Engineering of Immune Cells Inside the Body (EMBODY)
Health Science Futures (HSF) Office
Innovative Solutions Opening ARPA-H-SOL-24-03
April 29, 2024

Contents

PART I: OVERVIEW INFORMATION

Federal Agency Name – Advanced Research Projects Agency for Health (ARPA-H), Health Science Futures Office

ISO Title – Engineering of Immune Cells Inside the Body (EMBODY)

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Dates

- Posting Date: **April 29, 2024**
- Proposers' Day: **April 18, 2024, from 11:00 AM to 3:00 PM EST**
- Proposers' Day Registration Deadline: **April 15, 2024**
- Solution Summary Due Date and time: **May 2, 2024, 5:00 PM EDT**
- Proposal Due Date and Time: **June 11, 2024, 5:00 PM EDT**

Concise description of the opportunity – The EMBODY program aims to transform engineered cell therapies for devastating, life-threatening, and hard-to-treat diseases. Recently, genetically engineered cells have emerged as revolutionary therapies to treat selected diseases and malignancies. However, *ex vivo* production of these products pose major hurdles including 1) technical complexities that require substantial patient participation, 2) lengthy wait times with a large portion of eligible patients dying or becoming ineligible while waiting for their cell therapy treatments, 3) poor access with less than 2% of U.S. hospitals having infrastructure, expertise, and experience to be able to offer these treatments, and 4) prohibitively high costs of goods per dose. EMBODY aims to solve all major *ex vivo* cell therapy challenges with one *in vivo* solution. Specifically, EMBODY seeks to develop novel off-the-shelf agents and approaches to genetically engineer immune cells *in vivo* for treating devastating diseases. EMBODY will leverage recent advances in the fields of viral vectors, gene therapies, nanoparticles, genetic engineering, genetic editing, cell/vector manufacturing, and advanced *in vitro* and *in vivo* models of the human immune system. Successful EMBODY outcomes will include platform approaches to genetically engineered immune cells *in vivo/ in situ*, cost effective production methods, and preclinical validation platforms to enhance translation to clinic, as well as specific therapy candidates developed through early clinical proof of concept.

Anticipated individual awards – Multiple awards are anticipated.

Potential award instruments – Other Transaction Agreements (OT).

Cost Sharing - Cost sharing is not required but may be proposed where appropriate.

Agency Contact – All inquiries shall be sent to EMBODY@arpa-h.gov.

PART II: FULL TEXT OF ANNOUNCEMENT

1. ISO Description

This publication constitutes a merit-based process in accordance with 42 U.S.C. § 290c. Any resultant award negotiations will follow all pertinent laws and regulations.

The mission of ARPA-H is to accelerate better health outcomes for everyone by advancing innovative research that addresses society's most challenging health problems. Awardees will develop groundbreaking new ways to tackle health-related challenges through high potential, high-impact biomedical and health research. ARPA-H seeks proposals to develop technologies that advance immune cell engineering *in vivo* to treat devastating and life-threatening diseases in an equitable, accessible, and cost-effective way. These key aims may be accomplished using technological advances in viral vectors, nanoparticles, gene editing, genetic engineering, as well as novel manufacturing techniques and advanced *in vitro* and *in vivo* models of the human immune system.

Specifically excluded are: 1) proposals that incrementally improve performance of existing approaches, 2) proposals that are not evaluating cost of goods, manufacturability, and product quality from the onset of the program, 3) proposals that do not address the objectives of the program, and 4) proposals directed towards policy changes, traditional education and training, or center coordination and construction of physical infrastructure, which are outside the scope of the ARPA-H mission.

1.1. Program Overview

Recent therapeutic advances have demonstrated that many diseases have an underlying immune component and may be tackled using immunotherapies. Genetically engineered cell therapies are revolutionary treatments that have shown durable efficacy in some terminal cancers (e.g., Chimeric Antigen Receptor (CAR) T cells for the treatment of advanced multiple myeloma, lymphomas, and leukemias). CAR T treatments are produced from patients' own immune cells via genetic engineering *ex vivo*. The production cycle of these therapies is several weeks, starting from blood draw and ending with the re-infusion of the final product into the same patient for autologous approaches. Since 2017, the FDA has approved six *ex vivo* CAR T cell therapies for cancer, all of which are autologous products, i.e., a patient is the source of cells and the recipient of the final product. The main barriers to getting cell-modifying gene therapies are cost of goods (COG) per dose, access to a qualified medical facility, and time to receive the therapy.

Cost of production: The manufacturing of *ex vivo* engineered autologous cell therapies is a complex and labor-intensive process. This process requires specialized clean rooms, highly qualified technical staff, and expensive materials and equipment. Currently, the COG (i.e., materials and labor) to produce the therapy to treat one patient is ~ $100,000, which is driven primarily by labor, plasmid, and media costs.

Access to highly specialized centers: Patients are only able to receive the existing *ex vivo* CAR T therapies at highly specialized network of hospitals with appropriate infrastructure. The network encompasses less than 2% of hospitals in the U.S., with ~25% of states having no qualified centers. Therefore, the avalanche of CAR T cell therapies and other cell therapies in clinical development does not guarantee that the needed infrastructure and capabilities would be expanded

geographically and would reach remote and rural America. This represents a tremendous issue of access and equity for the patient population. Travelling to a qualified center is burdensome for sick patients and requires significant financial and caregiver resources to commit.
Vein-to-vein time for the therapy: Although the typical vein-to-vein time (i.e., the time between blood draw and the time when a patient is infused with the manufactured CAR T therapy) is approximately six weeks, the vein-to-vein time may be drastically extended due to waiting times for manufacturing slot availability or failed steps in the process. During the waiting period, ~30% of patients worsen and become ineligible for the therapy or deceased.

EMBODY will overcome current limitations by:

1. Developing cell-specific targeting platforms that can deliver genetic cargo *in vivo* to any desired immune cells, but preferably mature lymphocytes, with low off-target delivery.
2. Optimizing delivered genetic cargo to engineer immune cells for efficacy, safety, and expression control.
3. Lowering COG, optimizing manufacturability, and ensuring high product quality.
4. Developing preclinical validation tools to enable quick and efficient translation of these approaches to clinic.

In this document, *in vivo* is defined as in animals or in humans, and *in situ* refers to modifications of immune cells *in vivo*

1.2. Technical Approach and Structure

1.2.1. Technical Areas (TAs)

The EMBODY program will catalyze the discovery and development of platforms and approaches for genetically engineering immune cells *in vivo* to treat devastating diseases like cancer, autoimmune disorders, chronic infections, etc. The EMBODY program will also catalyze the development of low-cost production approaches and more biologically relevant and robust preclinical models to validate and efficiently translate these approaches to engineering immune cells *in vivo*. The discovery process includes two technical areas (TA):

> Technical Area 1 (TA1): **Platforms and approaches for *in situ* generation of genetically engineered immune cells.** Development of cell-specific targeting approaches for immune cells. Development of genetic cargo that contains elements needed for therapeutic effects and genetic control elements, i.e., for control over gene expression, gene regulation, and gene editing. Combining the cell-specific and genetic cargo approaches to develop pharmaceutical candidates (herein, called "agents").
>
> Technical Area 2 (TA2): **Advanced production and validation of products developed using TA1 platforms.** Development of strategies and/or technologies to significantly reduce costs of goods of TA1 agents, ensure product scalability and high quality. Development of new or enhancement of existing advanced physical *in vitro* and/or *in vivo* models and systems that can be used for screening, validating, and quality control of TA1 agents.

Performers must submit proposals that cover both TAs. Proposals without both TAs will be deemed non-conforming and will not be reviewed.

Each proposal must be milestone driven and must be structured in four Phases with Go/No-Go criteria to proceed to the next phase. See Sections 1.2.2 Program Structure and Options, 1.2.5 Go/No-Go Checkpoints, and 1.3 Program Goals and Metrics for details.

1.2.1.1. TA1: Platforms and approaches for *in situ* generation of genetically engineered immune cells.

Recent advances in viral capsid engineering and non-viral particles have a great promise to deliver therapeutic payloads to specific cells. Novel promoters, gene regulation elements, and gene editing approaches have been recently developed to customize and control the payload function. Combinations of these carriers and genetic cargos open numerous opportunities to create therapeutic agents that could treat previously undruggable disease targets. However, even for therapeutic agents created by elegant combinations of carriers and genetic cargoes, off-target effects have been observed.

TA1 aims to develop agents that comprise delivery approaches and genetic cargos to target specific immune cells of choice and to genetically modify them for a therapeutic gain. An example of this approach includes generation of CAR T cells *in vivo* (instead of *ex vivo*).

To accomplish this, performers will pursue the following objectives simultaneously. They will design approaches to target specific immune cells *in vivo*. These approaches may include but are not limited to viral vectors, extracellular vesicles, nanoparticles, implantable scaffolds, and other synthetic carriers, that could be delivered *in vivo*. Performers will also design appropriate genetic cargo that could include but not limited to a gene of therapeutic interest, a gene for a functional receptor, a gene for intracellular protein, control elements like cell-specific promoters, logic gates, on/off switches.

To validate the platform approaches, performers must select at least 2 different indications (disease types) of which **at least 1 must be a non-oncology** indication **to develop product candidates towards an IND application.**

A proposal must consider and provide information on each of the following aspects.

Phase I (24 months) – completion expected in Q4Y2 (Q8):

- The proposal must detail a research plan to develop cell specific moieties that can deliver genetic cargo to an immune cell of choice. Mature lymphoid cells are preferred; however, other immune cell types may be selected. Target reservoirs of immune cells could be peripheral blood, lymph nodes, bone marrow, spleen. Performers must not target muscle, brain, eye, lung, gastrointestinal organs. Performers must aim to de-target the liver. If the proposed therapy aims to target liver-resident immune cells, then other liver cells (e.g., hepatocytes) must be de-targeted.
- The proposal must include detailed methodologies and rationale to develop and choose the therapeutic genetic cargo for engineering selected immune cells. Performers are encouraged to implement genetic controls or other control approaches.

