Antigens Predicted for Broad Viral Efficacy through Computational Experimentation (APECx)
Health Science Futures (HSF) Office
Research & Development Solicitation 75N99224R00001
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PART I: OVERVIEW INFORMATION

- **Federal Agency Name –** Advanced Research Projects Agency for Health (ARPA-H), Health Science Futures Office (HSF)
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  - Proposal Due Date and Time: **January 19, 2024, 5:00 PM EDT**

Concise description of the funding opportunity – The APECx program aims to transform vaccine antigen (Ag) discovery by leveraging recent advances in protein structure resolution, high-throughput (HT) functional characterization, predictive modeling, and platform vaccine technologies to deliver genus-level evolution-resistant vaccine candidates against various viral infections, including cancer-causing viruses and viruses that cause acute and chronic illnesses. APECx seeks to develop novel Ag design workflows to achieve this goal by coupling advanced experimental techniques for viral protein structure determination, high-throughput functional analysis, and high-throughput immunological assays with structural and functional prediction and modeling algorithms. Current protein structure prediction algorithms have limitations in accurately modeling viral protein structures due to the limited viral structure representation in the protein database (PDB) and the unique characteristics of viral proteins. These algorithms also face challenges in predicting the impact of mutations, post-translational modifications, multi-domain structures, and protein-protein interactions. These structure prediction and modeling capabilities play a crucial role in designing effective vaccine Ag. When these capabilities are improved and combined with high-throughput epitope mapping, Ag discovery and functional analysis, they have the potential to support genus– and family-level chimeric Ag design with predictive immunology markers. APECx seeks to mature and adapt these emerging technologies towards vaccine development for viral diseases and will incorporate equity outcomes for vaccine delivery in the U.S., resulting in a substantial decrease in the disease burden experienced by patients, healthcare systems, and the overall economy.

- **Anticipated individual awards –** Multiple awards are anticipated.
- **Potential award instruments –** Cooperative Agreements or Other Transaction Agreements (OT).
- **Agency Contact –** All inquiries shall be sent to APECx@ARPA-H.gov

PART II: FULL TEXT OF ANNOUNCEMENT

1. Funding Opportunity Description

This publication constitutes a merit-based process in accordance with 2 Code of Federal Regulations (CFR) § 200.205 and is in accordance with section 499A of the Public Health Service Act (PHSA). 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 is soliciting proposals to develop toolkits to identify and design chimeric and highly effective vaccine Ag. The focus will be on leveraging high-throughput functional analysis, protein structure prediction and protein engineering to achieve this goal. It is important to note that proposals will not be considered 1) if they merely offer incremental improvements in the existing state of the art, such as Ag discovery leading to vaccines with limited coverage across a viral genus. Additionally, proposals concentrating on virus families that are well-funded and heavily studied (e.g. viral families that include influenza, SARS-CoV-2, and HIV) will be excluded, 2) proposals that do not address the objectives of the program, 3) proposals directed towards policy changes, traditional education and training, or center coordination and construction of physical infrastructure are outside the scope of the ARPA-H mission.

1.1. PROGRAM OVERVIEW

The APECx program aims to create a toolkit to enable accurate chimeric and broadly efficacious vaccine Ag discovery through predictive modeling, high-throughput functional experimentation, and protein engineering. To fundamentally transform the vaccine research and development (R&D) sector, APECx will develop an innovative viral Ag prediction pipeline for broad efficacy by combining expedited experimental protein structure and function determination with high-throughput Ag screening. This will be enhanced with structural and functional prediction and protein modeling algorithms. Product developers will contribute to modeling tool evaluation from the start of the program to ensure discoveries satisfy the translational requirements. The combined effort of all the teams will create a toolkit that will enable the U.S. to achieve genus-level vaccine goals and prevent multiple viral diseases, including those responsible for cancer, acute disease, and chronic illness across the country and the world.

Current approaches to vaccine development are costly, time-consuming, and have not yielded broadly-efficacious vaccines for viral disease. Due to the technical complexities, most developers target a single virus species as the indication for a given vaccine, as the cost and time associated with evaluating the clinical efficacy of a vaccine leads to a risk-averse "one-virus, one-vaccine" development strategy. Novel protein structure prediction algorithms, such as AlphaFold2 (AF2)

and RoseTTAFold (RF), have revolutionized protein structure prediction for various applications and have the potential – when combined with high-throughput functional experimentation discoveries – to unlock new possibilities within vaccine development approaches. However, the effectiveness of these algorithms correlates with the amount of experimentally-resolved structure data found in the open-source Protein Data Bank (PDB). The PDB's structural repertoire is significantly biased toward soluble eukaryotic and bacterial proteins, with viral proteins constituting less than 6% of the total. Additionally, the existing prediction algorithms face challenges in accurately predicting the impact of mutations, post-translational modifications, multi-domain structures, and protein-protein interactions. These core capabilities are essential for *in silico* approaches to design vaccine Ag that create immune responses that are protective at the relevant mucosal surfaces and provide durable protection beyond a single virus species. These tools have not been paired with orthogonal data generation from functional assessments that would generate data beneficial to vaccine Ag design.

APECx will address these limitations by:

1. Discovering and optimizing new methodologies to generate the necessary structural and functional data needed for modeling viral Ag and incorporating these data into vaccine design tool development – and sharing these data openly
2. Building Artificial intelligence (AI)/Machine learning (ML)-enabled vaccine design tools for translational vaccine and therapeutic development – and sharing these tools openly
3. Demonstrating the predictive and learning abilities of these tools through proof-of-concept studies that evaluate their applicability to broad-spectrum vaccine development
4. Challenging the developers to demonstrate **genus/family-level** efficacy of these vaccine candidates with independent and validated assays and models
5. Down-selecting the most promising candidates for evaluation in Phase I human clinical studies to demonstrate the capabilities built into the antigen development pipeline

The utilization of these advanced technologies will revolutionize the approach to viral disease prevention, resulting in a substantial decrease in the disease burden experienced by patients, healthcare providers, and the overall economy. Discoveries and toolkits made through APECx will also impact all disease research and development as the principles required for vaccine Ag design apply to understanding protein function/dysfunction related to human disease mechanisms.

1.2. TECHNICAL APPROACH AND STRUCTURE

1.2.1. Technical Areas (TAs)

The APECx program will catalyze the discovery of Investigational New Drug **(**IND)-ready, broad-spectrum medical countermeasure (MCM) candidates against unknown and existing threats at the viral genus-level. The discovery process includes three technical areas (TA): high throughput biochemical analysis and protein engineering (TA1), protein modeling toolkit for antigen design and discovery pipeline development (TA2), and translational candidate development and clinical evaluation (TA3).

