Precision Mitochondria

FAQs from the webinar

The Precision Mitochondria team hosted a webinar on 9 October to provide an overview of the programme's objectives, scope, and application process, and to give potential applicants an opportunity to ask questions to the ARIA team.

The following questions were submitted:

Q: Is the call open to Principal Investigators (PIs) hosted by a company or incubator?

A: We are completely flexible regarding where the Principal Investigator (PI) is hosted. We can fund teams based in universities, research labs, companies, or other organisations, and can even fund individuals who are "unhosted".

The only requirement for proposals with multiple collaborators is that you designate one organisation as the lead applicant. This lead will be the entity we formally contract and fund. While this doesn't need to be finalised for the concept paper, we prefer it to be settled by the full proposal stage. That said, we remain open to facilitating collaborations and finalising lead arrangements even after full proposals are submitted.

Q: Are early-stage biotech companies eligible to apply?

A: Yes, absolutely. Applications from early-stage biotech companies and other entities like focused research organisations are encouraged.

Q: Can an investigator participate in more than one grant application?

A: Yes. However, if multiple proposals you are on are successful, the programme team will discuss with you to ensure you have sufficient time to contribute meaningfully to all funded projects.

Additional information

Applicants can submit two separate proposals to a funding call. The ideas in each application must be different and form unique projects, but they could be complementary. This will not disadvantage the applicant and each proposal will be evaluated individually on its own merit against the criteria outlined in the funding call.

Q: Is it better to apply as a team or as an individual?

A: Either is fine. At the concept paper stage, the primary goal is to show how you can contribute to the programme's objectives. Individual proposals are welcome and should not be discouraged.

Additional information

Where applicants wish to collaborate and submit a joint application, a lead applicant (and organisation if relevant) should be chosen to submit the application with all other collaborators identified as proposed subcontractors to the project. For the purposes of the funding agreement between ARIA and the lead organisation, we refer to these other parties as subcontractors. It is up to the lead organisation to decide how best to formalise these arrangements - for example, this could be via a collaboration agreement.

Q: Are smaller, more focused projects acceptable, or do you prefer large multi-institutional teams?

A: Smaller, focused projects are absolutely fine. It is anticipated that some funded projects will be smaller and tackle a specific technical aim or bring a particular technology to the programme.

Q: Is there a preference for a certain team size or project scale?

A: No. There is no preference for team size or scale, especially at the concept paper stage. We are open to all structures and budget sizes. The key is how the proposed work helps achieve the programme's ultimate goal.

Q: Will you "mix and match" teams from different proposals?

A: Yes. The process is dynamic. After the concept paper stage, thoughtful feedback may include suggestions for different teams or individuals to collaborate. Please note - we will not disclose any information about your proposals, and will not introduce you to other teams without your prior consent.

Q: How important is having preliminary data for the concept paper?

A: It's helpful but not required. We fully anticipate that many groups, especially those bringing new enabling technologies from other fields, will not have extensive mitochondria-specific preliminary data.

Q: How much flexibility is there to change a proposal between the concept and full proposal stages?

A: There is a huge amount of flexibility. You can add partners, adjust technical areas, or refine your direction based on the feedback you receive from the programme team.

Q: The guidelines mention feedback between the concept and full proposal stages. Can you explain what form that feedback takes? Is it written, scored, or through a meeting with the programme team?

A: The feedback provided to teams who are encouraged to submit a full proposal is multi-faceted and designed to be as constructive as possible. Rather than a simple score, our feedback is holistic and can include one or more of the following:

- Written Summary: you will receive an email containing specific written feedback from the programme team. This will highlight the strengths of your concept and may offer suggestions for refinement, potential adjustments to scope, or areas to elaborate on in the full proposal.
- Direct Engagement: the programme team may invite you to a follow-up meeting or send additional questions to better understand specific aspects of your proposed work.
- Teaming and Collaboration Suggestions: a key part of our process is building a cohesive and

collaborative programme. If we identify a strong potential synergy between your proposal and another, we may suggest a collaboration. To facilitate this, we ask for your consent in the concept paper to share your name and email address with other potential partners. We will never share the details of your proposal, only facilitate an introduction. It is then entirely up to the teams to decide whether to pursue a joint proposal.

This interactive process is designed to help shape the strongest possible portfolio of projects to achieve the programme's objectives.

If you are not encouraged to submit a full proposal, then we are unable to provide feedback due to the volume of submissions.

Q: For teams that are encouraged to submit a full proposal, how much flexibility will we have to refine or change direction between concept and full proposal stages? Can we add partners or adjust technical areas?