- Note: a combination of cell targeting, and genetic cargo approaches is called an "assembled product" or an "agent" herein thereafter.
- The agents must be amenable to routes of administration that do not require specialized expertise not found in every community hospital.
- The proposal must include a technical plan that describes designing, screening, and testing each component separately and assembled products.
- The proposal must include plans for reproducibility testing.
- The proposal must include a technical plan to submit an INTERACT meeting package to the FDA for feedback by the end of Phase I. Performers are encouraged to consider biology, off-target effects, manufacturing, QC, animal testing strategies, and a rough clinical strategy as elements of the INTERACT package. It is recommended that performers start preparing for the INTERACT request submission in the first half of the second year to ensure timely completion. It is recommended that academic performers seek strategic, and document review regulatory services if they have not had INTERACT experience before. In the full proposal, proposers must provide a high-level timeline of regulatory activities including preparation, submission, and regulatory agency interactions for INTERACT (FDA), pre-IND (FDA), IND (FDA), and IRB (institution dependent). High-level clinical strategy must be developed in collaboration with expert clinicians for the first-in-human (FIH) trial. Performers are encouraged to include considerations for meaningful and feasible FIH readouts, site selection, availability of eligible patients, and the speed of recruitment that can realistically be achieved at the selected site. Additionally, performers are encouraged to consider the timeline and requirements for a future IRB approval and how the IRB timeline and requirements inform clinical activities from Day 1. At minimum, performers must engage with expert clinicians on Day 1 to start developing a realistic and actionable plan to enter clinic in Phase IV without major obstacles.
- It is encouraged that the INTERACT meeting package includes both TA1 and TA2 innovations.
- Consideration of potential obstacles that could require a revision in the work plan or milestones with a discussion of alternative approaches.
- A detailed schedule or timeline for each milestone and the overall goal.
- The first high-level Target Product Profile (TPP) drafts for selected candidates that would enter Phase II must be generated and may include but not limited to key product attributes, indication, dosing regimen, efficacy, safety, durability.
- For performers who pursue gene editing, additional requirements are outlined in the Gene Editing section below.

Phase II (12 months) – completion expected in Q4Y3 (Q12):

- Up to three (3) performers from Phase I could be selected to be tested in Phase II. Preference will be given to non-oncology indications. These candidates will have cleared performance thresholds set by metrics (see Section 1.3 Program Goals and Metrics).
- The proposal must include a technical plan that details the preclinical proof of concept experiments needed to show dose responses, efficacy, and safety profile at an efficacious dose *in vivo*.
- The tests must include dose finding, efficacy, assessment of off-target effects. Off-target effect assessment must include both delivery to undesired cell types and off-target genetic modifications, including expression of protein in undesired cells, integration and/or gene

editing (if editing is proposed) events near or in the loci of known oncogenic activity. When measuring off-target effects, kinetics must be considered. For example, if protein expression is expected at 1 week post injection, then off-target expression must be measured around that time. Several timepoints are encouraged.

- The proposal must have a technical plan to incorporate successful preclinical models developed in TA2. Performers are encouraged to use newly developed advanced *in vitro* models (if deemed successful) in both preclinical proof-of-concept (POC) testing and QC assay development.
- Proposals must include a strategic plan to submit the required documentation for a pre-IND meeting with the FDA. Ideally, performers must receive the pre-IND feedback by the end of Phase II to be able to begin incorporating this feedback from the start of Phase III. To stay on track, it is recommended that proposers begin pre-IND preparation at the beginning of Phase II to leverage the materials and feedback from the INTERACT meeting.
- It is encouraged that the package for the required pre-IND meeting include both TA1 and TA2 innovations.
- Performers must continue engaging with clinicians and refining the clinical plan using new information obtained in Phase II studies. A refined clinical plan must be available for ARPA-H to review as part of end-of-Phase II review.
- Performers must generate an updated TPP version for the selected candidate that would enter Phase III.
- Performers are required to share relevant data with the preclinical model developers to start developing correlative datasets. A data sharing plan must be provided.

Phase III (24 months) – expected completion in Q4Y5 (Q20):

- The ARPA-H Program Manager will select one candidate from Phase II to proceed to Phase III for IND-enabling studies if it meets pre-specified end-of-Phase II metrics.
- Performers must include a strategic and technical plan that details IND-enabling studies with corresponding metrics required for an IND application submission.
- If performers have submitted a pre-IND package to the FDA but have not received FDA feedback in Phase II of the project.
- Proposers must provide a description, a vendor/location, a timeline, and a budget line for IND-enabling GLP toxicology studies. To stay on track, it is recommended that the study begins no later than mid-Year 4.
- Proposers must provide a Phase III plan for analytical method development and clinical GMP product production for the first-in-human clinical trial.
- The proposal must include a strategic plan to use preclinical models successfully developed in TA2 (Phases I and II) for the IND-enabling studies.
- Performers must continue engaging with clinicians and refining the clinical plan using new information obtained in Phase III studies. A clinical operations plan outlining steps from the IND acceptance to dosing the first patient must be ready before the end of Phase III. This plan must aim at dosing the first cohort in the first half of Year 6 and collecting interim readouts at the end of Year 6.
- Throughout Phase III, performers must continue refining the clinical protocol, with a final version being ready to be submitted with an IND application by the end of Phase III. It is recommended that proposers begin preparing the IND application at the beginning of Year 5 (i.e., mid-Phase III) to stay on track to submit the IND application a month or two before

the end of Phase III. In the proposal, proposers must identify and budget for the operational and publishing support of the IND application.
- Performers must generate a refined TPP for the candidate that enters the first-in-human (FIH) trial.
- Performers are required to share relevant data with the *in vitro*, small animal, and large animal model developers to continue developing correlative datasets. A data sharing plan must be provided.

Phase IV (12 months) – expected completion in Q4Y6 (Q24):
- The proposal must include a strategic and technical plan for a FIH trial and must define clinically meaningful and feasible interim readouts that can be achieved within one year. Performers may propose a longer FIH trial; however, ARPA-H will fund only one year of a FIH trial for a successful candidate. If performers plan on conducting a longer study, they must seek additional funding and partnerships to see the study through completion.
- Performers should consider a high likelihood of the FDA asking for long-term follow-up (LTFU) of the FIH patients given that the tested candidate is likely to have unknown long-term effects. ARPA-H is not responsible for funding LTFU.

To achieve the goals of the program, performers may propose a variety of drug delivery approaches. These approaches can be separate or combined, and may include but are not limited to viral carriers (lentivirus, adeno-associated virus, other), lipid nanoparticles, non-lipid nanoparticles, virus-like particles, extracellular vesicles, exosomes, scaffolds, artificial lymph nodes, etc.

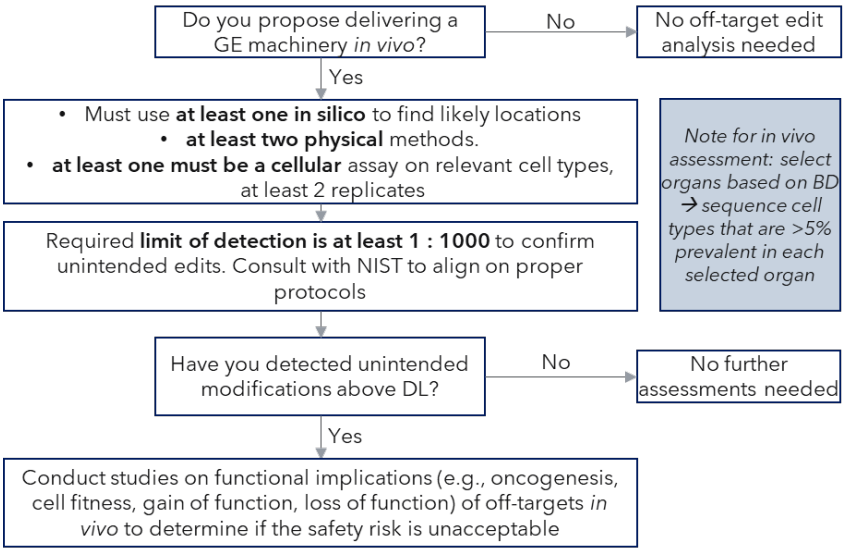
To achieve the goals of the program, performers may propose a variety of genetic engineering and gene modulation approaches. These approaches can be separate or combined, and may include but are not limited to gene editing (base editors, prime editors, gene writing, etc.), RNA interference, transcriptional activators and repressors, riboswitches, logic gates, miRNA binding sites, cell/tissue-specific promoters, etc.

Gene editing
If performers choose to deliver gene editing machinery *in vivo*, then rigorous testing of unintended modifications is required.
- Performers must consult with a NIST Gene Editing Consortium representative at least annually to align on the latest on methods, protocols, and reporting norms/standards (this consultation can/will be coordinated through the ARPA-H Program Manager).
- The required limit of detection (LOD) is at least 1:1000 to confirm unintended edits. If unintended edits are detected above LOD, then performers must conduct studies on functional implications (e.g., oncogenesis, cell fitness, gain of function, loss of function) of off-targets *in vivo* to determine if the safety risk is unacceptable.
- Performers must use at least 1 *in silico* method to find likely locations and at least 2 physical (non-computational) methods, of which at least 1 must be a cellular assay on relevant cell types. At least 2 replicates are required.
- Chromosomal re-arrangements must be tested by at least 1 method that detects aberrations of ≥5 Mb in size (e.g., karyotyping) and at least 1 method that detects aberrations between 5kb-5Mb (e.g., long-range PCR sequencing, optical genome mapping, target locus

amplification). On-target, hybrid capture NGS and long-range sequencing must detect similar frequencies of <10% of large (>30bp) insertions/deletions to prove that no inter-chromosomal translocations occur.

- The rigor must gradually increase from Phase I (discovery) through Phase II (pre-IND) to Phase III (IND).

The following decision chart outlines the requirements for assessment of unintended edits (BD = biodistribution, DL = detection limit, GE = gene editing):



This concludes the Gene Editing section.

Proposers must provide the following information in the proposal for TA1:

- Any preliminary data that has already been generated in support of this proposal.
- Funding sources that already cover aspects of the proposed research.
    - It is critical that the proposers clearly articulate how ARPA-H funding is complementary and not duplicative to the existing funding.
    - All active and pending grants (e.g., NIH, HHS, NSF, etc.) must be mentioned. Please see the Administrative & National Policy Requirements Document for submission requirements.
- List of patents (see Section 4.2.3 “Intellectual Property”).
- Gantt chart timeline.
- Proposed budget and team members per task.
- Risk mitigation (contingency plans) and alternative approaches.
- Timeline of regulatory events for each of four phases (please indicate not only when a regulatory event should occur, but also when the preparation for such an event should begin to stay on track; also indicate a responsible person for each event and preparation for it).
- Brief description of commercialization path (it is preferred that performers conduct a brief market landscape assessment for their choice of cells and indications).
- Equity and accessibility plan.