- **Technical Area 1 (TA1)- High-throughput (HT) Biochemical Analysis and Protein Engineering**: Accelerated throughput of viral Ag discovery with high accuracy, utilizing techniques including but not limited to HT experimental structure determination, HT functional analysis, and model system development for screening of lead Ag candidates.

- **Technical Area 2 (TA2)- Protein Modeling Toolkit for Antigen Design**: Leverage 3-dimensional (3D) structural and HT functional data information from TA1 and existing viral protein structure data to confidently model challenging targets and predict and design consensus chimeric Ag suitable for genus-level vaccines against existing and emerging viral diseases. (**TA2)- Discovery Pipeline Development**: **APECx will also prioritize integrated model development by soliciting TA2 Only performers to** develop, train, and test team-developed toolkits across the performers (inclusive of training data and models developed).

- **Technical Area 3 (TA3)- Translational Candidate Development and Clinical Evaluation**: Utilize the dataset generated by TA1 and TA2 to discover novel MCMs, optimize them for relevant delivery platforms that are efficacious at a viral genus-level and easily accessible to the public, and iteratively validate approaches generated by TA1 and TA2.

Performers will have the option of submitting proposals that address all TAs (TA1 – 3) or TA2 only. Teams that apply for TA2 independently will have an additional, unique set of milestones and deliverables to perform as an integrative function across the TA1/2/3 teams. If two highly similar proposals address TA2 only and all TAs, respectively, preference will be given to the proposal that addresses all TAs. Ag design iteration and validation will occur mostly within TA1 and TA2, although many of the design features of a translatable vaccine (immunogenicity, manufacturability, and platform delivery technologies) need to align with the goals of TA3 from the onset and be incorporated early on. As teams advance product candidates through proof of concept studies, challenges, and clinical studies, there are opportunities within TA1 and TA2 to iterate and improve on the protein functional design, resolution, and modeling approaches. The iterations will be validated and guided by animal and human data for safety, immunogenicity, and efficacy.

To ensure the applicability of tools developed to the broader community and for the success of APECx candidates, proposers must have demonstrated team capabilities in TA2 alone or across all TAs. Proposals that fail to address all the required technical areas will be deemed non-conforming and may be rejected without further review. Proposing teams that address all TAs (TA1–3) must also include data access plans and commercialization plans including Food and Drug Administration (FDA) meeting milestones, technology transfer milestones to contract manufacturing organization (CMO) partners, preclinical proof of concept objectives, and market analysis and partnership models for commercialization. The candidates and MCMs for TA1–3 must meet the specifications listed in the "Metrics and Objectives" sections below.

TA1: High-throughput Biochemical Analysis and Protein Engineering

The current protein structure prediction algorithms, such as AF2 and RF, have been a significant breakthrough in the field of structural biology. These algorithms have demonstrated impressive capabilities in accurately predicting protein structures, which has wide-ranging implications for drug discovery and vaccine development applications. The capabilities of the prediction tools were attainable due to the large quantity of experimental structures available in the PDB. Likewise, high-quality, unbiased, and verifiable data generation is essential for developing AI/ML-based applications, ensuring training accuracy while mitigating the likelihood of errors in the pipeline.

The PDB is biased towards soluble eukaryotic and bacterial proteins, with a limited representation of viral proteins. This lack of diversity in viral protein structures hinders accurate predictions using the modeling tools. Furthermore, these prediction algorithms often struggle to predict the impact of mutations, post-translational modifications, multi-domain structures, and protein-protein interactions, which are all critical modeling capabilities needed for MCM development.

TA1 aims to produce an unabridged structural database of viral proteins and their interactions with host targets from a chosen genus and enhance the capabilities of existing algorithms for modeling and expediting the discovery of MCM against viral targets. Accurate structures of viral proteins and viral protein-host receptor complexes are instrumental to discovering immunogenic epitopes. Combining these structural data with HT functional analysis, biochemical data, and immunological assay data will enhance the discovery of effective viral Ag.

To accomplish this, TA1 performers will carefully select a viral genus and identify viral proteins or protein complexes that play a significant role in pathogenic events. The performers will resolve protein structures that are missing in the PDB and perform functional immunological characterization of the proteins for MCM discovery, utilizing various techniques in structural biology and immunological characterization.

This program announcement outlines the broad scope of the TA1 objectives. A successful proposal will consider each of the following, and include strategies and information to achieve each goal:

- A detailed plan for HT Ag characterization of native viral proteins and consensus chimeric Ag.
    - The proposal should provide a detailed description of the HT experimental and technological plans for rapid data generation for Ag selection and evaluation, which includes the initial choices, down-selection and refinement of HT technologies.
    - The proposal should provide a detailed description of the HT experimental and technological plans for functional serological analyses and immune cell responses for Ag.
    - The readout should reflect the reactivity profile and antigenic diversity.
    - The discoverable Ag should include conformational and linear Ag for B and T cells and structure-guided epitope mapping should be considered.
    - The proposal should provide clearly defined tractable metrics for each high-throughput screening (HTS) technology.
- A list of relevant antigenic targets from a single genus or multiple, related genera, and a determination of their 3D structures either by themselves or in complex with host proteins in physiologically relevant forms.

  - High-value targets refer to viral proteins or protein complexes that play a significant role in pathogenic events, and their structural information can be used to develop MCMs, including vaccines and neutralizing antibodies (nAbs).
  - The proposal should outline detailed protein production and structure determination strategies, including novel strategies to address the required throughput.
  - The proposal should outline a detailed plan for the utilization of United States Government (USG) infrastructures, such as national synchrotron sources, national nuclear magnetic resonance (NMR) facilities, Cryo-electron microscopy (Cryo-EM) centers, and Cryo-electron tomography (Cryo-ET) centers.
- Rationale for the chosen macromolecules or macromolecular complexes that could lead to novel MCMs.
  - One of the program goals is to develop genus-level (or beyond) broad-spectrum vaccines.
  - One of the program goals is to contribute to viral structural protein databases for a chosen genus and to provide novel and chimeric structures of proteins relevant to human viral pathogens.
- A plan to produce and supply designed consensus chimeric Ag for immunogenic screenings.
- A plan to elucidate experimental 3D structures of designed consensus chimeric Ag to confirm the accuracy of the structural models created in TA2.
- A plan to elucidate experimental 3D structures of chimeric Ag-nAb complexes to characterize epitopes and correlates of immune response (TA3).
- A 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.

