Programme Thesis

Precision Mitochondria — A platform for engineering the mitochondrial genome

v1.0

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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.

If approved, we will launch the programme solicitation (funding call) later this year.

PROGRAMME THESIS, SIMPLY STATED

An overview of the programme thesis, accessible & simply stated

Mitochondria are central to complex life, and their dysfunction is implicated in many of our most pressing chronic diseases and the ageing process itself[1]. Yet our ability to investigate the precise nature of that link is severely limited, because the tools to manipulate mitochondrial DNA remain rudimentary. Genetic engineering—which has revolutionised so much of biology—has mostly left mitochondria behind.

This programme aims to unlock a transformative capability: **to reliably and effectively engineer vertebrate mitochondrial DNA (mtDNA) in vivo**. Success would establish a foundational, versatile toolkit to systematically study, manipulate, and ultimately reprogramme mitochondrial DNA, opening the door to a powerful new class of therapeutics across ageing and chronic disease. In the long term, this could include rewiring mitochondria for new metabolic capabilities or even functions as biosensors or in situ therapeutic factories.

Current approaches, which largely rely on manipulating nuclear-encoded genes, face fundamental limitations. Proteins destined for the mitochondria often fail to import or integrate correctly, and these methods lack the means for precise, localised genetic control within the organelle itself. Bringing the full power of genetic engineering to mtDNA directly would overcome these constraints, enabling a new wave of scientific and therapeutic innovation.

Realising this vision requires breaking through long-standing technical barriers that have resisted incremental approaches. *This programme will unite a new community, bringing together experts from mitochondrial and cellular biology with pioneers in fields like synthetic biology, virology, nanotechnology, and high-throughput screening platforms.* By integrating these diverse fields, we will provide a new generation of researchers across the life sciences with the practical and reproducible tools needed to finally bring the full power of genetic engineering to the mitochondria.

This programme thesis is derived from the ARIA Opportunity Space: Bioenergetic Engineering.

[1] Suomalainen, Anu, and Jodi Nunnari. 'Mitochondria at the Crossroads of Health and Disease'. *Cell* 187, no. 11 (May 2024): 2601—27. https://doi.org/10.1016/j.cell.2024.04.037.

PROGRAMME THESIS, EXPLAINED

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

Why this programme?

What we hope to accomplish

The goal of the programme is to equip researchers with the ability to reliably read, write, and regulate mitochondrial DNA, realising a toolkit comparable in power to the one available for bacterial genomes today. A galvanising minimum demonstration of this capability would be **the persistent, reproducible expression of a short acting reporter from within the mitochondria of a vertebrate model**—independently replicated to ensure broad applicability and robustness. The demonstration can be achieved through direct in vivo editing of mitochondrial DNA or by delivery and functional persistence of ex vivo engineered mitochondria, or both.

A persistent obstacle in mitochondrial biology has been the lack of shared tools and standardised methods, making it difficult to compare results across studies[2]. This programme will address that directly by prioritising reproducibility and comparability from the start. Programme creators (i.e. funding recipients) will develop and adopt shared benchmarks for key variables—such as mtDNA haplotype, cell type, and cell age—to enable meaningful comparisons across approaches. These standards will underpin integration across technical areas and creators and help ensure that programme outputs are interpretable, transferable, and primed for follow-on research, collaboration, and investment.

Why it's worth shooting for

Mitochondrial dysfunction is a common thread in many pressing health challenges, including neurodegenerative diseases (e.g., Alzheimer's, Parkinson's), cancer, diabetes, and the ageing process. The societal and economic burden of these conditions is immense. Yet our ability to precisely study or modulate mitochondrial function at the genetic level, remains limited. As a result, much of the field's research and funding has focused on the more tractable, rare (though important) primary mitochondrial diseases,

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[2]Jusic, Amela, Zoi Erpapazoglou, Louise Torp Dalgaard, et al. 'Guidelines for Mitochondrial RNA Analysis'. *Molecular Therapy. Nucleic Acids* 35, no. 3 (2024): 102262. https://doi.org/10.1016/j.omtn.2024.102262

which are often associated with single-point mutations in mtDNA. A core goal of this programme is to make the full spectrum of mitochondria-associated conditions accessible to rigorous scientific study and, ultimately, therapeutic intervention using biology's most powerful tools—unlocking billions of pounds for targeted mitochondrial R&D, and eventually trillions in societal value tied to improved human health.