1.2.1.2. TA2: Advanced production and validation of products developed using TA1 platforms.

Innovative strategies to reduce COG, ensure scalability, and enable robust product quality are needed for these advances to reach a broad patient population. Robust and predictive preclinical validation is critical to reduce the translation risk and to increase the translation speed.

TA2 is focused on creating best-in-class production and validation approaches for TA1 agents.

Production:
In parallel to designing and testing the TA1 approaches for efficacy and safety, performers will work on COG reduction and quality control (QC) strategies from Day 1. Performers are encouraged to implement manufacturability/scalability and QC criteria early in the design/screening of best agents. Such criteria may include but are not limited to yield, scalability, quality (e.g., full/empty ratios), reproducibility. Performers are encouraged to conceive of and propose drastically innovative ideas for COG reduction.

Validation:
Performers must propose to develop new or enhance existing physical (*in vitro* and/or *in vivo*) models to improve predictive value, speed, and cost of translation of TA1 agents to humans. Performers may choose to pursue the development, validation, and implementation of any number of *in vitro* and/or *in vivo* models as long as the models aim to address TA2 objectives and meet metrics outlined in this section and Section 1.3.3.

- Performers must propose to develop at least 1 new or enhance at least 1 existing physical (*in vitro* or *in vivo*) model to address two objectives:
  - Objective 1: be more predictive of responses to TA1 agents, and
  - Objective 2: allow for faster measurements and/or be cheaper to implement.
  - The improvement of chosen parameters (i.e., predictive value, speed, or cost) must not be at the expense of the other parameters.
- Preclinical models should represent platform technologies, i.e., they should be either disease agnostic or should be suitable for a large group of disease indications with minimal or no manipulations required to adjust to specific indications.
- Performers may select to pursue the development of *in vitro*, or *in vivo*, or both (*in vitro* and *in vivo*) model systems.
- Selected models must be suitable for genetic therapies that aim to generate *in situ* engineered immune cells.
- Testing of these models using TA1 agents must be proposed.
- *In silico* model must include a physical model.
- Development of models that have a clear potential to be off-the-shelf, i.e. not customized for each patient, is encouraged.
- Equitable genetic diversity of model systems is encouraged.
- *In vitro* models should be validated using at minimum a small animal model.
- All proposed animal models must recapitulate both human phagocytic and non-phagocytic immune cell types simultaneously.
- If large animal model development is pursued, interim metric(s) of success must be proposed (e.g., survival, pregnancy rates, number of embryos).

Examples of models and improvement areas may include but are not limited to the following areas:

a) Advanced *in vitro* systems:
   - 3D spheroids recapitulating immune cells and tumor microenvironment.
   - *In vitro* pharmacology methods that may satisfy the FDA requirements in lieu of *in vivo* pharmacology.
   - *In vitro* dose selection methods.
   - 3D spheroid systems that revolutionize quality control assays.
   - *In vitro* models with increased sensitivity of off-target effect detection.
   - *In vitro* models that allow for a drastic increase in the number of candidates screened, or in the number of immune cells tested, or in the number of tumor types tested simultaneously.
   - *In vitro* systems that allow for comprehensive and human-relevant measures of immune response.
   - *In vitro* systems for early reads on yield/titer or key quality attributes.
   - *In vitro* systems that can substitute *in vivo* models (i.e., substitute more complex models with less complex models).
   - *In vitro* systems that allow for testing of a much larger number of parameters in the same model.

b) Advanced *in vivo* models:
   - Next-generation animal humanization. Existing humanized models do not fully replicate human immune systems, immune tissues, or all relevant immune cells. This presents a gap in effective utilization of animal models to fully characterize safety profiles of TA1 agents including comprehensive characterization of potential off-target effects. If humanization is pursued, both mature lymphoid and mature myeloid cells must be recapitulated with durable phenotype.
   - Ambitious *in vivo* models to measure multiple safety and efficacy parameters at once.
   - Small and large animal models are in scope. Congruent animal models are a plus.
   - Optimization of small and large animal models for large candidate library screening.
   - Approaches to reduce the number of *in vivo* models needed.

c) Correlative datasets from *in vitro*, small animal, and large animal models that enable prediction of responses to TA1 agents in less complex models.

d) Computational approaches for (not sufficient without a physical model but can be pursued as complementary techniques):
   - COG, yield, quality, product lot variability, and other critical CMC parameters.
   - Interpatient variability analyses to ensure robust unintended genetic modifications testing, as well as to inform optimal design of gRNA, miRNA, and other relevant genetic elements of TA1 agents.

Performers may suggest other areas for improvement of predictive value, speed, and cost of preclinical tools. All suggested areas must have rationales provided.

<u>Not in scope for TA2 validation model development:</u>

- Preclinical models for other biologics, small molecules, or any other modality that is not for *in situ* immune cell engineering.

- Preclinical models that are suitable only for a specific disease indication and cannot be used for a variety of indications.
- Solely mathematical modeling that does not support physical testing.
- Artificial intelligence (AI)/ Machine Learning (ML) that does not drive development of *in vitro* models.
- AI/ML models with insufficient dataset size.
- Disease models that do not incorporate immune system components.
- Model development in non-human primates (NHP).
- Development cycles for pre-clinical models beyond Phase I for a prototype (except for a large animal models, for which the development cycle should be within the Phase I+II timeframe). This will allow for testing in Phase III.

A proposal must consider and provide information on each of the following aspects.

Phase I (24 months) – completion expected in Q4Y2 (Q8):

- The proposal must include strategies to produce pilot material of the assembled product at low COG by the end of Q4Y2. When estimating COG, performers must consider future contributions of scale-up and GMP grade components to COG.
- Pilot material for preclinical POC studies in Phase II must be successfully produced in Phase I.
- Performers must propose a plan to develop, characterize, and validate tools/ technologies that improve the predictive value of discovery and preclinical studies of TA1 agents. In addition, these tools and technologies must improve speed and/or cost of discovery and preclinical development. Any number of novel tools and technologies is allowable as long as their utility for TA1 agent development and translation is justified.
- Preclinical models should represent platform technologies, i.e., they should be either disease agnostic or should be suitable for a large group of disease indications with minimal or no manipulations required to adjust to specific indications.
- *In vitro* and/or *in vivo* models may be developed. *In vivo* models may include small and/or large animal models.
- In addition to applications for discovery and preclinical studies, it is preferred that *in vitro* models support CMC activities of TA1 agents.
- *In silico* system development is not required but is welcome if such systems can meaningfully augment or enhance *in vitro* and *in vivo* tools and technologies.
- Performers may choose to initiate the development of a compatible set of small and large animal models that are congruous and aim to improve translation of TA1 agents.
- If performers chose to pursue large animal model development, they may aim to complete this development at the end of Phase II (not Phase I). However, they must develop interim metrics of success for Phase I (see Section 1.3.3. for examples).
- Performers must make attempts to discuss the use of these optimized or new *in vitro* and *in vivo* models in the INTERACT briefing book for the FDA. It is encouraged that at the end of Phase I, performers obtain FDA feedback on the usefulness of these models for preclinical/IND-enabling studies.

Phase II (12 months) – completion expected in Q4Y3 (Q12):

- The proposal must include technical plans to generate a sufficient supply of the product suitable for GLP IND-enabling toxicology studies in Phase III.
- The proposal must include a technical plan to test the scalability of the production process (see Metrics).
- For Phase II studies, performers should select the best performing Phase I *in vitro* systems for process development and QC of TA1 agents. If none of the *in vitro* systems meet pre-specified metrics or do not significantly improve over existing models, then existing models must be used in TA1 Phase II Preclinical POC studies and QC efforts.
- For Phase II studies, performers must select the best performing small animal models for preclinical proof of concept experiments. If none of the small animal models meet pre-specified metrics or are not a significant improvement over existing models, then existing models must be used in TA1 Phase II Preclinical POC studies.
- During Phase II preclinical POC studies, performers must collect response and other data to start generating correlative datasets (the goal of Phase III).
- If performers pursue large animal model development, they must aim to complete development of their large animal model by the end of Phase II.
- It is encouraged that performers obtain feedback from the FDA on the TA2 models as part of the pre-IND meeting.

Phase III (24 months) – expected completion in Q4Y5 (Q20):

- By the end of Phase III, performers must produce a sufficient clinical-grade material supply for the FIH trial.
- The proposal must include a technical plan to test the scalability of the production process (see Metrics).
- During Phase III of the projects, performers must use best *in vitro*, small animal, and/or large animal models as part of IND-enabling studies or CMC activities, if appropriate.
- Performers should strive to build correlative datasets for *in vitro* systems and animal models in response to TA1 biological agents. One of the goals of such datasets is to determine when/which simpler models can be used in lieu of more complex models to speed up development and validation of TA1 agents and ensure translation to clinic.

Phase IV (12 months) – expected completion in Q4Y6 (Q24):

- Successful small and large animal models should be selected for deposition and dissemination through the NIH and commercial vendors for broad use by the research and biopharmaceutical community. Animal models should be thoroughly documented and registered with up-to-date resource tagging and plans to provide access to animals or cryopreserved germ cells should be put forward.
- Specific plans for protocol, tool, and reagent sharing should be prepared and distributed to provide community resources and encourage rapid adoption without undue intellectual property constraints.

Proposers must provide the following information in the proposal for TA2:

- Any preliminary data that has already been generated in support of this proposal.
- Funding sources that already cover aspects of the proposed research.
    - It is critical that the proposers clearly articulate how ARPA-H funding is complementary and not duplicative to the existing funding.

    - All active and pending grants (e.g., NIH, HHS, NSF, etc.) must be mentioned. Please provide a detailed description of the research that is covered. Please see the Administrative & National Policy Requirements Document for submission requirements.
- List of patents (see section 4.2.3.3 "Intellectual Property").
- Gantt chart timeline.
- Proposed budget and team members per task.
- Risk mitigation (contingency plans) and alternative approaches.
- Model depositing and dissemination plan.