To achieve the goals of the program, performers may propose a variety of technical approaches to elucidate high-value target structures. These approaches can be separate or combined. These may include but are not limited to:

- X-ray crystallography
- Cryo-electron microscopy single particle analysis (Cryo-EM)
- Cryo-electron tomography (Cryo-ET)
- Micro-electron diffraction (Micro-ED)
- Nuclear magnetic resonance (NMR) spectroscopy
- Mass-spectrometry techniques
  - Hydrogen-deuterium exchange mass-spectrometry (HDX-MS)
  - Cross-linking mass-spectrometry (XL-MS)
- Atomic force microscopy (AFM)
- Other biophysical techniques suitable to study macromolecular structures

To achieve the goals of the program, performers may propose a variety of functional biochemical and immunological characterization techniques in HTS format. These approaches can be separate or combined. These may include but are not limited to:

- Single cell sequencing

- Phage display technology
- Peptide library array technology
- Protein microarray technology
- Next-generation sequencing (NGS)
- Mass spectrometry
- Flow cytometry
- Surface Plasmon Resonance (SPR)
- Enzyme-linked immunosorbent assay (ELISA)
- Enzyme-linked immunosorbent spot (ELISpot)
- Biosensor technology
- Epitope binning technology
- Other immunological functional assays

TA1 metrics and timelines are outlined in **Table 2** of **section 1.3** will increase in difficulty and complexity over the course of the APECx program. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team at monthly meetings. ARPA-H may request performer data as deemed necessary throughout the program to validate progress toward achieving the program goals. The resolved structural datasets and assays developed by performers will be shared with Independent Verification & Validation (IV&V) partners, which consist of extramural and intramural USG labs for analysis and comparison.

TA2: Protein Modeling Toolkit for Antigen Design and Discovery Pipeline Development

MCMs are often designed to target a specific strain of viral species, limiting our capacity to respond to rapidly evolving viruses or multiple viral pathogens that cause similar diseases. A broad-spectrum MCM can protect or treat infections against multiple strains, variants, or species within a viral genus.

Such MCMs can be designed by targeting conserved viral surface proteins that do not vary significantly among different strains, variants, or species. Alternatively, T cell mediated immunity can be targeted by focusing on protein core sequences, which are often the most conserved region of protein orthologs. Vaccines designed using these approaches could provide broader protection and may even have the potential to protect against newly emerging variants.

Obtaining accurate structures of viral surface proteins and understanding how they interact with host cell receptors can provide important information for developing MCMs. Additionally, non-structural viral proteins may provide additional opportunities to identify T cell Ag and future MCM discovery targets. As highlighted in the TA1 overview, TA1 aims to bridge the knowledge gap in viral protein structures and accurately map immunogenic epitopes through various HT biochemical and functional assays. The knowledge of comprehensive Ag structures, along with precise mapping of highly immunogenic epitopes, will facilitate future advancements in the development of broad-spectrum MCMs.

TA2 aims to enhance the understanding of viral structures at the genus level through accurate structure prediction of viral Ag and their interaction with host receptors. Performers will achieve

the goal by generating precise protein models using the structural information obtained from TA1 and pre-existing structural information in the PDB. These protein models will provide a comprehensive account of all the protein structures within the genus. Utilizing the structural information and the functional readouts obtained in TA1, TA2 performers will identify targetable Ag and generate consensus chimeric Ag that represent protein orthologs at the genus-level. By doing so, TA2 outcomes will facilitate the development of broad-spectrum MCMs that can effectively target multiple viral species within the genus.

With the anticipation of large datasets produced from the program through HT functional analysis and biochemical and immunological assay results associated with the Ag structures, TA2 Only performers will facilitate and implement data standardization and automated data curation in data generation workflow. Additionally, TA2 performers will make efforts to gather relevant functional and immunological data from public sources. The AI/ML-centric data curation effort will enable the design of an automated Ag prediction pipeline.

This program announcement outlines the broad scope of the TA2 objectives. A successful proposal will consider each of the following, and include strategies and information to achieve each goal:

- A plan to coordinate data across TA1 and TA3 and provide accurate *de novo* models of physiologically relevant protein structures for a chosen genus or genera.
    - One of the program goals is to establish a viral structural genome database of a chosen genus to provide an unbiased structural database of human viral pathogens. TA2 performers will identify missing model templates and inform TA1 approaches to generate experimental structures that can be used as a template for structure prediction of orthogonal proteins within or near the viral genus.
- Performers will utilize existing or novel algorithms to predict accurate viral macromolecular structures utilizing the structure data generated by TA1 tasks.
- Detailed plans and the development of tools to accurately predict the impact of point mutations, order/disorder boundaries, multi-domain structures, and protein-protein interactions.
- Toolkits to generate synthetic chimeric targets from the high-value targets identified in TA1/3 to be used for MCM discovery in a manner beneficial to TA3 for performing broad-spectrum MCM discovery.
- Strategies and laboratory tools to predict the safety, thermostability, and bioprocessing scalability of the biologics candidates using existing or new protein design algorithms.
    - Performers should recognize the importance of developing thermostable vaccines and biologics, as these may have to be transported and stored in various environmental conditions. Protein modeling and design teams should help analyze protein structures, predict their stability, and guide the engineering of proteins to enhance thermostability.
    - Performers should recognize that efficient and cost-effective bioprocessing is vital for large-scale manufacturing of vaccines and biologics.
- A discussion 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 TA2 Only performers have unique set of objectives. A successful proposal will consider each of the following, and include strategies and information to achieve each goal:

- Plan for building a program data repository, data curation and harmonization pipeline
    - The proposal should provide a detailed plan for curating the data generated during the program in a user-friendly manner for the scientific community. The data will include high-confidence models, experimental structures, biochemical assays, and functional data.
    - The proposal should provide a detailed plan for curating publicly available structures, biochemical assays, and functional data relevant to the program and integrating them into the repository to develop an Ag prediction pipeline.
- A plan for building an Ag prediction pipeline utilizing the program-specific protein prediction and modeling toolkits, and publicly available toolkits.
    - Single Ag and consensus chimeric Ag.
    - Conformational and linear Ag for B cells and T cells.
    - Combined with immunological functional data for prediction.
    - Adaptability of the Ag for vaccine platform for optimal efficacy.
- A discussion 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.

To achieve the goals of the program, performers may propose a variety of technical approaches to produce high-accuracy protein models and consensus chimeric Ag. These approaches can be separate or combined. These may include but are not limited to:

- Existing prediction algorithms or *de novo* prediction algorithms
    - Template-based homology modeling
    - Physics-based modeling
    - Deep learning-based modeling
    - Template-independent *ab initio* modeling

TA2 metrics and timelines are outlined in **Table 3** of **section 1.3** will increase in difficulty and complexity over the course of the APECx program. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team at monthly meetings. ARPA-H may request performer data as deemed necessary throughout the program to validate the project progress. The modeling datasets, toolkits, and the pipeline developed by performers will be shared with Independent Verification & Validation (IV&V), which consists of extramural and intramural USG labs, for analysis and comparison. Additionally, they may also serve as IV&V during certain aspects of the program to validate findings.

