for respiratory viruses across at least 3 viral families. Creators may choose the specific respiratory viruses that they test against, and may additionally choose to demonstrate intra-family breadth of efficacy.

Since many Explorer teams will be starting at an early stage, we will not require, nor necessarily expect, that proposed Explorer projects advance to first-in-human trials by the end of the programme (although some may). Nevertheless, we believe the programme's impact will largely depend on the confidence it generates in the future clinical success of innate vaccines. Thus, while we do not specify the models to use for demonstrations of safe, effective, and durable broad-spectrum antiviral prophylaxis, ideally teams should aim to gather data that is expected to be as predictive of human clinical outcomes as possible. Explorer teams may choose to select different models to meet this criterion, and may consider a combination of various small animal, large animal, and *in vitro* and *ex vivo* tissue models. We encourage the use of *in vitro* and *ex vivo* tissue models when possible to add scientific value, e.g. to complement animal studies with an assessment of candidate safety and efficacy in a human biology context. Note that ARIA-funded research must comply with ARIA's policy on research and innovation involving animals.

Generally, we expect that Explorer proposals take into account the precision, accuracy, and durability required for approaches to meet the programme target, and for teams to be formed with the required expertise accordingly. Given the interdependencies we expect in design considerations for maximising precision, accuracy, and durability, we encourage

integrated teams that can address all aspects required to meet the programme target, rather than teams that would attempt only one aspect in isolation.

Key guiding questions that we would expect teams to consider include:

+ **Precision:** Does the proposed candidate incorporate elements of biological, spatial, and temporal control (ideally at least two out of three)?

+ **Accuracy:** Does the proposed development plan include rationale based on existing evidence or plans for experimental assessment for why the targeted innate immune profile would be expected to be associated with broad-spectrum antiviral protection?

+ **Durability:** Is the proposed candidate in theory compatible with >3-month-long biological activity?

Finally, even if technically successful, it may be that not all Explorer projects will be directly "translation-ready" by the end of the programme—in particular, because the complexity or cost of manufacturing may be too high. We believe that such projects still provide significant value to the ecosystem, either to provide additional examples to technically de-risk the broader concept of innate vaccines, to become translation-ready in the future when manufacturing costs or other factors change, or to incentivise the development of cheaper or simpler alternatives that work by the same mechanism of action. As such, we will be interested in Explorer projects that could technically meet the programme target even if the proposed candidates would not appear to be immediately cost-competitive for further development.

Accelerators and Translators

Accelerators and Translators develop the shared infrastructure necessary for innate vaccines to mature as a class—Accelerators via the development of tools, platforms, models, standards, and datasets, and Translators via the conduct of enabling research for clinical translation and commercialisation. While we see Explorers as taking individual "shots on goal", Accelerators and Translators broadly improve the playing field for current and future innate vaccine developers, increasing the likelihood that any shot on goal will be successful.

Accelerator activities might include the following:

+ **Model development:** Are there new animal models that could be developed that might better recapitulate human innate immunophysiology? Could better innate immunocompetent human nasal or lung tissue models be developed?

+ **Establishment of innate immune correlates of protection against infection:** What innate immune biomarkers might be used to estimate protection against infection by different viruses, in the absence of viral challenge — in the same way that neutralising antibodies are used by vaccine developers today?

+ **Creation of datasets to identify innate immune targets:** What datasets might broadly enable the discovery and development of new innate vaccines in the future?

Translator activities might include the following:

+ **Market and competition analysis:** What indications/target product profiles are most commercially attractive? What is the competitive landscape across different product categories today, and what might the competitive landscape be expected to look like in 10 years?

+ **Regulatory science and innovation:** What are the regulatory considerations that are specific to innate vaccines? How do these considerations differ across regulatory jurisdictions?

+ **Patient and public engagement:** What are patient preferences regarding dosing frequency and route of administration, which may shape product development? What patient populations most stand to benefit from products developed through this programme? What features of innate vaccines would the public be most hesitant about?

+ **Funder engagement:** Who might fund further innate vaccine development after the programme ends? What data packages would be most appropriate to prepare to secure follow-on investment from these funders?

+ **Clinical trial design:** What creative clinical trial designs (e.g., adaptive, platform) could best support the testing of innate vaccines?

+ **Scientific journalism:** Communication of the scientific and non-scientific challenges and opportunities associated with innate vaccines to the general public or other stakeholder audiences.