Performance reporting will be required throughout the program:

- Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager team.
- More frequent interactions to discuss underlying science, project challenges, and other project-related topics are recommended but not required.
- End-of-Phase project reports are required for ARPA-H to make Go/No-Go decisions.
- ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress.

1.2.2. Program Structure and Options

The EMBODY program is structured as a 6-year effort consisting of four sequential phases of increasing drug development complexity as shown in **Figure 1**. EMBODY includes realistic and measurable goals for performers to ensure the success of the program as well as checkpoints at the transitions between EMBODY phases:

- Phase I - Base = (24) Months
- Phase II – Option = (12) Months
- Phase III – Option = (24) Months
- Phase IV – Option = (12) Months

ARPA-H may elect to not proceed to a subsequent phase and, thus, the **option may not be exercised**.

For TA1, Phase I is 24 months and includes the design, screening, and testing of cell specific targeting approaches and genetic cargo. Iterative optimizations of assembled candidates are likely to occur in the second year of Phase I. Progression to Phase II of the project is designed to occur upon meeting specified metrics and selecting up to 3 successful candidates. It is important that the INTERACT meeting package is submitted to the FDA and the meeting is requested by the end of Phase I.

In Phase II, the performers will have 12 months to focus on preclinical POC studies in relevant animal models. Performers are expected to implement the INTERACT meeting feedback from the FDA if the meeting is granted. Successful *in vitro* assays and/or small animal models from TA2 will be utilized in this Phase. Successful *in vitro* assays are expected to be used in both preclinical POC studies and in quality control criteria development, if relevant. Progression to Phase III of the project is designed to occur upon meeting specified metrics and selecting 1 successful candidate for the IND-enabling studies. It is important that a pre-IND package is submitted to the FDA and a pre-IND meeting is requested by the end of Phase II of the project.

In Phase III, performers will have 24 months to perform IND-enabling studies and prepare for an IND application submission. It is expected that the performers implement pre-IND meeting feedback in this Phase. During Phase III, the IRB protocol for the future FIH is prepared and, ideally, approved by the end of Phase III. Progression to Phase IV of the project will occur upon meeting specified metrics.

In Phase IV, performers will have 12 months to start the FIH trial, recruit patients, and acquire interim data on relevant biomarkers, on- and off-target effects, and safety. It is important to note that ARPA-H may support only a small FIH trial, with up to three dose escalation cohorts (~10 patients) and only up to readouts at a 12-month mark. ARPA-H will not support an extension cohort or readouts beyond 12 months. If the sponsor wishes to design and execute a larger and longer study, they are expected to find full support for the trial in the form of other complementary funding sources or in the form of a commercial license to a for-profit company.

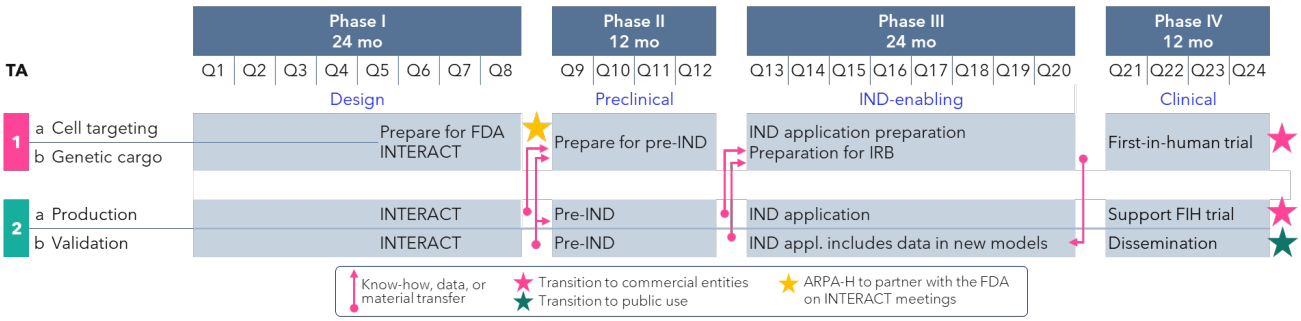
For TA2, performers will have 24 months to design the COG reduction and other CMC strategies and to start the development of validation models/systems to use in TA1 Phase II Preclinical POC studies and quality control assay development. Performers should consider including new *in vitro* and small animal models into the INTERACT package for the FDA mentioned above. To transition to Phase II, if applicable, performers must select the best systems that meet specified metrics. If performers proposed to develop a large animal model, due to technical hurdles associated with larger animal model development, such as elongated gestation and weaning periods, performers will have to propose interim Phase I metrics of successful ongoing development but will not have to demonstrate a viable large animal model.

In Phase II, the CMC teams will pursue process development to implement COG reduction and other CMC strategies. In parallel, *in vitro* systems and small animal models will be used in testing TA1 agents, and the response data will be collected to develop correlative datasets on all preclinical models. Performers are expected to implement the INTERACT meeting feedback from the FDA if the meeting is granted. At the end of Phase II, it is expected that performers obtain FDA pre-IND feedback that would cover TA2 CMC and the use of TA2 validation models for TA1 agents.

In Phase III, the performers will have to tighten up the release criteria and produce clinical material for the first-in-human (FIH) trial. Performers must ensure that at this scale and grade the product still meets COG metrics. Performers will also have to demonstrate that their production process is scalable. All successful models from TA2 will be utilized in the IND-enabling studies. Successful *in vitro* systems will be used in product QC. Performers will have 24 months to generate correlative response data between *in vitro*, small animal, and/or large animal models. Correlative datasets will be developed. There is no specific metric of success after TA2 Phase III. Instead, there is a requirement that if preclinical models developed in TA2 will have been used to generate data for the IND application (and if the IND application was accepted by the FDA), then performers are obligated to disseminate these models to a broader research community and prepare requisite documentation to facilitate broader use.

In Phase IV, performers must prepare a plan for characterization, use, deposition, and dissemination of successful and well characterized preclinical models to the scientific community, along with correlative datasets developed for these models.

Figure 1. Program structure by phase and year.



1.2.3. Equity Requirements

ARPA-H has indicated it is committed to equitable healthcare access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. The EMBODY program is committed to equitable access, and the genetic cargoes and cell specific carriers **must** be designed to take into account the patient mix (genetic, sex, etc.) relevant to the selected applications. Importantly, EMBODY is enabling off-the-shelf therapies that can be administered at any U.S. hospital. Finally, EMBODY is laser focused on drastically reducing production costs of these therapies not only to create room for lower competitive prices, but also to reduce barriers for generic versions of these produces (i.e., bioequivalents/biosimilars) to enter the market post patent expiry and to enable product and method standardization.

1.2.4. Data Sharing Plan

The proposers must provide a detailed plan of what types of data they will be sharing with the scientific community as the result of this project. All non-proprietary data should be shared with the scientific community promptly within a year of generation. The specific repository method should be discussed and chosen in agreement with the ARPA-H Program Manager.

In addition, the proposers must provide an explicit plan for timely material and data exchange between all team members on the proposal. The data exchange between TA1 and TA2 performers must not be impeded. Especially, in TA2 Phase III, correlative datasets on responses in preclinical models to TA1 agents should be generated based on the data acquired in TA1 Phases II and III. The data should be transmitted frequently, in a timely manner, and in its entirety.

Preclinical model dissemination will require performers to prepare plans for sharing and distribution of non-data resources that will be generated by the proposed project, including animal strains, cryopreserved germ lines, protocols, biomaterials, and reagents.

1.2.5. Go/No-Go Checkpoints

For details on Go/No-Go decisions, please see tables in Section 1.3 Program Goals and Metrics and Figure 1 in Section 1.2.2.

Progression into future phases will be determined by the ARPA-H PM.

1.3. Program Goals and Metrics

To evaluate the effectiveness of a proposed solution in achieving the stated program objectives, the following program metrics will serve as the basis for determination of satisfactory progress to warrant continued funding. Although the program metrics are specified below, proposers should note that the Government has identified these goals with the intention of bounding the scope of effort while affording maximum flexibility, creativity, and innovation of proposed solutions to the goals. Proposals must cite the quantitative and qualitative success criteria that the effort will achieve at each phase's program milestone, as well as the measurement of intermediary metrics. If the metrics are not meaningful for a particular case, proposing teams are expected to provide their own metrics and describe the quantitative improvement that those metrics represent over the state-of-the-art. Power analysis calculations may be needed to support the proposed metrics.

1.3.1. Overall Program Goals

The overall EMBODY goal timeline is shown in **Figure 1**. The overall program goals are listed in **Table 1**. The expected metrics and Go/No-Go decision points by phase are listed in **Table 2** (for TA1) and **Table 3** (for TA2). In addition to frequent performance reviews throughout the phases, performers must provide an end-of-phase final report that summarizes all efforts and data for each completed EMBODY Phase.
Note that in their proposals, performers must provide relevant quantitative and qualitative metrics by Phase as well as Go/No-Go decision points. Performers who have not had experience in biopharmaceutical product development from discovery through FIH testing should consider seeking consultations and project management experts with experiences in setting milestones and metrics, as well as in crafting Gantt charts, overlaying timelines of critical activities, and product development plans.

Table 1. Overall Program Goals

Parameter	**Goals**
Cell targeting specificity	• Sufficient cell targeting of selected cells *in vivo* must be achieved to provide therapeutic effect after genetic engineering of the cells for a selected indication.
Off-target effects	• Off-target effects must be minimized and rigorously measured. • For performers who chose to pursue gene editing delivery as part of their platforms/products: No evidence of integration or editing events for loci known to have oncogenic activity. No evidence of unacceptable/detrimental functional implications of off-target edits.
Therapeutic efficacy	• Developed therapeutic candidates must demonstrate meaningful efficacy for at least two selected indications, of which at least one must be a non-oncology indication.
Durability	• Product candidates must exhibit a durable therapeutic effect; specifically, they must not require chronic administration. One-and-done treatment schedules are preferred.
Safety	• Developed candidates must demonstrate acceptable safety for chosen indications. • Genetic material delivered to undesired cells must be silent or harmless.