TA3: Translational Candidate Development and Clinical Evaluation

Vaccines are universally acknowledged as one of the most cost-effective and equitable MCMs for preventing infectious diseases, particularly viral infections. They play a vital role in reducing the strain on healthcare systems, resulting in substantial savings in medical costs. Vaccines contribute significantly to achieving herd immunity, where a sufficient portion of the population acquire immunity, protecting even those who cannot be vaccinated. Beyond their local impact, vaccines have a profound global health effect. The high efficacy and safety of vaccines make them a

cornerstone of public health initiatives, effectively safeguarding individuals and communities against infectious pathogens.

Vaccination induces protective immunity through two arms of the adaptive immune system: humoral immunity (Abs and memory B cells) and cellular immunity (involving helper $CD4^+$ T cells and cytotoxic $CD8^+$ T cells). Abs block infection by binding to viruses and preventing their entry into host cells (among other functions) and serves as correlates of protection for many vaccines. Memory T cells offer an important additional layer of immunity, responding rapidly to limit virus replication and spread once an infection has occurred. The immune response generated at the mucosal surfaces is equally crucial for many viral infections, as it is often the first contact point between infectious virus and the host. For viruses that are associated with mucosal routes of entry and mucosa-based pathogenesis, immunological endpoints including mucosal IgA, mucosal resident memory B and T cells, and mucosal availability of IgG should be pursued.

Unfortunately, there are vaccines for less than 7% of viruses known to infect humans, and many of them provide protection against a single viral species (or even strain/isolate) in ways that are susceptible to evolution. TA3 aims to generate broad-spectrum vaccines based on recursively designed consensus chimeric Ag as described in TA1 and TA2 to provide protection against multiple viral pathogens at a genus-level.

While broad-spectrum vaccines with strong protective immunity are the key characteristics that APECx seek, the program will also emphasize other critical factors. These include ease of administration, safety, low reactogenicity, low production cost, stability, and equitable access to all. Therefore, a vaccine design should carefully consider these factors during the early stages of development, including selecting an appropriate vaccine platform. The choice can significantly impact the vaccine's characteristics, including its immune response, administration, and manufacturing.

As highlighted in the TA2 overview, TA2 will identify targetable Ag and design consensus chimeric Ag. TA1 will then produce these Ag with high purity. TA3 will perform lead optimization screening and validation to confirm the broad-spectrum efficacy. The identification of nAbs and effector T cells during this process can be used to characterize the target epitopes using structural biology techniques. This will enhance the understanding of the designed consensus Ag and inform the next round of design efforts. The process will recursively iterate until the most effective chimeric Ag is identified. The final candidates will undergo functional assays in animal models or equivalent systems to determine immunogenicity, safety, and efficacy, as well as developability and manufacturability. Suitable candidates will be supported by IND submission to the FDA and for progression to Phase I clinical trials. Therefore, the proposers should document compliance with guidelines that govern Good Laboratory Practice (GLP), as defined by 21 CFR (58), and current Good Manufacturing Practice (cGMP), as defined by 21 CFR (211), manufacturing and IND enabling studies that will be performed under the program as they should be critical for the application.

The recursively designed broad-spectrum vaccines must meet the following specifications:

- Performers must seek rationally designed vaccines that can offer significant protection in *in vivo* preclinical models, exceeding 60%, against all known viral species within the selected genus.
- Onset of protection must occur within 2 weeks of vaccination and durable > 1 year.
- Vaccine formulation must ensure stability (> 5 years at -80 ºC) with enhanced storage capabilities (-20 ºC viability for 6 months and 4 ºC viability for 2 weeks).
- Ensure safety and reactogenicity are sufficient to provide a highly favorable benefit/risk profile with minimal adverse events.
- Progress candidates to an IND-ready stage.
- If applicable, IND submission and approval.
- Candidate vaccines that progress to Phase I clinical trial must target all populations, including healthy adults, pediatric and marginalized populations.

The desired attributes of the vaccine candidates encompass a robust T cell and B cell response, a high level of nAbs, and the presence of long-lasting memory B and T cells. Achieving strong mucosal immunity, which involves protective IgA and tissue-resident memory T cells (T_{RM}), may necessitate a combination of formatting and adjuvant formulation. To meet the program's objectives, performers must utilize platforms with a proven track record of success and have received support from the USG. Additionally, the selected platform should be scalable and allow for low-cost manufacturing that ensures accessibility to all. Various platforms can be considered, including but not limited to:

- mRNA
- Virus-like particles (VLP)
- Recombinant subunit
- Nanoparticles
- Viral vectors

To achieve the goals of the program, performers may propose various technical approaches to assess vaccine efficacy *in vitro* and *in vivo*. These approaches can be separate or combined. These may include but are not limited to:

- Hybridoma technology
- Phage display technology
    - Natural library
    - Synthetic library
    - Semi-synthetic library
- Single B cell technology
    - FACS-based analysis
    - Nanowell-based technologies
- Flow cytometry
- ELISA
- Microscopy (confocal and intravital)
- Next-generation sequencing (NGS)

Proposers must include on their teams as a co-Investigator at least one vaccinology expert with substantial experience in bringing preclinical products through an IND application and to a Phase

I clinical trial. A virology expert for the selected viral genus will also need to be included on the team as a co-investigator or consultant.

This program announcement outlines the broad scope of the TA3 objectives. Performers must also provide the following information in the proposal:

- Intended *in vitro* assays and *in vivo* models to examine potential human efficacy.
- Justification for the number of animals to be used and other models employed *in vitro* and *in vivo*.
    - The approval process of the IACUC protocol and OLAW submission will likely take a minimum of 3 months. Performers should have the protocol ready for approval in anticipation of the APECx program award and should include a milestone for IACUC and OLAW approval in synchronization with the program timeline.
- Any prior *in vitro* and *in vivo* data for viral genus of interest.
- Viral genus of interest and ability to work with those pathogens, for example, access to high containment facilities (BSL3/4) if applicable and access to the viruses within the genus.
- Anticipated risks/pitfalls and alternative solutions to working with high containment pathogens.
- Strategic plan for collaborations with other TA experts to facilitate the development of IND-ready products.
- Potential obstacles that could require revising the work plan or milestones with a discussion of alternative approaches.
- A detailed schedule or timeline for each milestone and the overall goal.

The progress made by TA3 will be evaluated by program-wide goals before the 36-month APECx Phase 1 period ends. The main goal aims to demonstrate that the candidate vaccines provide correlate or surrogate of protection against the entire genus of their target. The USG labs and resources will oversee and evaluate the candidates, and the results will play a significant role in making Go/No-Go decisions for APECx Phase 2 and determining the advancement of candidate vaccines into clinical trial evaluations.