Current approaches to mitochondrial genome engineering fall short. Existing mtDNA editing tools—such as targeted nucleases and base editors—have had a profound impact on the field, but they do not yet enable insertion of new genes, replacement or targeted deletion of large DNA segments, or the integration of complex synthetic circuits. They also exhibit lower precision and higher off-target effects than their nuclear or prokaryotic counterparts[3]. In contrast, capabilities such as whole-genome delivery and RNA-guided gene editing could enable precise insertions, deletions, and sequence modifications.

Nuclear-based strategies (e.g. allotopic expression of mitochondrial genes) continue to face major challenges[4]. Protein import into mitochondria is often unreliable, especially for the hydrophobic proteins involved in oxidative phosphorylation, and even proteins that navigate the inner and outer membrane transport (TIM/TOM) complexes may misfold or fail to integrate functionally. RNA import remains largely unachievable[5]. These limitations extend to expression control. Achieving precise, localised regulation of mitochondrial gene expression—responsive to conditions within the organelle—is extremely difficult when expression is driven from the nucleus. Conversely, local production of proteins and RNA within the mitochondrion allows for concentration at the point of need and may reduce off-target effects and cellular toxicity.

Vertebrate mitochondrial genomes represent a particularly stringent test case, and tools capable of functioning in this context are more likely to generalise across the diversity of eukaryotic systems. Vertebrate mitochondrial genomes are extremely compact, lack introns and noncoding spacers, rely on minimal RNA import, and possess limited endogenous repair mechanisms. While not every method will generalise across all species, success in vertebrate systems is expected to yield core strategies, design

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[3] Silva-Pinheiro, Pedro, and Michal Minczuk. 'The Potential of Mitochondrial Genome Engineering'. *Nature Reviews Genetics* 23, no. 4 (April 2022): 199–214. https://doi.org/10.1038/s41576-021-00432-x.

[4] Nieto-Panqueva, Felipe, Diana Rubalcava-Gracia, Patrice P. Hamel, and Diego González-Halphen. 'The Constraints of Allotopic Expression'. *Mitochondrion* 73 (November 2023): 30–50. https://doi.org/10.1016/j.mito.2023.09.004.

[5] Gammage, Payam A., Carlos T. Moraes, and Michal Minczuk. 'Mitochondrial Genome Engineering: The Revolution May Not Be CRISPR-Ized'. *Trends in Genetics* 34, no. 2 (2018): 101–10. https://doi.org/10.1016/j.tig.2017.11.001.

principles, and platform technologies that dramatically lower the barrier to progress throughout the field.

This programme seeks to catalyse a fundamental shift in capability: moving from merely "repairing" mitochondrial genomes to authoring them. In the long term, this would enable the design of fully programmable organelles with bespoke functions. These capabilities could eventually extend beyond human health, enabling efforts to rewire cellular energy flows from algae to fungus and protists for applications as varied as ecosystem resilience.

Why us, why now?

Mitochondrial genome engineering has long been considered a massive technical challenge due to the unusual properties of mitochondria—multiple membranes, a compact circular genome, limited nucleic acid import, and poorly characterised DNA repair mechanisms. While scientists have made consistent efforts to address these challenges over the past decades, progress has been sporadic and often irreproducible, making it a target considered too high-risk for most funders.

Realising the vision of this programme will require a broad interdisciplinary effort and creative solutions involving the deep integration of expertise and tools from traditionally disconnected fields as diverse as virology, parasitology, nanotechnology, systems biology, synthetic biology, and computational biology. It will also require the adoption of measurement techniques, model systems, and high-throughput automated methods that are new to mitochondrial biology, and in some cases, entirely novel. The central purpose of this programme is not merely to fund this science, but to catalyse the convergence of these disciplines, forcing the integration of tools and expertise to solve a grand challenge in cellular engineering. ARIA is especially well positioned to support speculative integration across these domains.

Recent developments suggest that meaningful progress is now within reach. Advances in nucleic acid delivery, synthetic biology, and mitochondrial biology provide a far stronger foundation than existed even a few years ago. For example, the rapid development and deployment of mRNA vaccines during COVID accelerated progress in gene delivery technologies. Leverageable advances span a range including programmable intracellular delivery methods; high-fidelity cell-free models; and precise, high-throughput, multi-modal analysis of individual cellular compartments.