A: There's a huge amount of flexibility. You can respond to the feedback that you receive. You may go away and conversations may develop with other potential applicants or other collaborators. Sometimes we've had people who are discouraged from submitting a full proposal who still also go on to submit a full proposal because they've come up with a completely different idea.

Q: We are newly co-licensing a new protein nanoparticle technology from a non-UK university. Can we submit an application with the inventor in the non-UK university?

A: Yes, absolutely. If it's a UK lead with collaborators outside of the UK, we just ask for information in terms of how much money is going to those collaborators so we can see what proportion of the funding is staying in the UK and what's going outside.

Additional information

Our primary focus is on funding those who are based in the UK. For the vast majority of applicants, we therefore require the majority of the project work to be conducted in the UK (i.e. >50% of project costs and personnel time). However, we can award funding to applicants whose projects will primarily take place outside of the UK if we believe it can boost the net impact of a programme. In these instances, you must outline in proposals any proposed plans or commitments in the UK that will contribute to the programme within the project's duration. If you are selected for an award subject to negotiation, these plans will form part of those negotiations and any resultant contract/grant.

Q: How should international teams consider applications?

A: Please apply!

Q: Can the research be conducted outside of the UK?

A: Yes, but UK-based projects are prioritised. Non-UK applicants should detail how their project will bring benefit to the UK (e.g., collaborating with a UK entity, starting a UK company, moving to the UK). However, exceptionally innovative proposals with highly talented teams may be funded without a direct UK link.

Q: If we are currently outside the UK but willing to move or set up a UK company, should we state that?

A: Yes, please make this clear in your proposal. We can fund people based outside the UK and build in a process for them to establish a UK-based company. You can include the associated costs in your budget (note: company incorporation fees are ineligible).

Additional information

Where you intend to create a subsidiary in the UK, the subsidiary does not necessarily need to be in place prior to the commencement of any funding. You must however outline a credible plan for achieving this within the project's duration. If you are successfully selected for an award, subject to negotiations, this plan will form part of those negotiations and any resultant contract/grant.

Q: Can a UK-based company provide a sub-award to a collaborating academic lab in another country?

A: Yes, please provide details on the proportion of funding that will be allocated outside the UK.

Q: All five TAs are interconnected. Are we open to proposals that focus on a certain subset of TAs?

A: Absolutely - for concept papers, we're focused on what the best team and the best approach for the objective is. For full proposals, we encourage applications that address TAs 1-4.

Q: Does TA5 mean that it cannot be included in the same proposal as the other TAs and has to be a standalone proposal?

A: No. The most natural and easy way for us to imagine it is as an independent group. Having said that, if there's a particular consortium that feels like its integration with TA5 would be particularly useful and it's able to sort of firewall TA5 off appropriately... or maybe it just wants to accomplish certain elements of TA5. We will not be dogmatic about that.

Q: If an organisation or consortium were to apply under TA5 (Standardisation, Translation, and Reproducibility), how does ARIA envisage coordination with other applicants to ensure that outputs are standardised, reproduced, and translated in a timely and consistent manner?

A: In your proposal we want to hear what you'd need from the programme team and from other creator teams to achieve the mission of TA5. Our intention is to align everyone's incentives around the aims of TA5: the goal of the programme is not to publish irreproducible papers on one-off results. The TA5 team is meant to be critical to the definition of success for all of the other teams.

Q: Does TA5 include educational programmes or only scientific developments?

A: We would imagine or it's easy to imagine that an applicant for TA5 would include educational features within the programme. But in terms of a general educational programme outside of the programme is not something that we currently envision. Going back to the galvanizing demonstration. Does it move it forward or not should be the main question.

Q: Can you explain species preferences for cell lines in TAs 1-4 as well as in vivo models?

A: The final galvanising demonstration will need to occur in a mammal, as the goal of the programme is to create tools with a path to human translation, including in vivo delivery. We are agnostic to which culture and vertebrate systems are used in TAs 1-4, but proposals should make clear how proposed models will ultimately facilitate translation into mammals.

Q: What tools or mechanisms does the team envisage as being required to evidence phenotypes resulting from successful mitochondrial DNA edits?

A: We're quite open here. We do imagine that a reporter gene might be an obvious first one to introduce because it would accomplish more than one objective. We are open to a range of different solutions.

Q: You mentioned high throughput screening and mitochondria free several times in the call. So where does this fit into the final aims?

A: The idea is these are approaches and they're just examples of approaches, new assays or things that can be developed as part of the programme that will assist. We see these as fundamentally enabling approaches that will assist teams, and the more that they can be developed and distributed among the groups working on the programme the better.