	• Safety must be ensured not only by optimizing genetic cargo and cell-specific carriers, but also through stringent QC criteria.
COG	• COG must be at least 10x lower than what can be achieved with the current production methods. Synthetic or LNP-based products must have COG of <$1,000 and viral-based products must have COG of <$10,000 of a GMP grade product needed to treat one patient.
QC	• QC assays must be well developed and validated to ensure product safety.
Repro-ducibility	• Results must be reproducible (see metrics for reproducibility requirements).
Preclinical systems	• Improve predictive value, speed, and/or cost of preclinical validation systems for translation of TA1 agents to humans. • Develop preclinical models that are either disease agnostic or suitable for a large group of disease indications. • Successfully developed models must be used in Preclinical POC and in IND-enabling studies and/or CMC activities. • Correlative datasets based on responses to TA1 agents should be developed for *in vitro*, small animal, and/or large animal models. Correlative datasets should help identify when and where simpler models could predict responses in more complex models. • Preclinical models must be disseminated to a broader research community.

1.3.2. TA1 Metrics

Table 2.

Metrics	**Specifications**
	Phase I (24 months): Program Quarters Q1-Q8
Efficacy	• Performers must propose a minimum percent of targeted cells based on cell of choice, indication, and therapeutic effect sought. **At least 2** different indications (disease types) must be proposed of which **at least 1 must be non-oncology** indication. • Preference will be given to targeting non-phagocytic cells as it is much more technically challenging to target non-phagocytic cells *in vivo.* • For non-phagocytic cell (e.g., T, NK, and B cells), **> 5%** (or the minimum required to achieve a therapeutic effect) **of cells** must be targeted *in vivo*.* If the proposed minimum is <5%, then it would have been defined in the proposal before the funding approval and would have been supported with a strong rationale. ARPA-H does not guarantee that it would accept the rationale. • For phagocytic cells (e.g., monocytes, macrophages, and dendritic cells), **>30%** (or the minimum that is required to achieve a therapeutic effect) **of cells** must be targeted *in vivo*. Similarly to the previous metric for mature lymphocytes, prior approval of a different metric is required if it is <30%. • Demonstrate **reproducibility**: the percentage of cells of choice targeted *in vivo* must be reproducible in **at least 2 different laboratories** in hands of different investigators. An independent lab for independent validation and verification (IV&V) studies is preferred.

	• *In vitro* **viability** of transduced targeted cells must be demonstrated at **>80%**. • If cell expansion is critical for the indication pursued, an *in vitro* cell expansion assay must show **≥100x expansion potential** of transduced and expressing cells. • For gene editing only: on-target editing must be demonstrated in **≥10%** of immune cells of choice, stable overtime, **>50% bi-allelic** (unless a strong biological/clinical rationale is provided to the contrary). • **Positive** readouts from functional assays demonstrate that genetically engineered cells have proper biological activity. **"> 5%" of T cells means that, of all circulating T cells, >5% have been successfully transduced, and the delivered genetic material can be detected by PCR.*
Durability	• The duration of expression must be estimated in **at least 1 *in vitro* assay**. Durability of the expression must be acceptable for designed functional efficacy.
Safety	• **No evidence of** integration (for integrating viral vectors) or editing (for performers pursuing gene editing) events near or within loci known to have oncogenic activity tested by appropriate well-powered analytical techniques using cells from multiple animal and human donors. • For gene editing only: Must use at **least 1 *in silico*** method to find likely locations and **at least 2 physical (non-computational) methods**, of which **at least 1 must be a cellular assay** on relevant cell types. **At least 2 replicates** are required**.** • For gene editing only: Required limit of detection (LOD) is **at least 1:1000** to confirm unintended edits. Consult with NIST to align on proper protocols. If unintended edits are detected above LOD, then conduct studies on functional implications (e.g., oncogenesis, cell fitness, gain of function, loss of function) of off-targets *in vivo* to determine if the safety risk is unacceptable. • For gene editing only: Chromosomal re-arrangements must be tested by **at least 1 method that detects aberrations of ≥5 Mb** in size (e.g., karyotyping) and **at least 1 method that detects aberrations between 5kb-5Mb** (e.g., long-range PCR sequencing, optical genome mapping, target locus amplification). On-target, hybrid capture NGS and long-range sequencing must detect similar frequencies of <10% of large (>30bp) insertions/deletions to prove that no inter-chromosomal translocations occur. • For gene editing only: in WT mice, human DNA must be below the limit of quantification in reproductive organs (testis, prostate, uterus, ovary). • Genetic cargo must contain **at least 1 genetic control element**. • The rigor of genetic control must be proportional to half-life of the proposed candidates. On/off switches, cell-specific promoters, and other regulatory elements can be engineered if they may address product safety concerns.

	• Expression of delivered genes in undesired (non-target) cells must be **below the limit of detection** to ensure safety. • Preliminary readouts on liver toxicity markers in humanized mice or an alternative model are encouraged. • For gene editing only: Meet with NIST to align on methods and protocols for measuring unintended editing events.
Regulatory	Submit an **INTERACT** package for the FDA feedback.
Clinical	Provide a high-level draft of a clinical synopsis that has been generated in collaboration with an expert clinician.
TPP	• Generate the first high-level TPP drafts for selected candidates that would enter Phase II. Include key product attributes, indication, dosing regimen, efficacy, safety, durability.
	Phase II (12 months): Program Quarters Q9-Q12
Efficacy	• **At a selected dose, using the pilot material** (from TA2)**, in a relevant animal model**, demonstrate that the targeting rate of selected cells is still above the threshold selected in Phase I. • **>50%** of transduced cells of choice express a detectable amount of protein. If the expression level is <50%, then a strong rationale must be provided as to why the level of expression is sufficient for efficacy. ARPA-H does not guarantee that the rationale would be accepted. Expression must be measured at appropriate timepoints (see discussion in Section 1.2). • A disease-specific biomarker of response is detected at a level suggesting that functional efficacy can be achieved **in at least 2 relevant animal models**. • Demonstrate **reproducibility** of functional efficacy results in **at least 2 different laboratories** in hands of different investigators. An independent lab for IV&V studies is preferred. • Demonstrate **a dose response** in small animals. • If cell expansion is critical for the pursued indications, an *in vivo* cell expansion potential must be at least **≥100x** for transduced and expressing cells.
Durability	• Estimate duration of response **in animals**. Chronic administration of these products is not acceptable. • Estimate the number of doses required to elicit efficacy and complete the treatment. The number of doses must be taken into account when estimating the COG per patient in the COG metric (TA2 metrics below).
Safety	• **At selected dose, maintain no evidence of integration** (for integrating vectors) **or editing events** (for gene editing) near or within loci known to have oncogenic activity. • **At selected dose**, maintain expression of delivered genes in undesired (non-target) cells **below the limit of detection as determined in *in vivo* models.** • Acceptable safety profile at efficacious dose.

	• For gene editing only: Off-target and off-tissue gene editing by organ and cell analyses (multiple immune and non-immune cell population separation) with similar quantitation requirements must include **at least 1 cellular assay** with **LOD of at least 1:1000**. • For gene editing only: *in vivo* assessment of unintended gene editing must be based on selected organs based on biodistribution studies, then sequencing cell types that are >5% prevalent in each selected organ. • For gene editing only: Meet with NIST to align on methods and protocols for measuring unintended editing events. • Complete biodistribution studies of TA1 agents in different organs and multiple immune and non-immune cell populations. • Confirm Phase I findings in organ toxicity and reproductive toxicity in small animals.
Regulatory	• Receive **pre-IND meeting feedback** from the FDA to be implemented in Phase III of the project. At minimum, a pre-IND package must be ready for submission by the end of Phase II.
Clinical	• To inform Phase III studies, complete **a clinician-vetted list of interim endpoints** that are meaningful to measure in the FIH trial. Ideally, pre-IND feedback would be used to refine the interim endpoints. • A refined version of the clinical synopsis including insights from Phase II POC studies and CMC activities must be available.
TPP	• Generate an updated TPP version for the selected candidate that would enter Phase III. Include more details on key product attributes, indication, dosing regimen, efficacy, safety, durability.
	Phase III (24 months): Program Quarters Q13-Q20
Efficacy	• Demonstrate **clinically meaningful level of efficacy** of the selected candidate for treatment of the disease of choice.
Durability	• Demonstrate durability of the candidate for treatment of selected disease
Safety	• Demonstrate safety of the candidate for treatment of the disease of choice. GLP tox in NHP – biodistribution of drug product (DP) and of *in situ* generated engineered immune cells of choice. Includes complete necropsy, following the **FDA-pathology organ list**, **at 3 time points**. • For gene editing only: Meet with NIST to align on methods and protocols for measuring unintended editing events. • For gene editing only: GLP tox in NHP – determine off-targets using **at least 1 cellular assay**.
Regulatory	• An IND application accepted by the FDA.
Clinical	• Receive IRB approval for the FIH trial.
TPP	• Generate a refined TPP for the candidate that enters the first-in-human trial.
	Phase IV (12 months): Program Quarters Q21-Q24
Clinical trial outcomes	• **Meet interim endpoints** on safety and efficacy.

	• At minimum, dose **the first cohort** and **readout** safety and biomarker endpoints **at 3 months.**

1.3.3. TA2 Metrics

The expected TA2 metrics and Go/No-Go decision points by phase are listed in **Table 3**.

Table 3. TA2 Metrics and Go/No-Go Decision Points by Phase.