What we expect to fund

We anticipate funding a variety of organisations and institutions (e.g. academic research groups, startups, non-profit research organisations, established industry players, individuals, and consortiums of the above) across four technical areas.

Technical areas: Core building blocks of the programme

Achieving the programme demonstration will require confronting a set of foundational technical barriers that have long frustrated mitochondrial science: delivering nucleic acids to the matrix, enabling their expression, and ensuring their persistence. These challenges form the core of the four Technical Areas (TAs) that we believe make up the essential building blocks of the programme. These are not sequential phases but **parallel, interconnected tracks of research** designed to encourage integration and collaboration from the outset.

A central theme across all TAs is the development and adoption of unified measurement tools, standards, and simplified model systems to ensure that progress is verifiable, reproducible, and comparable across the programme. Ideally, these standards could be developed by creator teams, and codified by the programme team (us), early in the execution of the programme and used in evaluating programme milestones and establishing success. *We are still seeking to understand how this can be achieved in practice.*

We also seek to enable acceleration where possible, by funding the development and effective use of high-throughput experimental platforms, automation, simulation, and machine learning models to accelerate discovery, enable AI-driven design, and generate more robust and predictive results.

TA1: Deliver — Delivery of Nucleic Acid Payloads to the Mitochondrial Matrix

Goal

Achieve reliable and quantifiable delivery of genetic payloads (minimally, 1000bp DNA or 25 bp RNA) into the mitochondrial matrix of vertebrate cells.

Scope and Context

This TA focuses on overcoming one of the core technical challenges in mitochondrial genome engineering: the delivery of nucleic acids into the mitochondrial matrix. Success here is foundational and will accelerate work across TAs. Approaches with a clear path to in vivo relevance are encouraged, but both in vivo and ex vivo strategies remain within scope. This TA is agnostic to the topology and type of payload—gene templates, minimal plasmids, or whole genomes could all be transformative. Robust delivery of guide RNA alone would represent a major breakthrough.

Evaluation

Progress will be assessed through quantitative assays that measure delivery efficiency, localisation, and payload integrity. These may include molecular readouts (e.g. qPCR, long-read sequencing, or in situ hybridisation) and compartment-specific verification methods. Where appropriate, results should be demonstrated across more than one model system or experimental context to support generalisability.

Measurement capabilities developed under this TA—such as quantification tools, compartment-specific reporters, or matrix-isolation protocols—will be shareable across the programme and will contribute to cross-team comparability and reproducibility. Reproducibility will be supported through independent replication, validation across labs, or demonstration of results in multiple systems.

Enabling Technologies

Progress will be accelerated by the development or adaptation of tools such as high-throughput screening platforms for nanoparticle, phage, or peptide libraries to identify effective delivery vectors, or the use of AI-driven methods to design and optimise delivery constructs. Simplified models—such as cell-free eukaryotic systems or permeabilised cells—may also support rapid screening and iteration before advancing to more complex biological systems. Computational tools, including simulations and machine learning models, could help prioritise candidates, predict mitochondrial uptake, or optimise targeting sequences, but should be grounded in testable hypotheses and integrated with experimental validation and well scoped use cases.

Examples of Possible Activities

+ Adapting viral vectors (e.g., bacteriophages), non-viral nanoparticles, or synthetic vesicles to deliver DNA or RNA into the mitochondrial matrix;
+ Engineering microbe-inspired mechanisms for vesicle fusion or gene transfer;
+ Developing peptide-mediated transport systems that exploit native mitochondrial import machinery;

+ Creating conjugated delivery systems using targeting sequences or chemical carriers;
+ Exploring physical delivery methods such as pressure-driven "mitopunch," electroporation, or microinjection for early validation.
+ Designing and validating scalable quantitative assays or imaging-based methods to confirm matrix-localised delivery;
+ Developing simplified or cell-free systems to rapidly screen and optimise delivery vectors before applying them in complex models.

TA2: Express — Mitochondrial Genome Engineering and Expression

Goal

Enable the stable expression of functional proteins from engineered genetic constructs—such as DNA templates or whole genomes—maintained within mitochondria.

Scope and context

This TA focuses on ensuring that nucleic acids delivered to the mitochondrial matrix (via TA1 or other means) can be stably expressed as functional proteins. This includes designing and assembling expression constructs (e.g. minimal genomes), as well as any auxiliary systems required to support transcription, translation, insertion, or compatibility with the native mitochondrial genome.