Q: Would the programme benefit from a targeted protein assay platform currently in development? It quantifies over a thousand mitochondrial proteins. While orthogonal to the engineering focus, it could offer significant metrological value.

A: Returning to the demonstration, does it help us move forward the demonstration? Things that are really orthogonal in such a way that won't support the technical objectives of the programme would be considered out of scope.

Q: Mitochondrial genome engineering in vertebrates seems like the major goal here but if in vivo experiments are not included in the proposed, would this be seen negatively?

A: No, absolutely not. We expect that a tremendous amount of this work will be done in culture. A group that was working on TAs 1 to 3, could very well do so without including any in vivo experiments at all.

Q: Is a proposal likely to be viewed negatively if it doesn't include in vivo experiments?

A: No, not at all. A significant amount of the work (especially for TAs 1-3) is expected to be conducted in cell culture. Teams can focus exclusively on in vitro or in vivo aspects.

Q: Are you open to alternative methods for modifying mitochondrial DNA beyond CRISPR-type approaches?

A: Yes, absolutely. We welcome novel and creative solutions.

Q: Would you be interested in technologies that permit imports of functional RNA into the mitochondria?

A: Yes, but in the context of ultimately having a novel functional gene which is expressed in vivo in mitochondria. For example, a CRISPR solution would totally be game for us, but it would likely be focused on the stated objectives.

Q: Could you clarify why invertebrate models e.g. Drosophila or C. elegans are not eligible for the programme given that they have historically been important for mitochondrial genetics and hetrolasm studies. Is this restriction driven by translational considerations, regulatory requirements or technical reasons related to mtDNA engineering?

A: The potential for translation to lead to kind of a massive human impact is one of the conditions. The general feeling was that in order to get approval for this particular programme we needed to make it all the way through into vertebrate systems. However, the use of invertebrate models in early-stage work is not entirely ruled out if it strongly supports the ultimate goal.

Q: For projects on human mtDNA, are cell line models sufficient or more physiologically relevant iPSC & organoid models required?

A: Creators should specify the models they think are most relevant. Likely a range of cell lines should be used as models to assure generalizability and translation in vivo.

Q: Is there a preference for medically oriented versus fundamental science elements?

A: No. The science in the programme should be oriented towards achieving the programme's galvanizing demonstration.

Q: I have a very interesting mitochondrial research problem. I can see how, if successful, it might help in the future to address elements of a TA or even the broader programme, but how it fits in is unclear.

A: Our goal is to have a successful galvanising demonstration within 5 years. Basic research that has a compelling path to supporting this is welcome, but a lack of clarity on how it will support the success of and be integrated into the demonstration will likely mean it is out of scope.

Q: How is confidential information in our proposal protected?

A: We treat all proposal information with strict confidentiality. Our process ensures integrity by:
- Requiring all external reviewers to sign confidentiality agreements.
- Vetting all reviewers for conflicts of interest and blocking access to any proposals where a conflict exists.

For information that is highly sensitive due to an active or imminent patent application, please reach out to us. We can put a specific Non-Disclosure Agreement (NDA) in place to protect those details. We limit the use of ad-hoc NDAs to maintain an efficient administrative process.

Additional information

Subject to the conditions of each call, ARIA will treat your proposal confidentially. You should provide enough information to allow us to evaluate your proposal, but you should not submit potentially patentable information before a patent application is filed or commercially sensitive information. If there is information that would support your application, but that you do not wish to disclose because you believe it may be patentable or commercially sensitive, please make this clear in your application. We may enter into an NDA where you have been shortlisted and you want to discuss potentially patentable or commercially sensitive information. ARIA does use external evaluators as part of its programme solicitation review process. Any external evaluators will be subject to non-use restrictions, confidentiality agreements and conflicts of interest

checks. We will not use evaluators that present a conflict of interest. ARIA Board members and advisors are not part of the decision making process for ARIA research funding; as such, they will not have access to proposals.

Q: If the methods are under IP protection, would you accept sharing services, i.e. the product of using this method instead of methods?

A: This is a dynamic area, and we will work through the specific details with each team. Our general philosophy is to make every effort to ensure you can maintain and protect your IP. However, given the programme's collaborative nature, we will be encouraging creative solutions when IP sharing is necessary. The goal is always to pose the minimum possible risk to your IP. Examples of how we facilitate this include:
- Research-only licensing or usage agreements.
- Material transfer agreements (MTAs).
We are committed to working directly with you to protect your IP. We want the foreground IP generated here to benefit the whole community, and we are dedicated to protecting your rights while that happens.