Notably, Accelerators and Translators are distinct from partners who would provide acceleration- and translation-related services directly to our Explorer Creators. Specifically, while Accelerators and Translators produce general research to build the innate vaccine ecosystem at large (i.e., for this programme and beyond), partners would service the specific needs of our Explorer Creators. While some of these needs could be fulfilled by existing ARIA Activation Partners, others would be more programme-specific (e.g., a biofoundry for synthetic biology needs). We expect to seek programme-specific partnerships after Creators have been selected and their specific needs can be assessed.

Altogether, we expect our Creators to benefit from frequent interaction across roles. The challenges that Explorers encounter in innate vaccine development could inform the work of Accelerators and Translators, and the work of Accelerators and Translators might be leveraged directly by Explorers. We hope that a dynamic programme ecosystem of

Explorers, Accelerators, and Translators can form the seeds of a larger innate vaccine ecosystem that continues to grow after the programme ends.

What we are still trying to figure out

+ How much should we standardise safety and efficacy assessments across Explorers at the cost of flexibility?
+ How do we best encourage the formation of Explorer teams that have all the expertise needed to design and develop a candidate capable of meeting the programme target?
+ How do we balance approaches that are/are not expected to be "translation-ready" by the end of the programme across our portfolio of Explorers?
+ What can we do to ensure that larger teams can execute quickly and not be hindered by cross-institutional legal and cross-disciplinary knowledge barriers?
+ How should we expect to allocate budget across Explorers, Accelerators, and Translators?
+ How frequently should we down-select among Creators at the cost of disincentivising longer-term project planning?
+ Are there non-traditional institutional structures that might be more amenable to execute the work of Explorers, Accelerators, or Translators? If so, how can we leverage those?

SOURCES

References cited in this document.

1. E. Mathieu et al., "Excess mortality during the Coronavirus pandemic (COVID-19)," Our World in Data, Accessed: Aug. 19, 2025. [Online]. Available: https://ourworldindata.org/excess-mortality-covid.
2. R. Agarwal et al., "A Global Strategy to Manage the Long-Term Risks of COVID-19," International Monetary Fund, Washington, DC, USA, Rep. no. WP/22/68, Apr. 2022. Accessed: Aug. 19, 2025. [Online]. Available: https://www.imf.org/en/Publications/WP/Issues/2022/04/04/A-Global-Strategy-to-Manage-the-Long-Term-Risks-of-COVID-19-516079

3. World Health Organization, "Influenza (Seasonal)," World Health Organization. Accessed: Aug. 19, 2025. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).
4. World Health Organization, "HIV," World Health Organization. Accessed: Aug. 19, 2025. [Online]. Available: https://www.who.int/data/gho/data/themes/hiv-aids.
5. H. Hayes et al., "Employer Costs from Respiratory Infections," Office of Health Economics, London, U.K., Dec. 16, 2024. [Online]. Available: https://www.ohe.org/publications/employer-costs-from-respiratory-infections/.
6. T. Greenhalgh, M. Sivan, A. Perlowski, and J. Ž. Nikolich, "Long COVID: a clinical update," *The Lancet*, vol. 404, no. 10453, pp. 707-724, Aug. 17, 2024, doi: 10.1016/S0140-6736(24)00908-1.
7. R. Chang et al., "Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study," *eClinicalMedicine*, vol. 54, 2022, Art. no. 102693, doi: 10.1016/j.eclinm.2022.101693.
8. M. Taquet, J. R. Geddes, M. Husain, S. Luciano, and P. J. Harrison, "6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records," *The Lancet Psychiatry*, vol. 8, no. 5, pp. 416-427, May 2021, doi: 10.1016/S2215-0366(21)00084-5.
9. K. S. Levine et al., "Virus exposure and neurodegenerative disease risk across national biobanks," *Neuron*, vol. 111, no. 7, pp. 1086-1093.e2, Jan. 2023, doi: 10.1016/j.neuron.2022.12.029.
10. Y. Xie, E. Xu, B. Bowe, and Z. Al-Aly, "Long-term cardiovascular outcomes of COVID-19," *Nat. Med.*, vol. 28, pp. 583-590, Feb. 2022, doi: 10.1038/s41591-022-01689-3.
11. J. C. Kwong et al., "Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection," *N. Engl. J. Med.*, vol. 378, no. 4, pp. 345-353, Jan. 2018, doi: 10.1056/NEJMoa1702090.
12. N.-S. Tzeng et al., "Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections—a Nationwide, Population-Based Cohort Study in Taiwan," *Neurotherapeutics*, vol. 15, no. 2, pp. 417-429, Apr. 2018, doi: 10.1007/s13311-018-0611-x.