For example, DNA templates may require a mechanism for insertion into the wild type genome at a suitable location, a plasmid may require introduced transcription factors, and a genome may require synthesis and construction of a suitable D-loop to maximise compatibility with the native expression system.

This TA is agnostic to construct topology but should account for the distinct features of mitochondrial gene expression—such as unique genetic codes and compact genome architecture. Work under this TA may involve testing multiple expression strategies, including systems that are fully synthetic or minimally dependent on endogenous mitochondrial machinery.

Evaluation

Progress will be assessed based on the successful expression of mitochondrial-localised proteins from introduced constructs, along with initial evidence of stability and functional performance. Evaluation metrics may include the level of protein expression, validated

through quantitative or compartment-specific assays such as reporter fluorescence; and evidence of proper localisation, folding, and function within the mitochondrial matrix.

Measurement tools developed to support this TA—such as expression reporters, promoter activity assays, imaging-based localisation methods, or functional readouts—should be sharable across the programme and support comparability between expression systems. Reproducibility will be supported through validation in multiple models or independent replication of expression outcomes.

Enabling technologies

Progress may be accelerated through the development of minimal cell-free model systems adapted for mitochondrial gene expression, or through the use of machine learning models to design synthetic promoters, terminators, or mitochondrial-optimised coding sequences. Early-stage methods—such as direct microinjection of nucleic acids—may also enable initial expression testing ahead of more scalable delivery. Work that addresses known limitations in mitochondrial expression—such as enhancing transcript stability, introducing novel transcription factors, enabling targeted recombination, or developing mechanisms to mimic or bypass native D-loop regulation—may also unlock broader capabilities across this TA.

Examples of possible activities:

+ Designing minimal cell-free mitochondrial gene expression models.
+ Synthesising and assembling synthetic mitochondrial plasmids or genomes.
+ Engineering gene expression systems (e.g., promoters, terminators, and maybe even orthogonal RNA polymerases) compatible with the mitochondrial environment.
+ Developing mitochondrial-specific genome editing tools (e.g., base/prime editors, CRISPR variants).
+ Designing and validating quantitative assays, reporter systems, or imaging-based methods to evaluate expression levels, localisation, and functional output;
+ Using machine learning models to design or optimise synthetic promoters, terminators, or regulatory sequences;
+ Exploring early-stage delivery methods (e.g., microinjection) or simplified biological models to test expression construct concepts.

TA3: Maintain — Control and Maintenance of Engineered mtDNA

Goal

Ensure that engineered mitochondrial genomes are stably maintained, replicated, and functionally propagated over time.

Scope and context

This TA focuses on ensuring that engineered mitochondrial genomes are retained, replicated, and functionally sustained over time. This could be accomplished by a variety of approaches such as direct strategies to bias replication and heteroplasmy, or indirect approaches that improve the competitive fitness of engineered genomes (e.g. influencing the design of genomes in TA2) or limit the propagation of wild-type variants. Efforts should be robust across cell types and mitochondrial haplotypes, and may draw on both natural control mechanisms and synthetic systems.

Evaluation

Success in this TA will be measured by the precision, durability, and robustness of control over mtDNA heteroplasmy across diverse mtDNA variants in a range of cell types.

Progress will be evaluated against a hierarchy of goals. At a minimum, a successful intervention must demonstrate the ability to maintain a target mtDNA variant at a stable, detectable level indefinitely within a proliferating cell line. A significant advancement would be the ability to predictably 'dial' the level of heteroplasmy to a desired percentage and hold it there. Finally, the robustness and generalisability of the intervention will be gauged by its effectiveness across a wide range of cell types and its applicability to multiple, distinct mtDNA variants.

Early success can be demonstrated prior to the availability of successfully engineered mitochondria. The deliberate and durable up- or down-selection of naturally occurring mtDNA variants in a range of cell types would represent substantial progress.

This TA requires precise tools for tracking heteroplasmy and the persistence of engineered mtDNA over time. Creators will be expected to collaborate on developing and sharing these tools, and to test their persistence strategies using naturally occurring

haplotypes and diverse cell types to understand variability prior to the availability of engineered mitochondria.