Metrics	**Specifications**
	Phase I (24 months): Program Quarters Q1-Q8
CMC	• Estimated COG/patient for a GMP grade product is **at least 10x lower** than what it would have been with the current process (i.e., **<$1,000** for synthetic nanoparticles and EVs, **<$10,000** for viral or other biological agents).** • Successful production of pilot material for Phase II Preclinical POC studies. • At minimum, a CMC potency assay should read **>50% expression-positive transduced cells** when isolated immune cells of choice are treated with candidates selected for Phase II. ***"<$1,000" means that the COG of a one-and-done (single dose) treatment must be <$1,000; a two-dose treatment course - <$500 per dose; a 10-dose treatment - <$100 per dose.*
Preclinical models *(see Section 1.2.1.2 for details)*	• Must propose to develop **at least 1** new or enhance **at least 1** existing physical (*in vitro* or *in vivo*) model to address two objectives: o Objective 1: be more predictive of responses to TA1 agents, and o Objective 2: allow for faster measurements and/or be cheaper to implement. o The improvement of chosen parameters (i.e., predictive value, speed, or cost) must not be at the expense of the other parameters. o Preclinical models should represent platform technologies, i.e., they should be either disease agnostic or should be suitable for a large group of disease indications
In vitro model examples with metrics (illustrative, not exhaustive)	• **≥10x** increase in sensitivity of off-target effect detection. • **≥10x** increase in number of candidates screened, or in number of immune cells tested, or in number of tumor types tested **simultaneously**.
In vivo model examples with metrics (illustrative, not exhaustive)	• Recapitulated **all** mature **myeloid** and **lymphoid** human immune cells **in the same model** and maintained the phenotype for **≥6** weeks. • Develop a model in which **≥3** different routes of administration can be tested **at once**. • Develop a model where **both efficacy and safety** can be assessed **in the same animal**.
Regulatory	• Receive feedback from the FDA (INTERACT). Feedback must be either positive or feasible to address in Phases II and III of the program.
	•

	Phase II (12 months): Program Quarters Q9-Q12
CMC	• Maintain the goal of **10x reduction** in COG **at stringent product release** requirements. (<$1,000 for synthetic and <$10,000 for biologics). • Demonstrate that COG remains at the acceptable threshold in **at least 2 repeat productions**. • Developed a list of product quality attributes, ideally implementing successful novel advanced *in vitro* systems from TA2 Phase I. • Produce enough product suitable for GLP IND-enabling toxicology studies. • Demonstrate **≥10x scale-up** potential in the number of produced **doses** (per production run) vs Phase I pilot production. • For gene editing only: Characterization product lot for off-targets using hybrid capture NGS.
Preclinical validation models	• Validated the models and approaches selected after Phase I in preclinical POC studies and in CMC activities. • Received the FDA feedback (pre-IND) on using the methods for IND-enabling studies and in the IND application.
	•
	Phase III (24 months): Program Quarters Q13-Q20
CMC	• Maintain the achieved **10x reduction in COG for the clinical product** for FIH with stringent release criteria. Synthetic product COG <$1,000 and biological/viral-based product COG <$10,000 per patient. • Produce a sufficient supply of the clinical GMP product for the FIH trial. • Demonstrate **≥100x scale-up** potential in the number of produced **doses** (per production run) vs Phase II.
Preclinical validation models	• Validated the selected models in the IND-enabling studies. • Reviewed positively by the FDA as part of the IND application. • For performers who chose to develop models with increasing complexity (i.e., *in vitro* → small animal, or small animal → large animal, or *in vitro* → small animal → large animal), developed correlative dataset to ensure translation and the use of less complex models in lieu of more complex models.
	•
	Phase IV (12 months): Program Quarters Q21-Q24
Dissemination	Disseminate successful models, requisite documentation, and resources developed in TA2 through publicly accessible resources.

1.4. General Requirements

1.4.1. Proposing Teams

It is expected that proposals will require diverse teams with the **expertise needed to achieve the goals** of both TA1 and TA2. While ARPA-H expects proposer teams to encompass a variety of organizational types (e.g., commercial organizations, academic institutions, etc.), to ensure future commercialization success and adherence to project timelines, it is highly encouraged that the

entity proposing as the single prime awardee be a commercial organization[1] (e.g., biotech/biopharma or another for-profit company).

Specific content, communications, networking, and team formation are the sole responsibility of the proposer[2]. Proposers must submit a single, integrated proposal led by a Principal Investigator (PI), under a single prime awardee[3] that addresses all program Phases, as applicable. Proposers may submit only one proposal[4] as the prime proposer. A group may participate in two proposals but cannot be the prime proposer on both. Proposer's Day will be an additional platform for proposers to find co-performers, especially across TA1 and TA2, who rarely work with each other. It is likely that performer groups will be collaborations between multiple academic institutions and for-profit organizations. We encourage performers in TA2 to leverage manufacturing and quality control expertise of for-profit companies or of cGMP cell and vector manufacturing facilities at academic institutions or hospitals. TA1 performers should include biomedical engineers (broadly defined), genetic engineers, chemists, and other relevant experts. TA2 performers must comprise CMC experts and model development experts (depending on the model selected: animal biologists, engineers, computational scientists, etc.).

If animal models are pursued in TA2, then TA1 performers would need to pursue partnerships with institutions that have deep expertise and infrastructure to accommodate development of animal models. In such cases, TA2 performers would comprise a team of animal model scientists and clinicians with access to husbandry facilities and infrastructure to generate and test novel animal models, especially long-term development of larger animal models. Performers must demonstrate that they are able to secure the required infrastructure for animal model development and that they have a clear plan of disseminating successful animal models to broader research communities. Additionally, **it is critical that an independent team (with experience in *in vivo* testing) executes animal studies in Phase II and Phase III of the project**, and not the same team that developed TA1 agents or TA2 validation models. This will ensure unbiased execution of animal experiments and additional reproducibility and robustness of the obtained data for TA1 agents. Importantly, clinicians must be consulted with respect to dose ranges, routes of administration, interim readouts for the FIH clinical trial, and other disease-relevant parameters throughout the entire project length.

If a proposal has one Principal Investigator (PI), the PI must commit at least 50% effort. If proposed, co-PIs must have at least 20% effort each and co-Is must have at least 5% effort each.

A full-time experienced Project Manager (PM) must be budgeted for in the proposal and must be onboarded by performers upon successful award to ensure efficient communication between performer teams and subcontractors, and with ARPA-H. A PM candidate resume or a qualification requirements description (if PM is to be found) must be provided as part of the proposal.

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1. Commercial organization means an organization, institution, corporation, or other legal entity, including, but not limited to, partnerships, sole proprietorships, and limited liability companies, that is organized or operated for the profit or benefit of its shareholders or other owners. The term includes small and large businesses and may be used interchangeably with "for-profit organization."

2. Proposer refers to all respondents to this Innovative Solutions Opening at all stages of the ISO.

3. Awardee is synonymous with performer and in this announcement refers to any entity entering into an award with the Government. Prime awardee is thus synonymous with prime performer. Subawardees refer to entities performing in support of a Government award, without a direct award from the Government (i.e., support is provided directly to the prime performer or other tier subawardee).

4. In this document, proposal refers both to the solution summary and the full proposal unless otherwise indicated.

ARPA-H will hold a Proposers' Day (see Section 8, *Other Information*) to facilitate the formation of proposer teams and enable sharing of information among interested proposers.

2. Award Strategy

The ISO constitutes a merit-based solicitation, and the number of awards made will depend on the quality of the proposals received and the availability of funds. Proposals are expected to use innovative approaches that include novel technology, enabling revolutionary advances in medicine and healthcare. The ISO uses merit-based competitive procedures to the maximum extent practicable. It is highly encouraged that commercial organizations propose as the prime on teams (teams may comprise a wide variety of organizations, including academic institutions and other non-profit entities). ARPA-H has determined, based on extensive market intelligence and the nature of the EMBODY program, that this approach will be most effective in increasing the likelihood of programmatic success. A principal goal of the EMBODY program is driving down the COG of cell-modifying gene therapies. While many entities will be able to support this goal, this goal must be a day one consideration of any award and commercial organizations are best positioned to achieve this goal as the ultimate provider or provider partner for any resultant technology created under the EMBODY program. This arrangement also puts the Government in a direct relationship with the commercial organization, removing barriers between ARPA-H and the commercial organization that will provide EMBODY technology to patients. That direct relationship will help ensure the program does not lose focus of the ultimate end goal of significantly reducing the cost of gene therapies.

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this ISO and to make awards without negotiations with proposers. The Government also reserves the right to conduct negotiations if it is later determined to be necessary. Additionally, ARPA-H reserves the right to accept proposals in their entirety or to select only portions of proposals for negotiation and award. The Government reserves the right to fund proposals in phases, including as optional phases, as applicable. ARPA-H reserves the right to make multiple awards, a single award, or no awards. Multiple awards are anticipated.

Proposals identified for award negotiation will result in OTs. OTs are commercial-like contractual arrangements. Specific terms and conditions will be negotiated for each OT. An OT terms and conditions template will be provided if selected for award negotiations.

The Agreements Officer has sole discretion to negotiate all terms and conditions with selectees. ARPA-H will incorporate pre-publication reviews or other restrictions, as necessary, if it determines the research resulting from the proposed effort will present a high likelihood of disclosing sensitive information including Personally Identifiable Information (PII), Protected Health Information (PHI), financial records, proprietary data, and any information marked Sensitive but Unclassified (SBU), Controlled Unclassified Information (CUI), etc. Any award resulting from such a determination will include a requirement for ARPA-H permission before publishing any information or results on the program.

3. Eligibility Information

3.1. Eligible Applicants

Federal entities, such FFRDCs, UARCs, federal agencies, etc. may **not** propose to this ISO as either a prime or sub-awardee. However, ARPA-H is committed to working closely with its federal partners and federal entities interested in supporting the EMBODY program may contact ARPA-H directly at EMBODY@ARPA-H.gov.

3.2. Non-U.S. Organizations

ARPA-H will prioritize awards to entities (organization and/or individuals) that will conduct funded work in the United States. However, non-U.S. entities may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. In accordance with these laws and regulations, in no case will awards be made to entities organized under the laws of a covered foreign country [as defined in section 119C of the National Security Act of 1947 (50 U.S.C. Ch 44 § 3059)]; a foreign entity of concern meeting any of the criteria in section 10638(3) of the CHIPS and Science Act of 2022; [an individual that is party to a malign foreign talent recruitment program, as defined in Section 10638(4) of the CHIPS and Science Act of 2022; or entities suspended or debarred from business with the Government.

4. Submission Information

4.1. ISO Package

The official ISO and attachments are those posted on the System for Award Management (SAM) at SAM.gov. This announcement and any references to external websites herein constitute the total solicitation. If proposers cannot access the referenced material posted in the announcement found at https://www.sam.gov/, please contact the administrative contact listed herein.

4.2. Content and Form of Submission

NOTE: Non-conforming submissions that do not follow ISO instructions may be rejected without further review at any stage of the process.

All submissions must be written in English with type not smaller than 12-point font (Arial or Times New Roman) and 1-inch margins. Smaller font may be used for figures, tables, and charts. Documents submitted must be clearly labeled with the ARPA-H ISO number, proposer organization, and proposal title/proposal short title.