13. K. Bjornevik et al., "Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis," *Science*, vol. 375, no. 6578, pp. 296-301, Jan. 2022, doi: 10.1126/science.abj8222.
14. R. E. Baker et al., "Infectious disease in an era of global change," *Nat. Rev. Microbiol.*, vol. 20, pp. 193-205, Oct. 2021, doi: 10.1038/s41579-021-00639-z.
15. D. Bloomfield et al., "AI and biosecurity: The need for governance," *Science*, vol. 385, no. 6711, pp. 831-833, Aug. 2024, doi: 10.1126/science.adq1977.
16. S. Carpenter and L. A. J. O'Neill, "From periphery to center stage: 50 years of advancements in innate immunity," *Cell*, vol. 187, no. 9, pp. 2030-2051, May 2024, doi: 10.1016/j.cell.2024.03.036.
17. T. Pradeu, B. P. H. J. Thomma, S. E. Girardin, and B. Lemaitre, "The conceptual foundations of innate immunity: Taking stock 30 years later," *Immunity*, vol. 57, no. 4, pp. 613-631, Apr. 2024, doi: 10.1016/j.immuni.2024.03.007.
18. M. Xie and M. Fussenegger, "Designing cell function: assembly of synthetic gene circuits for cell biology applications," *Nat. Rev. Mol. Cell Biol.*, vol. 19, pp. 507-525, Jun. 2018, doi: 10.1038/s41580-018-0024-z.
19. Z. Chen and M. B. Elowitz, "Programmable protein circuit design," *Cell*, vol. 184, no. 9, pp. 2284-2301, Apr. 2021, doi: 10.1016/j.cell.2021.03.007.
20. P. S. Kowalski, C. Bhattacharya, S. Afewerki, and R. Langer, "Smart Biomaterials: Recent Advances and Future Directions," *ACS Biomater. Sci. Eng.*, vol. 4, no. [cite_start]11, pp. 3809-3817, Nov. 2018, doi: 10.1021/acsbiomaterials.8b00889
21. Z. Zhao, A. Ukidve, J. Kim, and S. Mitragotri, "Targeting Strategies for Tissue-Specific Drug Delivery," *Cell*, vol. 181, no. 1, pp. 151-167, Apr. 2020, doi: 10.1016/j.cell.2020.02.001.
22. T. Kortemme, "De novo protein design—From new structures to programmable functions," *Cell*, vol. 187, no. 3, pp. 526-544, Feb. 2024, doi: 10.1016/j.cell.2023.12.028.
23. J. Abramson et al., "Accurate structure prediction of biomolecular interactions with AlphaFold 3," *Nature*, vol. 630, pp. 493-500, May 2024, doi: 10.1038/s41586-024-07487-w.