Enabling technologies

Progress may be accelerated by the development and application of high-throughput platforms capable of screening libraries of components—such as engineered transcription factors, polymerases, or D-loop variants—to systematically measure and optimise heteroplasmy-shifting strategies over time and in a range of cell types. Computational models may be developed to predict heteroplasmy dynamics, and machine learning models could enable rational design of components to be screened.

Examples of possible activities:

- Designing cost-effective, scalable platforms for monitoring heteroplasmy at the single-cell level over time.
- Developing strategies to bias mtDNA replication towards engineered variants, such as:
    - Controllable methylation or other forms of inhibition of transcription factors for competing genomes.
    - Optimisation of engineered promoters or the introduction of specially adapted transcription factors that favor replication of the engineered variant.
- Designing systems to selectively degrade wild-type mtDNA.
- Studying and controlling heteroplasmy dynamics of naturally occurring or base edited mtDNA in multiple cell types.
- Studying natural examples of heteroplasmy regulation in non-model organisms such as bees, or in organisms with multi-uniparental inheritance.

TA4: Transfer — Delivery of Engineered Mitochondria to Cells

Goal

Develop robust methods for delivering whole, engineered mitochondria to target cells.

Scope and context:

This TA offers an alternative to direct in vivo mitochondrial engineering, focusing on the ex vivo modification and subsequent delivery of whole mitochondria. A successful approach in this area could offer more immediate clinical applications and may enable

complex genetic modifications that are difficult to perform directly within an organism. This TA must address the persistence challenges associated with cellular uptake, such as endosomal escape and the potential for triggering mitophagy upon engraftment.

Evaluation

Progress will be measured by the efficiency of mitochondrial uptake, the functional persistence of these transplanted organelles, and the reproducibility of the method. A key challenge will be developing standardised assays to assess mitochondrial health, function, and successful engraftment. This will involve using a range of mtDNA haplotypes, including naturally occurring or base-edited DNA barcodes, across various cell types to ensure broad applicability and allow for robust comparison between alternative methods.

Enabling technologies

To accelerate progress, high-throughput screening could be used to identify compounds or cell-surface modifications that enhance mitochondrial uptake. These systems will need to be able to quantify the location and continuing function of genetically barcoded mitochondria in targeted cells over time. With enough data, machine learning models could be developed to predict the success of engraftment based on specific mitochondrial or cellular features.

Examples of possible activities:

+ Developing methods for isolating, modifying, and maintaining healthy mitochondria outside of the cell.
+ Designing a scalable platform for tracking and quantifying the fate of delivered mitochondria over time.
+ Approaches for whole-organelle delivery, e.g., via exosomes, surface functionalisation, or induced intercellular transfer.
+ Engineering or pre-conditioning cells to enhance their uptake and retention of transplanted mitochondria.
+ Developing quality control standards to ensure only functional, correctly engineered mitochondria are used for transplantation.
+ Identification of features associated with durability of mitochondrial transfer (e.g. cellular duress).

Note: ARIA-funded research must comply with the principles of the 3Rs.

Programme Structure and Collaboration

We believe success in our programme will require fostering a deeply collaborative, adaptive, and outcome-focused research ecosystem. We aim to bring together a diverse community of creators, providing them with the flexibility to explore innovative approaches while ensuring that successful technologies are rapidly validated, standardised, and shared.

The following structure represents our current thinking on how to achieve this. We are actively seeking feedback on programme structure and how teaming of creators should be structured.

Creators

The programme will be built around three distinct but interdependent classes of creators:

Mitochondrial Biology Integrators

These are creators that are likely highly versed in mitochondrial science and will drive delivery of the programme's core technical area goals. They will coordinate a broad spectrum of interdisciplinary contributors, working closely with Technology Catalysts or other experts to adapt new approaches to solving challenges and accelerating progress within TAs.

Many mitochondrial biology integrators will work across multiple TAs, but mitochondrial biology integrators focused on a single TA are also welcome. While we imagine many of these creators will be mitochondrial biologists, we also *welcome creators from other disciplines who either have worked with mitochondria or otherwise feel confident of their ability to establish mitochondrial research programs that can solve TA challenges (e.g. systems biologists)*.

Example core areas of expertise:

+ **Mitochondrial DNA** — editing, replication, repair, and transcription.
+ **Mitochondrial import pathways** — hormones, proteins, and nucleic acids.
+ **Fission/fusion** — dynamics and regulation.
+ **Mitochondrial quality control** — Mitophagy, heteroplasmy dynamics, and intercellular mitochondrial transfer.