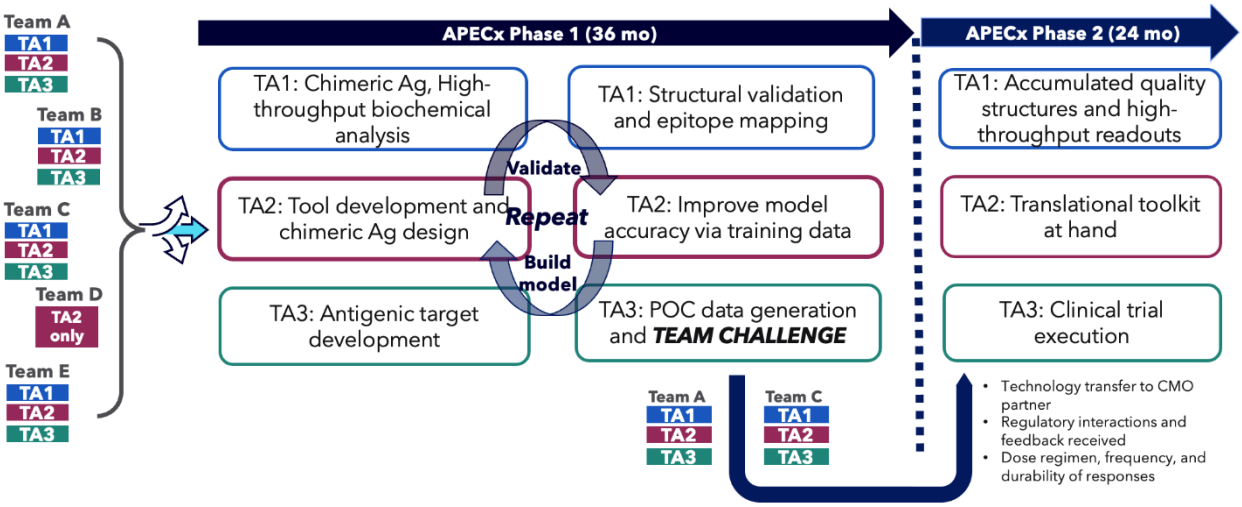
TA3 metrics and timelines outlined in **Tables 4** and **5** of **section 1.3** will increase in difficulty and complexity over the course of the APECx program. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team at monthly meetings. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress.

1.2.2. Program Structure

The APECx program is structured as a 5-year effort consisting of 2 phases: (36-month phase 1 and 24-month phase 2) as shown in **Figure 1**. APECx Phase 1 includes realistic and measurable goals for performers to ensure the success of the program. This also includes checkpoints at the transition between APECx phases. In order to progress towards APECx Phase 2, performers must utilize the resources provided by USG stakeholders, Project Accelerator Transition Innovation Office

(PATIO), and the Expert/Entrepreneur in Residence (XIR/EIR) network to develop marketable products capable of eradicating virus-related diseases as significant threats to public health.

Figure 1. Program Structure and General Overview



Antigen (Ag), Proof of concept (POC), Contract manufacturing organization (CMO)

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. Access to preventative healthcare tools, like vaccines, and adherence to full vaccine schedules for many viral diseases is inequitable across the U.S. Getting preventative healthcare is extremely challenging across the socioeconomic spectrum and studies have shown that lower socioeconomic status and minority populations have greater challenges in accessing vaccines and adhering to multi-dose vaccines schedules (such as hepatitis A/B, human papilloma virus, and the SARS-CoV-2 vaccine series). Further, resistance to needles and lack of educational marketing tools for vaccines and vaccine-preventable diseases prevents the full benefit of these public health tools from being realized across the U.S. and internationally. It is also the goal of the program to negotiate full coverage through all health insurance via USG entities (Center for Medicare and Medicaid Innovation (CMMI), Centers for Medicare & Medicaid Services (CMS), Indian Health Service (IHS), and more) so that APECx vaccines are accessible to all. To meet equity and accessibility goals, APECx is developing target product profiles (TPP – an example below in **Table 6 of section 1.3**) that will account for equitable access and acceptance of vaccine candidates and their delivery in formats that increase equity in vaccination for all. The final TPP requirements will be available to performers no later than Q3 Yr1 of APECx Phase 1. The APECx program team is also establishing an ethics steering committee to advise on scientific methods/approaches to advance health equity. Membership will consist of disease advocacy groups, ethicists, and external content experts (virologist, immunologist, vaccinologist, epidemiologist, etc.). Additionally, proposers should include a discussion on the disease burden of

selected viral genera, with emphasis on disease distribution in historically marginalized groups if such disparities exist.

1.2.4. Data Sharing Plan

Proposers must agree to openly share deidentified/sanitized data acquired during the period of performance. Any member of the scientific community should have access to the data; registration to a specific repository website is acceptable, but approval needs to be automatic. The specific repository where data will be deposited will be chosen in agreement with the ARPA-H program manager. The proposers will need to present explicit solutions to address the significant data storage and computing challenges presented by the program, with the understanding that the plans and repository may change later in the program.

1.2.5. APECx Go/No-Go Phase 2 Checkpoint

At Q3 Yr3 in APECx Phase 1, there will be a Go/No-Go determination and down selection of teams based on performance against APECx Phase 1 metrics as described in the metrics tables. Progression to Phase 2 will be also dependent on funding availability. Additionally, any performer across all TAs that does not meet the equity requirements may also be given a "No-Go" determination. APECx Phase 2 will not have specific TA1 and TA2 requirements, however, there may be funds available in Phase 2 for TA1 and TA2 to provide additional support to TA3 if necessary.

TA1 Goal – APECx Phase 1 (36 Months): High-throughput Biochemical Analysis and Protein Engineering

During the 36-month APECx Phase 1, performers will establish cloning, expression and purification, resolve structures, and perform functional immunological characterization of the targets. In collaboration with TA2, TA1 will accumulate and curate a viral structure database and determine experimental structures of designed consensus chimeric Ag structures to validate the models and perform additional functional characterization of the Ag. Performers will elucidate experimental 3D structures of chimeric Ag-nAb complexes to map epitopes. See Figure 1 for a full program overview.

- Goals of APECx Phase 1 (metrics defined in 1.3 PROGRAM METRICS)
    - By Q2 Yr1: establish a HT experimental workflow for Ag characterization.
    - By Q4 Yr1: identify high-value targets, screen for expression, and produce the proteins in preparation for experimental structure determination.
    - By Q2 Yr2: complete HT structure characterization of high-value targets.
        - The local resolution of the structures should be 3.2Å or better for MCM discovery.
        - The local resolution of the structures should be 2.0Å or better for protein complex analysis.

- By Q2 Yr2: complete functional immunological analyses and epitope mapping on single Ag and consensus chimeric Ag.
  - The HT data and its quality should be ready for AI/ML training and the development of the MCM discovery pipeline.
- By Q3 Yr2: produce proteins of designed consensus chimeric Ag and determine experimental structures for TA2.
- By Q3 Yr2: complete structural complexes of consensus chimeric Ag and nAb to support TA3's effort to characterize epitopes and nAbs.