Proposers are responsible for clearly identifying proprietary information. Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary." The government will protect any submissions marked as proprietary.

NOTE: "Confidential" is a classification marking used to control the dissemination of U.S. Government National Security Information as dictated in Executive Order 13526 and should not be used to identify proprietary business information.

4.2.1. Solution Summary Format

All Solution Summaries (formerly known as abstracts) submitted in response to this solicitation must comply with the content and formatting requirements in Appendix A. Solution summaries may not exceed four pages, excluding the cover page and Rough Order of Magnitude (ROM). The Government will not review pages beyond four (4) pages. Official transmittal letter is not required.

Based on the evaluation of Solution Summaries, selected teams will be invited to submit full proposals.

4.2.2. Full Proposal Format

All proposals submitted in response to this ISO must comply with the content and formatting requirements in the applicable Bundle of Attachments templates. Proposers should use the templates provided in the Bundle of Attachments. The Bundle of Attachments includes the following five templates:

1. Tech and Management (35 pages)
2. Task Description Document (no page limit)
3. Cost Proposal (no page limit)
4. Cost Proposal Spreadsheet (fill in applicable tabs)
5. Administration & National Policy (no page limit)

Documents requested to be submitted with the templates should be included as attachments to the applicable template (e.g., HSR/ASR documents included as attachments to the Administration & National Policy template, cost back-up as attachments to the Cost Proposal template, etc.). Each template includes instructions for completion.

4.2.3. Administrative and National Policy Requirements

Proposers must complete the Administrative and National Policy Requirements document. Additional information regarding completion of the document is included below.

4.2.3.1. Organizational Conflicts of Interest

Proposers are required to identify and disclose all facts relevant to potential organizational conflicts of interest (OCI) involving the proposer's organization and any proposed team member (proposed subawardee). Although the FAR does not apply to OTs, ARPA-H requires OCIs be addressed in the same manner prescribed in FAR subpart 9.5. Regardless of whether the proposer has identified potential OCIs under this section, the proposer is responsible for providing a disclosure with its proposal. The disclosure must include the proposer's and, as applicable, proposed team members' OCI mitigation plans, if necessary. The OCI mitigation plan(s) must include a description of the actions the proposer has taken, or intends to take, to prevent the existence of conflicting roles that might bias the proposer's judgment and to prevent the proposer from having unfair competitive advantage. The OCI mitigation plan will specifically discuss the disclosed OCI in the context of each of the OCI limitations outlined in FAR 9.505-1 through FAR 9.505-4. The disclosure and mitigation plan(s) do not count toward the page limit.

4.2.3.1.1. Government Procedures

The Government will evaluate OCI mitigation plans to avoid, neutralize, or mitigate potential OCI issues before award and to determine whether it is in the Government's interest to grant a waiver. The Government will only evaluate OCI mitigation plans for proposals determined selectable under the ISO evaluation criteria and funding availability.

The Government may require proposers to provide additional information to assist the Government in evaluating the OCI mitigation plan.

If the Government determines a proposer failed to fully disclose an OCI; or failed to provide the affirmation of ARPA-H support as described above; or failed to reasonably provide additional information requested by the Government to assist in evaluating the proposer's OCI mitigation plan, the Government may reject the proposal and withdraw it from consideration for award or cancel award.

4.2.3.1.2. Agency Supplemental OCI Policy

In addition, ARPA-H restricts performers from concurrently providing professional support services, including Advisory and Assistance Services or similar support services, and being a technical performer. Therefore, as part of the FAR 9.5 disclosure requirement above, a proposer must affirm whether the proposer or any proposed team member (proposed subawardee, etc.) is providing professional support services to any ARPA-H office(s) under: (a) a current award or subaward; or (b) a past award or subaward that ended within one calendar year prior to the proposal's submission date.

If any professional support services are being or were provided to any ARPA-H office(s), the proposal must include:

- The name of the ARPA-H office receiving the support;
- The prime contract number;
- Identification of proposed team member (proposed subawardee) providing the support; and

An OCI based on a performer currently providing professional support services, as described above, cannot be mitigated.

4.2.3.2 Current and Pending Support (Other) and Biographical Sketch Common Forms

Proposers must submit and complete the Pending Support (Other) and Biographical Sketch Common Forms. The forms are mandatory for all Senior/Key Personnel. Weblinks to the Common Forms may be found in the Administrative & National Policy Requirements Document.

4.2.3.3 Intellectual Property

Proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all intellectual property (IP) that will be utilized for the proposed effort. ARPA-H strongly encourages IP rights to be aligned with open-source regimes. Further, it is desired that all non-commercial software, software documentation, and technical data generated and/or developed under the proposed project is provided as a deliverable to the Government. IP

delivered to the Government should align with project or program goals and should be aligned with the level of Government funding provided to generate and/or develop the IP.

NOTE: IP rights assertions will be reviewed under evaluation criteria 2 stated in Section 5.2.

4.2.3.4 Human Subjects Research (HSR)

All entities submitting a proposal for funding that will involve engagement in human subjects research (as defined in 45 CFR § 46) must provide documentation of one or more current Assurance of Compliance with federal regulations for human subjects protection, including at least a Department of Health and Human Services (HHS), Office of Human Research Protection Federal Wide Assurance. All human subjects research must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46 and/or. 21 CFR § 56 The entities human subjects research protocol must include a detailed description of the research plan, study population, risks and benefits of study participation, recruitment and consent process, data collection, and data analysis. Recipients of ARPA-H funding must comply with all applicable laws, regulations, and policies for the ARPA-H funded work. This includes, but is not limited to, laws, regulations, and policies regarding the conduct of human subjects research, such as the U.S. federal regulations protecting human subjects in research (e.g., 45 CFR § 46, 21 CFR § 50, § 56, § 312, § 812) and any other equivalent requirements of the applicable jurisdiction.

The informed consent document utilized in human subjects research funded by ARPA-H must comply with all applicable laws, regulations, and policies, including but not limited to U.S. federal regulations protecting human subjects in research (45 CFR § 46, and, as applicable, 21 CFR § 50). The protocol package submitted to the IRB must contain evidence of completion of appropriate human subjects research training by all investigators and key personnel who will be involved in the design or conduct of the ARPA-H funded human subjects research. Funding cannot be used toward human subjects research until ALL approvals are granted.

4.2.3.5 Animal Subjects Research

Award recipients performing research, experimentation, or testing involving the use of animals shall comply with the laws, regulations, and policies on animal acquisition, transport, care, handling, and use as outlined in: (i) 9 CFR parts 1-4, U.S. Department of Agriculture rules that implement the Animal Welfare Act of 1966, as amended, (7 U.S.C. § 2131-2159); (ii) the Public Health Service Policy on Humane Care and Use of Laboratory Animals, which incorporates the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training," and "Guide for the Care and Use of Laboratory Animals" (8th Edition)." Proposers must complete and submit the Vertebrate Animal Section worksheet for all proposed research anticipating Animal Subject Research.

All Animal Use Research must undergo review and approval by the local Institutional Animal Care Use Committee (IACUC) prior to incurring any costs related to the animal use research.

4.2.3.5 Controlled Unclassified Information (CUI) on Non-Federal Information Systems

Further information on Controlled Unclassified Information (CUI) identification, marking, protecting and control is incorporated herein and can be found at 32 CFR § 2002.

4.2.4. Submission Information

Submissions must be made to:

1. Solution Summaries must be submitted to https://solutions.arpa-h.gov/
2. Proposals must be submitted to https://solutions.arpa-h.gov/Submit-Proposal/

Solution Summaries and proposals must be submitted by the deadlines outlined in Part I., Overview Information.

*NOTE: Submissions received after these dates and times will **not** be reviewed.*

4.3. Funding Restrictions

Pre-award costs will **not** be reimbursed unless a pre-award agreement is negotiated prior to award.

4.4. Questions

Interested entities may submit questions to the ISO Coordinator via the ISO mailbox EMBODY@arpa-h.gov Answers to questions received will be posted to the same website. ARPA-H will likely post answers to all relevant non-duplicative questions at intervals.

5. Application Review Information

5.1. Evaluation Criteria

Solution Summaries will be evaluated based on Evaluation Criteria #1 and #2, in descending order of importance.

Solution Summaries that are outside the scope of the ISO will not be evaluated further. In addition, Solution Summaries that do not meet the submission requirements or do not contain one or more of the required items listed above may be deemed non-conforming and will not be evaluated further.

Full proposals will be evaluated using Evaluation Criteria #1-4, listed in descending order of importance.

5.1.1. Evaluation Criteria #1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, and complete. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible. The proposal represents a revolutionary change rather than an incremental advance.

5.1.2. Evaluation Criteria #2: Proposer's Capabilities and/or Related Experience

Potential future research and development, commercial, and/or clinical applications of the project proposed, including whether such applications may have the potential to address areas of currently unmet needs within biomedicine and improve health outcomes. Degree to which the proposed project has the potential to transform biomedicine. Potential for the project to take an interdisciplinary approach. In addition, the evaluation may take into consideration the extent to which the proposed IP rights and software components will potentially impact the ability to commercialize the technology. Finally, the proposal is not only a request to fund clinical trials of an otherwise developed product, policy changes, traditional education and training, or center coordination, formation, or development, and construction of physical infrastructure.

5.1.3. Evaluation Criteria #3: Proposer's Capabilities and/or Related Experience Potential Contribution and Relevance to the ARPA-H Mission

The proposed technical team has the expertise and experience to accomplish the proposed tasks. The proposer's prior experience in similar efforts clearly demonstrates an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule. The proposed team has the expertise to manage the cost and schedule. Similar efforts completed/ongoing by the proposer in this area are fully described, including identification of other Government or commercial activities where they have led or participated.

5.1.4. Evaluation Criteria #4: Price Analysis

Price and/or value analysis will be performed to assess the reasonableness and value the overall proposed price provides to the Government for the technical solution selected.

When price and value analysis are inconclusive, cost realism analysis may be performed to ensure proposed costs are realistic for the technical and management approach, accurately reflect the technical goals and objectives of the solicitation, the proposed costs are consistent with the proposer's Scope of Work and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach.