24. A. Baysoy et al., "The technological landscape and applications of single-cell multi-omics," *Nat. Rev. Mol. Cell Biol.*, vol. 24, pp. 695–713, Jun. 2023, doi: 10.1038/s41580-023-00615-w.
25. L. Svensson, J. Nordgren, Å. Lundkvist, and M. Hagbom, "Recent Advances in Nose and Lung Organoid Models for Respiratory Viral Research," *Viruses*, vol. 17, no. 3, pp. 349, Feb. 2025, doi: 10.3390/v17030349.
26. Y. N. Abo et al., "Strategic and scientific contributions of human challenge trials for vaccine development: facts versus fantasy," *The Lancet Infectious Diseases*, vol. 23, no. 12, pp. e533-e546, Aug. 2023, doi: 10.1016/S1473-3099(23)00294-3.
27. M. G. Netea et al., "Defining trained immunity and its role in health and disease," *Nat. Rev. Immunol.*, vol. 20, pp. 375-388, Mar. 2020, doi: 10.1038/s41577-020-0285-6.
28. J. I. Gray and D. L. Farber, "Tissue-Resident Immune Cells in Humans," *Annu. Rev. Immunol.*, vol. 40, pp. 195-220, Apr. 2022, doi: 10.1146/annurev-immunol-093019-112809.
29. W. Li et al., "Clinical translation of long-acting drug delivery formulations," *Nat. Rev. Mater.*, vol. 7, pp. 406-420, Jan. 2022, doi: 10.1038/s41578-021-00405-w.
30. S. Döhrmann et al., "Drug–Fc conjugate CD388 targets influenza virus neuraminidase and is broadly protective in mice," *Nat. Microbiol.*, vol. 10, pp. 912-926, Mar. 2025, doi: 10.1038/s41564-025-01955-3.
31. W. R. Strohl, "Fusion Proteins for Half-Life Extension of Biologics as a Strategy to Make Biobetters," *BioDrugs*, vol. 29, no. 4, pp. 215–239, Jul. 2015, doi: 10.1007/s40259-015-0133-6.
32. R. Menacho-Melgar, J. S. Decker, J. N. Hennigan, and M. D. Lynch, "A review of lipidation in the development of advanced protein and peptide therapeutics," *J. Control. Release*, vol. 295, pp. 1–12, Dec. 2018, doi: 10.1016/j.jconrel.2018.12.032.
33. C. R. Brown et al., "Investigating the pharmacodynamic durability of GalNAc–siRNA conjugates," *Nucleic Acids Res.*, vol. 48, no. 21, pp. 11827–11844, Aug. 2020, doi: 10.1093/nar/gkaa670.

34. M. Hosseini-Kharat et al., "Enhancing non-viral DNA delivery systems: Recent advances in improving efficiency and target specificity," *J. Control. Release*, vol. 377, pp. 317-333, Dec. 2024, doi: 10.1016/j.jconrel.2024.12.002.
35. M. Pacesa, O. Pelea, and M. Jinek, "Past, present, and future of CRISPR genome editing technologies," *Cell*, vol. 187, no. 5, pp. 1076–1100, Feb. 2024, doi: 10.1016/j.cell.2024.01.042.
36. J. Ueda, T. Yamazaki, and H. Funakoshi, "Toward the Development of Epigenome Editing-Based Therapeutics: Potentials and Challenges," *Int. J. Mol. Sci.*, vol. 24, no. 5, pp. 4778, Mar. 2023, doi: 10.3390/ijms24054778.
37. N. Zaidi, E. M. Jaffee, and M. Yarchoan, "Recent advances in therapeutic cancer vaccines," *Nat. Rev. Cancer*, vol. 25, pp. 517–533, May 2025, doi: 10.1038/s41568-025-00820-z.
38. A. Ardain, M. J. Marakalala, and A. Leslie, "Tissue-resident innate immunity in the lung," *Immunology*, vol. 160, no. 1, pp. 3-12, Oct. 2019, doi: 10.1111/imm.13143.
39. S. Ko, M. Jo, and S. T. Jung, "Recent Achievements and Challenges in Prolonging the Serum Half-Lives of Therapeutic IgG Antibodies Through Fc Engineering," BioDrugs, vol. 35, no. 3, pp. 247-263, Jun. 2021, doi: 10.1007/s40259-021-00471-0.
40. AstraZeneca, "AstraZeneca signs licence agreement with RQ Biotechnology for monoclonal antibodies against COVID-19," May 17, 2022. [Online]. Available: https://www.astrazeneca.com/media-centre/press-releases/2022/astrazeneca-signs-licence-agreement-with-rq-biotechnology-for-monoclonal-antibodies-against-covid-19.html#
41. AstraZeneca, "The continued burden of COVID-19 for the immunocompromised," AstraZeneca, Updated: Apr. 11, 2024. Accessed: Aug. 19, 2025. [Online]. Available:https://www.astrazeneca.com/what-science-can-do/topics/covid-19/burden-of-disease.html.
42. The figure in Box 1 and the icons in Figure 2 were adapted from drawings in BioRender.

APPENDIX: TARGET SPECIFICATIONS

We believe that a well-specified target for the programme is important to guide and coordinate Creators. Here, we've proposed as a central target the demonstration of safe and effective antiviral prophylaxis for >3 months with a single course of administration against respiratory viruses across at least 3 separate viral families. Below, we explain our rationale for each component of the target.

Why prophylaxis and not treatment?