TA2 Goal - APECx Phase 1 (36 Months): Protein Modeling Toolkit for Antigen and Discovery Pipeline Development

During the 36-month APECx Phase 1, performers will coordinate with TA1 and TA3 performers and create accurate *de novo* models of physiologically relevant protein structures for a chosen genus or genera. TA2 outcomes will establish a viral structural genome database by combining high-accuracy model structures, the structures obtained from TA1, and pre-existing structural information in PDB. TA2 performers will generate consensus chimeric Ag from the high-value targets for MCM discovery. The TA2 Only performers will establish a program data repository, curate both program-generated data and publicly available data for training in AI/ML. The TA2 Only performers will use the data to create an automated Ag prediction pipeline.

- Goals of APECx Phase 1 (metrics defined in 1.3 PROGRAM METRICS)
  - By Q4 Yr1: complete prediction of 50% genus coverage with composite accuracy score > 90% in the core domains and accurate prediction of disorder boundaries. The genus coverage should reach 80% by Q2 Yr2.
  - By Q2 Yr2: improve structure prediction with composite accuracy score > 60% in physiological conditions relevant to viral proteins (Lysosome, cytosol, extracellular, etc). The prediction accuracy score should reach > 75% by Q1 Yr3.
  - By Q1 Yr3: improve structure prediction with additional metrics (order/disorder boundary, mutation, domain interaction, protein complexes).
  - By Q1 Yr3: improve structure prediction to include translational additions that can be represented/modeled in silico (i.e., sugar moieties) and to model multiple conformations with predictive modeling with composite accuracy score > 75%.

- Goals of APECx Phase 1 for **TA2 Only** performers (metrics defined in 1.3 PROGRAM METRICS)
  - By Q1 Yr2: complete program data repository and establish data harmonization pipeline.
    - The pipeline will be capable of unsupervised data curation, and the deposited data will be ready for AI/ML training.
    - The pipeline will include data curation and standardization of publicly available data relevant to the viral targets.
  - By Q3 Yr3: create a pipeline for consensus chimeric Ag prediction, specifically targeting viral vaccines.
    - The pipeline will have the capacity to predict chimeric conformational Ag, linear B cell Ag, and T cell Ag with the potential for genus-level efficacy.

        - The pipeline will have the capacity to predict the most suitable vaccine platform supported by USG for optimal efficacy.
    - By Q4 Yr3: compile all structural datasets and functional-immunological readouts generated by the APECx program to a data repository that is secure, accountable, and accessible to a broad scientific community.

TA3 Goal - APECx Phase 1 (36 Months): Translational Candidate Development and Clinical Evaluation

During the 36-month APECx Phase 1, performers will assess the efficacy of the recursively designed MCMs from TA1/2 in preclinical models.

- Goals of APECx Phase 2 (metrics defined in 1.3 PROGRAM METRICS)
    - By Q3 Yr2: selection of previously demonstrated and established vaccine platform.
    - By Q4 Yr2: selection of vaccine administration route for optimal efficacy.
    - By Q2 Yr3: establish *in vitro* and *in vivo* models to assess vaccines.
    - By Q4 Yr3: demonstrate vaccine efficacy against ≥ 60% of known viral pathogens within a genus.
    - By Q4 Yr3: determine vaccine durability, and protective immunity assessed by animal responses to vaccination and following vaccinated animals out 1 year.
    - By Q4 Yr3: profile functional immune response following vaccination to determine protective immunity versus immunopathology.
    - By Q4 Yr3: submit Pre-IND meeting package following challenge.
    - By Q4 Yr3: secure contract with an established partner for producing GLP/cGMP vaccines to advance to APECx Phase 2.

TA3 Goal - APECx Phase 2 (24 Months): Phase I Clinical Trials

During the 24-month APECx phase 2, performers will proceed with MCM candidates to Phase I clinical trials. APECx performers will adhere to the guidelines outlined by FDA in "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" and "Considerations for Developmental Toxicity Studies for Preventive and Therapeutic Vaccines for Infectious Disease Indications" during the clinical trials.

- Goals of APECx Phase 2 (metrics defined in 1.3 PROGRAM METRICS)
    - Phase I clinical trial
        - Having met all prior criteria in APECx Phase 1, the MCM candidates should meet or exceed all prior criteria in Phase I Clinical Trials.
        - Demonstrate safety in human trials.
        - Demonstrate established manufacturer of therapeutic with cGMP capacity for Phase II/III/Commercial (≥ 1000 patients).
        - Use PATIO assets to commercialize vaccine and exit the Program.

1.3. PROGRAM 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 should 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. TA1 and TA2 Metrics and Objectives

The overall APECx goal based on the timeline is shown in **Figure 1**. The overall program goals are listed in **Table 1**. The expected metrics per phase in TA1 are listed in **Table 2** and TA2 in **Table 3**. 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 APECx Phase.

Table 1. TA1, TA2 and TA3 Overall Program Goals for APECx
The overall program goals for all TAs are listed in **Table 1**, which includes the expected outcome for each goal.

Viral structure database	Completion of a viral structural database of a chosen genus supplemented with existing data, new experimental data and high-accuracy modeling data
Viral protein modeling toolkits	Accurate *de novo* models of physiologically relevant macromolecular structures for a chosen genus or genera
Ag design and discovery database	Compilation of viral structure and biochemical database to include functions for mucosal immunity generation and post-translational modifications through coordination with performer teams. Ensure the generated data is secure, accountable, and accessible to the broad scientific community for Ag design toolkit
Ag design, discovery and development toolkit	New algorithms and toolkits for antiviral vaccine development, utilizing the datasets generated from the program as well as publicly available data
MCM candidates	Durable, genus-level broad-spectrum MCMs that can be evaluated in vivo and in clinical studies to determine the effectiveness of the Ag design toolkit
***In vitro* models**	Diagnostic and functional toolsets to quantify virus immunity and potential correlates of efficacy that can be measured *in vivo*
Manufacturing goals(s)	≥ 1000 patients' doses (established cGMP manufacturing partner to scale)
Clinical trial goals	Complete IND-enabling studies & Phase I clinical trials
Equity requirements	MCMs that account for health inequalities – low number of doses, easy-to-administer platforms, protection regardless of

	socioeconomic status or ethnicity. Develop MCMs with the end goals in mind at the start

Antigen (Ag), Medical countermeasures (MCM), Investigational new drug (IND).

Table 2. TA1 Metrics and Objectives
The expected metrics of TA1 APECx Phase 1 are listed in **Table 2**.