Q: I have sensitive IP. Will I be forced to license it for research purposes in the programme?

A: Our goal is successful integration to achieve our galvanising demonstration so we will strongly encourage groups to find ways to share IP internally to facilitate this goal.

Q: How will intellectual property generated by the projects be handled?

A: ARIA's standard approach is to ensure that all foreground Intellectual Property (IP) remains with the creator or inventor who first generated it as a result of the funded project. We retain very limited rights to the IP, which are strictly for the purpose of internal programme management. Beyond this, our contracts incorporate founder-friendly principles to maximise the potential real-world impact of the research.

Additional information
ARIA's standard approach is that funding recipients will own any new intellectual property generated as a result of the grant/contract. We'll need some rights to the new intellectual property to help us evaluate the outputs during the funding agreement period. We've also included some provisions to support our mission of benefiting both the UK and the world, with this goal in mind, these provisions are carefully designed to avoid imposing significant hindrances on commercialisation. We'll need some rights to the new intellectual property to help us evaluate the outputs during the funding agreement period. We may adapt this approach depending on the needs of the programme, so please ensure to check the information specific to the funding call you are applying for.

Q: What are the terms for spinning out a company based on the research?

A: ARIA does not take any equity or royalties in spin-out companies. That agreement is strictly between you and your host institution. However, as part of our contracts, we place restrictions on the institutions we fund to ensure they do not take an excessive amount of equity. We put a cap on the equity the university can take to protect the founder's position.

Q: At what stage in the process could the details of equity and royalties be agreed upon?

A: ARIA is committed to supporting successful commercialisation, and our terms reflect this:
- ARIA does not take any equity or royalties in spin-out companies.
- The terms we sign with your host university (or research entity) ensure that if you spin out, the institution's stake is subject to a strict cap. Specifically, the university's potential equity is capped at 10%.
- These are fixed terms in our grant agreements and are not generally open to negotiation. You can find the full details of these policies, including the capped royalty rates, in the funding terms posted on our website.

Additional information
If you are successful, the type of funding agreement you will receive is dependent on a couple of factors: the activity being funded and the type of recipient.

- *Where the activity being funded is considered basic research (experimental or theoretical work undertaken primarily to acquire new knowledge of the underlying foundations of phenomena and observable facts, without any particular application or use in view/TRLs 1-3) and you are an Enterprise, ARIA will provide funding via a Basic Research Grant Agreement.*
- *Where the activity being funded is considered to be more technologically mature but still research and development (TRLs 3-6) and you are an Enterprise, ARIA will provide funding via a Research Contract.*
- *Where the activity being funded is between TRLs 1-6 and you are not an Enterprise (e.g. a university), ARIA will provide funding via a Standard Grant Agreement.*
- *If you are an individual working outside of any organisation, and are not an Enterprise (e.g. a sole trader), ARIA will provide funding via a Research Grant to an Individual.*

This framework of agreements has been developed to ensure compliance with the Subsidy Control Act.

Q: How is this grant different from a standard UKRI grant?

A: ARIA Programme Directors are more actively involved post-award to help manage projects and navigate challenges. Also, for collaborations, ARIA typically funds a single lead entity, which then manages sub-awards to partners.

Additional information
ARIA has a flexible approach to project management, recognising that managing projects across various fields and disciplines requires diverse methodologies. Our project management approach consists of:

1. *Project Initiation - We will ask you to document your project delivery plan, outlining your approach to project management, project plan, and key risks and opportunities you anticipate. These will be agreed upon between the Creators and Programme Teams, forming a baseline for the project and its delivery.*
2. *Quarterly Reviews - At the end of each quarter, we will ask for:*
   - Milestones Updates - Progress against specific contractual milestones.
   - Project Updates - A general update on your learnings, decisions, highlights, priorities, challenges, new collaborations, and team changes.
   - RAG Status - A simple way to communicate the project's health or status.

3. *ARIA Annual metrics - once a year, we will ask you to complete a metrics template, asking a set of standard questions which will help us measure ARIA's long term impact.*

Our standardised approach is flexible, allowing us to assess each project individually and tailor our methods to the project's size and scope.

Q: Once a project proposal is awarded will it be for the duration of the programme or is there a risk that the funds will be stopped at any point?

A: We plan to award funding for the full duration required for your project once it's successfully selected. However, the grant or contract will include pre-agreed milestones. These often feature "go/no-go" milestones—critical points where, if the research premise is not validated, the project may conclude. This structure is designed to be proactive, not punitive. The Programme Director and their team will be actively involved and have regular conversations with you to monitor progress. Since research is inherently unpredictable, we expect to pivot and adjust milestones as needed based on new learnings. This continuous dialogue ensures that if a project needs to end, it will be a comfortable, shared decision after exploring all viable paths, not a surprise.