Technology Catalysts

Technology catalysts will generally have unique research expertise in adjacent science and technology fields that can be applied in novel ways to address challenges within one or more TA. The techniques and technologies they focus on may have been successfully applied to mitochondrial biology already but many of the most exciting creators in this space will have the foresight to see how they can adapt their approaches in ways that have not previously been attempted.

Example areas of expertise:

- **Enabling Science & Technology**
  - **Gene Delivery** — creating bacteriophage or AAV capsids, lipid nanoparticles, peptides, and organelle-targeting constructs for mitochondrial gene delivery.
  - **Synthetic Biology** — designing or rewriting mitochondrial genomes; adapting base/prime editors and CRISPR tools; developing regulatory elements and gene circuits that operate in the mitochondrial environment.
  - **Parasitology & Symbiotic Biology** — leveraging natural examples of organelle transfer or genome integration from parasites and symbionts (e.g., kinetoplastids, rickettsia).
  - **AI-driven Protein Design** — computationally identifying or engineering proteins that modulate heteroplasmy, enable nucleic acid import into the mitochondria, or trigger vesicle fusion.
- **Laboratory method development**
  - **High-Throughput & Automation Platforms** — building or adapting systems that can enable mitochondrial biology integrators to rapidly address challenges, such as adapting cell-free systems used in prokaryotes for mitochondria or identifying new approaches to isolating or culturing appropriate cell lines or mitochondria themselves.
  - **Metrology Platforms** — advanced microscopy (e.g., super-resolution); development of reporters and biosensors; and single-cell, single-compartment multi-omics.
  - **Microfluidics & Cell-Manipulation Devices** — designing microfluidic systems and robotics for isolating and manipulating mitochondria, or for performing high-throughput and/or highly-specific combinatorial screens.

Translation & Validation Cores

These partners will operate like core facilities or CROs, consolidating resources and ensuring reproducibility and translation. They will build on the technical advances of other creators to establish standardised models; produce reagent kits, assay systems, and protocols; run blinded replication studies; and generally adapt successful approaches

for broader use. Their role is to transform bespoke discoveries into dependable capabilities for use in the programme and for translation to broad applications.

Example functions & expertise:

+ **Standardisation & Model Provision** — maintaining reproducible cell lines, animal models, assay systems, and detailed protocols for the entire programme.
+ **Reagent & Resource Production** — supplying DNA constructs, delivery vectors, organelles and assay reagents at scale.
+ **Replication, Evaluation & Quality Control** — performing independent validation of key findings, providing data curation, and ensuring comparability.
+ **Translation & Commercialisation** — adapting validated tools developed in the programme (or elsewhere), coordinating regulatory considerations, and supporting technology transfer.

Aligning incentives for radical collaboration

A core goal of this programme is to build a culture that prioritizes collective success. We recognize that traditional incentive structures—whether in academic institutions, startups, or non-profits—can sometimes hinder the open collaboration required to achieve ambitious, milestone-driven goals.

To better align our creators with the programme's objectives, we are exploring a new model of awarding unrestricted funds to teams that achieve key, independently replicated milestones. By directly rewarding reproducible results and open collaboration, we aim to build a cohesive community that moves faster and more effectively together.

What we are still trying to figure out

+ How should shared infrastructure (e.g., model systems, screening platforms, imaging tools) be organised—centralised, distributed, or hybrid?
+ How can we define specific, meaningful metrics for success and gating decisions that avoid rewarding arbitrary goals?
+ How do we balance performance-based down-selection with the need to retain a diversity of scientific approaches?
+ How will the programme capture and disseminate learnings from down-selected or discontinued approaches to ensure they provide value and inform the work of the remaining teams?
+ What is the most effective way to surface and model cost breakdowns and budget allocations across the different Technical Areas (TAs)?

+ How can we best design incentives to foster a culture of deep collaboration, collective success, and agile milestone-driven execution?
+ How can we best ensure programme-wide adoption of the tools from the Translation & Validation Cores and manage the resulting intellectual property for collective benefit?
+ Beyond adopting FAIR principles, what specific data infrastructure and governance will be required to create a durable, integrated data asset from the diverse measurements across the programme?

SOURCES

References cited in this document.

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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.