Metrics	Specifications			
	Overall	**Year 1**	**Year 2**	**Year 3**
Refinement of high-throughput experimental workflow for Ag characterization	Initial down-selection of technology workflow to rapidly generate structural and functional data relevant to Ag design and evaluation. Examples of technology platforms of interest include: • Library-on-library functional screens for conserved protein interaction and/or function • Rapid structural resolution workflows for genus-wide Ag conformations • Display approaches for genus-conserved viral proteome and MHC/TCR/BCR interaction identification	Q2/Yr1		
Protein production at scale for structural and functional study (genus-level, if necessary for the chosen genus)	• Selection of orthologs at genus-level to represent **100**% of unique epitopes (for the purpose of the program, orthologs with a sequence identity below **40**% are considered unique; production either through in-house or CRO) • All critical gene products to satisfy vaccine design concept, including viral structural and non-structural proteins and host viral receptors	Q4/Yr1		
High-throughput Ag characterization (structure)	Performer will define throughput metrics, but examples of data requirements include: • **100**% of representative structures of an entire genus	⇨	Q2/Yr2	

	• **100**% of physiologically relevant structural forms (viral proteins and host-viral protein complexes in relevant conformational states) • 3.2 Å or better local resolution (minimum identified resolution required for protein design) • 2.0 Å or better local resolution (minimum identified resolution required for protein complex analysis) • 100% native structures without truncation • Full structures with intact TM domain • Replicate physiological conditions by structure complexes with host proteins • Resolution of multi-conformational states			
High-throughput Ag characterization (function)	Performer will define throughput metrics, but examples of data requirements include: • *in vitro* readouts of viral protein function that correlate with evolutionarily conserved domains (corresponding to 100% of the viral genus) • Conformational and linear Ag discovery for B cells and T cells • Epitope mapping of B/T cells • Reactivity profile reflecting antigenic diversity • *in vitro/ex vivo* Cytokine/chemokine analysis • *in vitro/ex vivo* cellular marker identification and analysis	⇨	Q2/Yr2	
High-throughput protein production of designed Ag for functional studies	• Required (**95**% purity) for structural validation (either through in-house or CRO), on-demand	⇨	Q1/Yr2	
High-throughput protein production of	• Required (**95**% purity) for structural validation (either	⇨	Q1/Yr2	

designed Ag for structural studies	through in-house or CRO), on-demand • **100**% success with production yield of >10 mg/L bacterial, >50 mg/L transient mammalian expression			
Structures of designed chimeric targets	• Required for validation on-demand by TA2 • Independent Submission of Structures/Predictions	⇨	Q3/Yr2	
Target complexes for iterative structural and functional design	Required, on-demand by TA3 (i.e. antibody/epitope mapping)	⇨	Q3/Yr2	
Protein production for Translational Validation	• Meet or exceed 21 CFR Part 610, on demand by TA3 (either through in-house or CRO) • **100**% success with production yield of >2 g/L transient mammalian expression	⇨	⇨	Q1/Yr3

Contract research organization (CRO), Transmembrane (TM), High throughput screening (HTS), Antigen (Ag), Major histocompatibility complex (MHC), T cell receptor (TCR), B cell receptor (BCR)

Table 3. TA2 Metrics and Objectives

The expected metrics of TA2 APECx Phase 1 are listed in **Table 3**.

Metrics	**Specifications**			
	Overall	**Year 1**	**Year 2**	**Year 3**
Structure prediction accuracy	**50**% genus coverage with structure prediction of proteins with composite accuracy score > **90**% in the core domains and accurate prediction of disorder boundaries.	Q4/Yr1		
	80% genus coverage with structure prediction of proteins with composite accuracy score > **90**% in the core domains and accurate prediction of disorder boundaries.	⇨	Q2/Yr2	
Structure prediction accuracy (physiological)	Ability to predict structures with composite accuracy score > **60**% in physiological conditions relevant for viral proteins (lysosome, cytosol, extracellular, etc.)	⇨	Q2/Yr2	
	Ability to predict structures with composite accuracy score > **75**% in physiological conditions relevant for viral proteins (lysosome, cytosol, extracellular, etc.)	⇨	⇨	Q1/Yr3

Structure prediction tools (Ag target)	Inclusion of translational additions that can be represented/modeled *in silico* (i.e. sugar moieties). Ability to model multiple conformations with predictive modeling with composite accuracy score > **75**%	⇨	⇨	Q1/Yr3
Prediction of target-biologics complexes	Success with additional metrics (order/disorder boundary, mutation, domain interaction, protein complexes)	⇨	⇨	Q1/Yr3
Additional quality control measure	Independent submission of experimental (TA1) and predicted (TA2) structures and biochemical data. • Accurate prediction and modeling of the followings: conformational states, interaction with host receptors, immune system recognition, impact of mutations, post-translational modification	⇨	⇨	Q1/Yr3
Data transparency requirements	• Deposition of the data produced during the program cycle to the program data repository for evaluation by ARPA-H and TA2 Only performer. • Sharing IP-worthy proprietary result with TA2 Only performers is optional; consult with ARPA-H PATIO	⇨	⇨	Q4/Yr3
Teams exclusive to TA2 have the following supplementary metrics, which are discretionary for TA2 when operating within the broader scope of TA1–3				
Program data repository and harmonization pipeline	Automated data curation and repository ready for AI/ML training • Curation of data produced by all performer groups • Curation of publicly available data that are relevant to viral targets • Develop workflow allowing data deposition while retaining IP from TA1–3 performing teams	⇨	Q1/Yr2	
Data integration	Coordination with performer teams to compile a viral structure and biochemical database that is secure, accountable, and accessible to a broad scientific community	⇨	⇨	Q4/Yr3

Single Ag prediction workflow	Open-source availability of new algorithms targeted specifically for viral structures and protein function	⇨	⇨	Q1/Yr3
Consensus Ag prediction workflow	Chimeric conformational Ag, linear B cell Ag, and T cell Ag with the potential for genus-level efficacy	⇨	⇨	Q3/Yr3
Vaccine platform adaptability of Ag	Prediction of the most suitable demonstrated vaccine platform supported by USG for optimal efficacy and success	⇨	⇨	Q4/Yr3

Intellectual property (IP), Antigen (Ag), United States government (USG)

1.3.2. TA3 Metrics and Objectives

The overall program goals for APECx Phase 1 TA3 are listed in **Table 4**. The metrics and objectives are in place to be ready for the pre-IND meetings with the FDA. If selected to advance, TA3 will also proceed with clinical trial applications (APECx Phase 2). The metrics and objectives for APECx Phase 2are listed in **Table 5**.

Table 4. TA3 Metrics and Objectives
The expected metrics of TA3 APECx Phase 1 are listed in **Table 4**.