Innate immunomodulatory antiviral treatments and prophylactics have fundamentally different desired product characteristics, and also benefit from distinct acceleration- and translation-related resources. For example, while months-long durability is desirable for a prophylactic, it is unnecessary or undesirable for a treatment. Some innate immunomodulatory treatments will be immunosuppressive (targeting the mitigation of viral sepsis) rather than immunostimulatory, requiring different technical approaches. Different datasets would be useful to enable the discovery of treatments versus prophylactics, and distinct patient, funder, and regulatory engagement strategies would be required for their translation.

While we believe the discovery of innate immunomodulatory antiviral therapeutics remains important, we focus this programme on the development of innate vaccines (prophylactics) to maximise cohesion and shared learnings between Creators.

Why >3 months durability?

Current innate immunity-engineering interventions can deliver at most about one week of broad-spectrum antiviral prophylaxis. >3 month durability represents a >10x increase over the state-of-the-art, and thus necessitates innovative solutions to achieve. Specifically, innovations in both durability *and* safety will be required together; simply engineering an extended durability of an existing innate immunoprophylactic (e.g., extending the half-life of recombinant IFN-α) may not be sufficient, as what is safe and tolerable for one week may not be safe and tolerable for 3 months.

And yet, 3 months of durability appears achievable. Trained immunity responses can be observed for at least 3 months[27]. Lung-resident innate immune cells establish long-lived and self-renewing populations, suggesting that perturbations of these cells may be a possible route forward[38]. Several long-acting drug modalities can exhibit biological effects for months (e.g., Fc-engineered monoclonal antibodies[39]). Creators will therefore be able to pursue multiple independent avenues to hit the 3-month target.

Practically speaking, a 3-month-long innate vaccine may find use as a seasonal pre-exposure prophylactic for respiratory viruses over the winter season, during which influenza, RSV,

and COVID-19 have increased circulation, and may compete favorably with monoclonal antibodies currently on the market or in development (which may also provide months-long prophylaxis against individual viruses). At the early stages of a pandemic, a 3-month-long innate vaccine may also be practical enough to be deployed to the population prior to the development of targeted vaccines.

Why a single course of administration?

Theoretically, it may be possible to reach safe and effective 3-month-long prophylaxis through the repeated administration of an intervention that provides week-long (or shorter) prophylaxis. However, we hypothesise that for the general class of innate vaccines to achieve world-changing impact, a convenient dosing schedule is highly important. A single administration (or a small series of administrations) for seasonal protection against respiratory viruses would enable broad population use and coincides with existing seasonal vaccination schedules.

Why respiratory viruses?

A number of factors point toward respiratory viruses as a natural focal point of the programme, given their global importance, the scientific tractability of demonstrating effective prophylaxis against respiratory viruses, and the translatability of pre-exposure prophylactics for respiratory viruses:

+ Altogether, respiratory viral infections are the most common source of disease worldwide
+ Given the rapid transmissibility of respiratory viruses, they may be the most likely to be the source of the next pandemic
+ The most common respiratory viruses are rapidly mutating and respiratory viruses are highly diverse as a class, making innate immunity-based solutions well-suited to the challenge they pose
+ The entry point of infection is relatively localised, such that it may be sufficient to strengthen innate immunity locally rather than systemically
+ Human challenge models are the most well-developed for respiratory viruses, facilitating the clinical efficacy testing of innate vaccine candidates that arise from this programme
+ Significant market demand exists for months-long pre-exposure prophylactics against respiratory viral infections, e.g. by the immunocompromised patient population, which motivates pharmaceutical companies to partner in translational development[40,41]

By focusing Creators on respiratory viruses specifically, we expect there will be increased opportunity for collaboration and shared learnings between Creators. However, if a Creator believes that their proposed solution may be effective against both respiratory and non-respiratory viruses, they may also include efficacy studies against non-respiratory viruses in their proposal.

Why across at least 3 separate viral families?

We believe that the programme should aim at unlocking a technical capability that is fundamentally not possible with existing methods. By asking Creators to demonstrate prophylactic protection against viruses in 3 separate viral families, they will be incentivised to discover interventions that truly take advantage of the unique breadth of the innate immune system.

ENGAGE

*Our next step is to launch a funding opportunity derived or adapted from this programme formulation. Click **here** to register your interest, or to provide feedback that can help improve this programme thesis.*

Success in the programme requires multidisciplinary teams. For groups or individuals needing assistance in building these teams, you can register your capabilities and missing expertise to ARIA's teaming tool via the feedback form linked above, allowing us to support matching with other registered teams.