Additional information

Project reviews will be conducted at specified intervals to consider the Creators' progress against agreed outputs and the milestones (negotiated at the start of the project). Following a review PDs may, in consultation with the Creator, adjust grant funding amounts, redefine outputs. Where the Creator fails to make progress against the milestones (or identify alternative paths to contribute to programme success) we would choose to end the agreement on performance grounds. There are a number of other reasons why we might choose to end an agreement, these include: if a key individual departs without an acceptable replacement, material breaches, reputational damage, provision of misleading information, or change of control posing national security risks.

Q: Will funding be released in one tranche or can it be iterative? We're considering developing an enabling technology which is relatively easy to timeline and cost, but if successful, we would want to disperse the technology through the rest of the consortium in wider collaborations, which would require a further round of funding. Can we make a proposal along these lines?

A: Yes, you can certainly submit a proposal along those lines. We are highly interested in funding enabling technologies and will be flexible regarding how the funding is released. While our default is to award funding for the full duration of a project upfront, we recognise that a different approach may be necessary. Tailoring the funding schedule to meet the project's and the programme's needs is a key part of how we support research. Please ensure you clearly detail your proposed phases and subsequent funding needs in your application.

Q: Do you accept Full Economic Costing (FEC) for indirect rates?

A: Yes. For UK research institutes, we accept FEC with no internal cap, as determined by audited track principles.

Additional information

Where required, we'll fund 100% of the costs. Matched funding is not essential. That said, we welcome proposals for match funding in cases when such funding will strengthen the potential success or the UK benefit of a project. Where you or your organisation wish to fund elements of the proposed project this should be identified in your proposal. This should not be included in the cost breakdown of funds requested from ARIA. In these cases, this funding contribution will be considered as part of the overall strength of the project proposal.

Q: If we plan to start an ARIA funded UK based company in parallel to the proposed research work, shall we cost it in the requested funds?

A: Include all the costs. We can definitely give funding to people who are based outside the UK and build in a process of them setting up a UK based company. While we encourage you to include your plans for company formation in your application, please be aware that certain costs are ineligible. Specifically, we cannot cover company incorporation fees. Your plans do not need to be firmly established at this stage; these are details we can finalise with you after a funding award is made. For a complete list of allowable expenses, please review the eligible cost guidance linked in the solicitation.

Additional information

You are encouraged to include the estimated costs for everything you require to deliver the proposed project, however there are some restrictions on what you can include, guidance on this can be found in our Eligible Expenditure Guidance. Throughout the solicitation process we only ask for the level of information we need at each stage of the process. This means the amount of information required can range from a high level figure at the outset of a funding call, through to a full cost breakdown if you are shortlisted for the final stages. At concept paper stage we will require you to estimate the high level cost of the project (a short table included in the call documents). At the full proposal stage we will ask you to complete a summary cost template. Prior to contract signature when the scope of work has been agreed we will ask for a detailed cost breakdown. Since we aim to attract applicants from diverse sectors, our cost sheets are designed to be generic and are not tailored to specific types of institutions such as universities or companies. When filling out the cost sheets, third-party collaborators should be identified as subcontractors or sub-grantees in the cost sheet, with only the lead applicant's indirect costs included under indirect costs. How you contract with these organisations is up to you, whether through collaboration agreements, service contracts, partnership agreements, or other arrangements.

Q: Should planned customer discovery costs be included in this application?

A: You should include all costs required to successfully deliver your project, but there are some that are ineligible. Please review the detailed eligibility criteria linked in the solicitation. If a cost isn't explicitly listed as ineligible, you can generally assume we'll cover it. If you're still uncertain about a specific expense, please submit a question via the clarifications email.

Q: How should a TA5 application be budgeted when the nature, timing, and scale of the outputs requiring standardisation, reproduction, and translation are not yet known?

A: We will not encourage or discourage concept papers based on budget. Propose the work you see and

budget you think will facilitate that work. We understand that, particularly for TA5, some of that will be guesswork. What we want is to see how you imagine handling the inherent uncertainty in the role, how you plan to best support the programme, and that you have the capabilities to do so.

Q: If the main aim of the programme turns out to be too ambitious to achieve, do you already have a 'plan B' to redirect resources?

A: We believe that partial success by achieving the goals of any of the TAs could be incredibly valuable. That said, there is no "plan B" in terms of the overall aim of the programme.