It is expected that the effort will leverage all available relevant prior research to obtain the maximum benefit from the available funding. ARPA-H recognizes that undue emphasis on cost may motivate proposers to offer low-risk ideas with minimum uncertainty and to staff the effort with junior personnel to be in a more competitive posture. ARPA-H discourages such cost strategies. Proposed cost sharing may be considered as well.

NOTE: Proposers are encouraged to propose the best technical solution. Proposers are discouraged from proposing low-risk ideas with minimum uncertainty and to staff the proposed effort with junior personnel to be more appealing from a dollar threshold. ARPA-H seeks novel solutions that are accompanied by a Volume 2 proposal that is reflective of the level of effort and risk proposed.

5.2. Review of Solution Summaries and Full Proposals

5.2.1. Review Process

It is ARPA-H policy to ensure impartial, equitable, comprehensive Solution Summary/proposal evaluations based on the evaluation criteria listed in Section 5.1. and to select the source(s) whose proposed solution that best meets the Government's technical, policy, and programmatic goals.

ARPA-H will conduct a scientific/technical review of each conforming solution summary/proposal. Conforming solution summaries/proposals comply with all requirements detailed in this ISO; solution summaries/proposals that fail to do so may be deemed non-conforming and may be removed from consideration. Solution summaries/proposals may be considered non-conforming if:

- The proposed concept does not fit within the program structure described in Part II, Section 1.
- The proposer did not meet the eligibility requirements.
- The proposal did not meet the submission requirements including registration in the System for Award Management (www.sam.gov).
- The proposal did not meet the content and formatting requirements.
- The proposer's concept has already received funding or been selected for award negotiations for another funding opportunity, whether from ARPA-H or another Government agency.

Please note that ARPA-H reserves the right, at its discretion, to reject as non-conforming proposals that it determines are substantially duplicative of previously submitted solution summaries, abstracts, and proposals under this or other ARPA-H solicitations. However, submissions under previous or current ARPA-H solicitations will not be automatically eliminated based on the same or similar solution proposed to another ARPA-H solicitation.

Solution summaries/proposals will not be evaluated against each other since they are not submitted in accordance with a common work statement.

Award(s) will be made to proposers whose solutions are determined to be the most advantageous to the Government, consistent with instructions and evaluation criteria specified in the ISO, considering price reasonableness and availability of funding.

5.2.2. Handling of Competition Sensitive Information

It is the policy of ARPA-H to protect all proposals as competitive sensitive information and to disclose their contents only for the purpose of evaluation and only to screened personnel for authorized reasons, to the extent permitted under applicable laws. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by ARPA-H support contractors for administrative purposes and/or to assist with technical evaluation.

All ARPA-H support contractors are expressly prohibited from performing ARPA-H sponsored technical research and are bound by appropriate nondisclosure agreements. Input on technical aspects of the proposals may be solicited by ARPA-H from non-Government consultants/experts who are strictly bound by appropriate non-disclosure requirements. No submissions will be returned.

6. Award Administration Information

6.1. Selection Notices and Notifications

6.1.1. Solution Summaries

ARPA-H will respond to each responsive solution summary. At that time the proposer will be informed that:

1. ARPA-H does not request that the proposer submit a full proposal;
2. ARPA-H requests that the proposer submit a full proposal;
3. ARPA-H will contact the proposer for explanation on any unclear elements in the submitted solution summary in order to determine whether the solution summary will be selected.

Feedback will be provided to the administrative and technical points of contacts noted on the solution summary cover page.

Timelines for receipt of proposals will be provided to proposers as part of the request.

ARPA-H will review all conforming full proposals using the published evaluation criteria and without regard to any comments resulting from the review of a solution summary.

6.1.2. Full Proposals

As soon as the evaluation of a full proposal is complete, the proposer will be notified that:

1. ARPA-H has not selected the proposal; or
2. ARPA-H has selected the proposal for funding pending award negotiations, in whole or in part. Official notifications will be sent via email to the Technical POC and/or Administrative POC identified on the proposal coversheet.
3. ARPA-H requires an explanation of any unclear elements in the submitted proposal. Based on that discussion, ARPA-H may not select the proposal or select the proposal in whole or in part and enter into negotiations.

Feedback will be provided to the administrative and technical points of contacts noted on the proposal cover page.

6.2. Reporting

In addition to the reports noted above in the technical section, the number and types of reports will be specified in the individual award document. As a typical model, ARPA-H expects the reporting will include monthly financial status reports, monthly technical status reports, quarterly reports, and an end-of-phase report. The reports shall be prepared and submitted in accordance with the procedures contained in the award document and mutually agreed on before award. Reports and briefing material will also be required as appropriate to document progress in accomplishing program metrics. A Final Report that summarizes the project and tasks will be required at the conclusion of the performance period for the award, notwithstanding the fact that the research may be continued under a follow-on vehicle.

6.3. Electronic Systems

6.3.1. System for Award Management (SAM) and Unique Identifier Requirements

All proposers must have a valid Unique Entity ID (UEI) number and be registered in SAM, or have begun the SAM registration process, in order for their proposal to be found conforming. Proposers must maintain an active registration in SAM.gov with current information at all times during which a proposal is under consideration or have a current award with ARPA-H. Information on SAM.gov registration is available at SAM.gov.

NOTE: New registrations take an average of 7-10 business days to process in SAM.gov. Registration requires the following information:

- SAM UEI number
- Tax Identification Number (TIN)
- Commercial and Government Entity Code (CAGE) Code. If a proposer does not already have a CAGE code, one will be assigned during SAM registration.

  Electronic Funds Transfer information (e.g., proposer's bank account number, routing number, and bank phone or fax number).

6.3.2. i-Edison

The award document for each proposal selected for funding will contain a mandatory requirement for patent reports and notifications to be submitted electronically through i-Edison (https://www.nist.gov/iedisondison).

6.3.3 Section 508 of the Rehabilitation Act (29 U.S.C. § 749d)

All electronic and information technology acquired or created through this ISO must satisfy the accessibility requirements of Section 508 of the Rehabilitation Act (29 U.S.C. § 749d).

7. Agency Contacts

Points of Contact:

The ISO Coordinator for this effort may be reached at EMBODY@ARPA-H.gov.

Collaborative efforts/teaming are encouraged. Interested parties should submit a one-page profile with their contact information, a brief description of their technical capabilities, and the desired expertise from other teams, as applicable. The Embody Teaming Profile Form may be found here: https://forms.office.com/g/rwxDgT3jS2

8. Other Information

ARPA-H will host a Proposers' Day in support of the EMBODY Program on the date listed in Part I., *Overview Information* of this ISO. The purpose is to provide potential proposers with information on the EMBODY program, promote additional discussion, and encourage team networking.

Interested proposers are not required to attend, any materials formally presented at Proposers' Day will be posted to SAM.gov.

ARPA-H will not reimburse potential proposers for participation at the Proposers' Day or time and effort related to submitting solution summaries/full proposals. To participate in the event, proposers must complete the online registration form located at:
https://solutions.arpa-h.gov/Events/EMBODY/

Participants are required to register no later than the date listed in Part I., *Overview Information* of this ISO. This event is not open to the press. To facilitate easier access to underserved communities, Proposers' Day will be a hybrid event.

APPENDIX A: SOLUTION SUMMARY TEMPLATE

SOLUTION SUMMARY COVER LETTER

<PRIME ORGANIZATION LOGO (OPTIONAL)>

Innovative Solutions Opening	
Solution Summary Title	
Submitter Organization	
Type of Organization	**Choose all that apply:** Large Business, Small Disadvantaged Business, Other Small Business
Technical Point of Contact (POC)	Name: Mailing Address: Telephone: Email:
Administrative POC	Name: Mailing Address: Telephone: Email:
Total Basis of Estimate	Total: $
Place(s) of Performance	
Other Team Members (subawardees and consultants) if any	Technical POC Name: Organization: Organization Type:

SOLUTION SUMMARY FORMAT

CONCEPT SUMMARY

Describe the solution summary concept with minimal jargon and explain how it addresses the goals of the EMBODY program.

INNOVATION AND IMPACT

Clearly identify the outcome(s) sought and/or the problem(s) to be solved with the proposed technology concept. Describe how the proposed effort represents an innovative and potentially revolutionary solution to address the technical challenges outlined in the EMBODY ISO. Explain the concept's potential to be disruptive compared to existing or emerging technologies and how the proposed approach will go far beyond current existing capabilities. To the extent possible, provide quantitative metrics in a table that compares the proposed technology concept to current and emerging technologies which may include:

- A progression of increasingly complex technical challenges.
- State of the art / emerging technology "baseline."
- Aggressive metrics in for each year of the proposed project.
- Summary of specific outcomes from the proposed research.

PROPOSED WORK

Describe the final deliverable(s) for the project, key interim milestones, and the overall technical approach used to achieve project objectives. Discuss alternative approaches considered, if any, and why the proposed approach is most appropriate for the project objectives. Describe the background, theory, simulation, modeling, experimental data, or other sound engineering and scientific practices or principles that support the proposed approach. Provide specific examples of supporting data and/or appropriate citations to scientific and technical literature. Identify adoption challenges to be overcome for the proposed technology to be successful. Describe why the proposed effort addresses the EMBODY ISO and the key technical risks. At a minimum, the solution summary should address:

- Does the approach require one or more entirely new technical developments to succeed?
- How will technical risk be mitigated?
- What use cases, capabilities, or demonstrations will be featured?

TEAM ORGANIZATION AND CAPABILITIES

Indicate the roles and responsibilities of the organizations and key personnel that comprise the Project Team. Provide the name, position, and institution of each key team member and describe in 1-2 sentences the skills and experience they bring to the team.

ROUGH ORDER OF MAGNITUDE

Please include a ROM by phase for federal funds requested, as well as the total project cost including cost sharing, if applicable. The ROM should encompass all applicable costs and proposers should modify the below to best reflect expected costs. The ROM should also include a breakdown of the work by direct labor (fully burdened), labor hours, subcontracts, materials, equipment, other direct costs (e.g., travel), profit, cost sharing, and any other relevant costs. The ROM does not count toward the page limit. The below table may be used for this breakdown:

Categories	**Amount**
Direct Labor (Fully burdened)	
Labor hours	
Subawardees	
Materials	
Equipment	
Travel	
Other Direct Costs	
Profit	
Total	
Cost Sharing (if applicable/appropriate)	