Metrics	**Specifications**			
	Overall	**Year 1**	**Year 2**	**Year 3**
MCM requirements – Efficacy	Efficacy against > **60**% or more viral species within a genus	⇨	⇨	Q4/Yr3
MCM requirements – Durability	Projected long-lasting immunity (> **1** year) predicted by acute animal responses to vaccination and following vaccinated animals out 1 year	⇨	⇨	Q4/Yr3
Delivery platform selected	mRNA, subunit, nanoparticle, vector – platforms with demonstrated success and USG support	⇨	Q3/Yr2	
Administration route compatibility	IM, IN, oral (novel device collaborations or partnerships with other USG investments encouraged)	⇨	Q4/Yr2	
Functional serological analysis for chimeric Ags in HTS format	Performer-defined readout reflecting serological analysis in animal models: • Antibody isotype • Antigenicity • Neutralization capacity and affinity	⇨	⇨	Q2/Yr3

	Antigenic diversity			
Defined Immunity profile	To be determined based on the virus genus selected, but examples include: • Mucosal Immunity (cell-mediated and IgA presence at relevant mucosa) • IgG sub-serotype identified as a correlate of protection • Generation of neutralizing antibodies at relevant sites • Binding antibodies across epitopes designed in chimeric Ag • Functional and residency capabilities of CTLs • Functional and residency capabilities of ILCs • Signatures associated with protective immunity versus immunopathology	⇨	⇨	Q4/Yr3
Dose frequency	Maximum **2** doses (target **1** dose)	⇨	Q4/Yr2	
Animal model requirement	Efficacy and surrogates of protection demonstrated in small animals (mice, guinea pigs etc.) and NHPs	⇨	⇨	Q2/Yr3
Assay requirements	Viral quantifications, functional immunity readouts, pseudo-virus systems for handling at lower containment	⇨	⇨	Q2/Yr3
Additional requirements	IND-ready, if selected for APECx Phase 2 submit IND to FDA	⇨	⇨	Q4/Yr3

Intramuscular (IM), Intranasal (IN), Non-human primates (NHPs), Immunoglobulin A (IgA), Immunoglobulin G (IgG), Cytotoxic T lymphocytes (CTLs), Innate Lymphoid Cells (ILCs)

Table 5. TA3 Metrics and Objectives
The expected metrics of TA3 APECx Phase 2 are listed in **Table 5**.

Metrics	**Specifications**		
	Overall	**Year 4**	**Year 5**
Clinical operations	Study protocol, identification of principal investigator and study site	Q1/Yr4	
Manufacturing standards	1) GLP compliant assay development 2) Technology Transfer of assays, protocols, and starting material complete	Q1/Yr4	

	3) Produce cGMP material for 20 -100 patients		
Assay requirements	Immunologic and other assays to characterize the profile of the candidate vaccine should be developed, optimized for clinical use, and qualified	Q1/Yr4	
Trial requirements	Enroll patients, reach primary and secondary endpoints	⇨	Q3/Yr5
Additional requirements	Use PATIO Assets to commence commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.	⇨	Q4/Yr5

Intellectual property (IP)

1.3.3. Program Success

The success of the program will be evaluated based on the following criteria. Additionally, the target product profile (**Table 6**) should be utilized as a guideline throughout the process of discovery and development, in preparation for Phase I human clinical studies:

- Open-source generation of protein structure data, formatted to facilitate AI/ML computational approaches (i.e., raw data standardized across structure resolution tools), for previously unresolved virus protein structures.
- Delivery of open-source purpose-built AI/ML tools for translational vaccine and therapeutic development.
- Technology demonstration of the ability of these tools to iteratively design effective chimeric Ag through proof-of-concept studies that show broad-spectrum efficacy.
- Successful challenge execution that tests products for genus/family-level efficacy with independent and validated assays and models.
- Candidates showing strong proof-of-concept demonstrations and challenge performance to be selected for evaluation in Phase I human clinical studies.
- Study of the safety and immunogenicity of the candidate vaccine in a Phase I clinical trial.
- Product fit to TPP (example TPP below – further TPPs in generation with PATIO team and ARPANET-H's Customer Experience Hub for broad acceptability and accessibility).

Table 6. Example TPP (final is being developed in coordination with ARPA-H partners to determine the acceptability and accessibility criteria of vaccine design for U.S. population. Final TPP requirements will be available to performers no later than Q3 Yr1 of APECx Phase 1.

Product Properties	**Attributes (Ideal)**
Indication for use	For immunization of at-risk persons to protect against viral infection
Target population	Initial target population will be healthy adults, although pediatric and marginalized populations

	(pregnant/lactating women) must be considered in commercialization strategy for final label
Safety/Reactogenicity	Safety and reactogenicity sufficient to provide a highly favorable benefit/risk profile in the context of observed vaccine efficacy; ideally with only mild, transient adverse events related to vaccination and rare serious AEs related to vaccination
On Label Protection	Relevant species of virus (broader label could be developed in concert with FDA feedback)
Efficacy	Protection from severe viral disease caused by the virus indicated
Onset of protection	Rapid onset of protection within 2 weeks
Duration of protection	> 2 years
Dose regimen	Single-dose regimen
Administration route	Injectable (ID, IM, SC) and/or formulated for novel device delivery Oral, intranasal route
Shelf life	>5 years at -80 ºC
Storage temperature (long-term)	-20 ºC viability for 6mo
Storage temperature (clinical setting)	-20 ºC to 4 ºC
Freeze-thaw logistics	Stable after 3 freeze-thaw cycles

Adverse events (AEs), Intradermal (ID), Subcutaneous (SC)

1.4. GENERAL REQUIREMENTS

1.4.1. Proposing Teams

Proposals are expected to involve teams with **the expertise needed to collectively achieve** the goals of all 3 TAs except for TA2 Only performers. Specific content, communications, networking, and team formation are the sole responsibility of the proposer[1]. Proposers must submit a single, integrated proposal led by a Principal Investigator (PI), under a single prime awardee[2] that addresses all program phases, as applicable. Proposers may only submit one proposal as the prime proposer.

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

[1] Proposer refers to all respondents to this Solicitation/Notice of Funding Opportunity, regardless of resulting award instrument.

[2] 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).

1.4.2. Diversity in clinical trial populations for APECx Phase 2

While following the guidelines outlined by FDA on vaccine clinical trials, ARPA-H is also committed to equitable healthcare access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. APECx will ensure that all performers follow the FDA's guidance titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" and that clinical trial populations mirror the proportions of viral infections that the MCM development is targeting.

2. Award Information

2.1. GENERAL AWARD INFORMATION

Multiple awards are anticipated. The resources made available under this Research and Development (R&D) Solicitation, and number of awards made will depend on the quality of the proposals[3] received and the availability of funds. ARPA-H reserves the right to make multiple awards, a single award, or no awards.

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this R&D Solicitation 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.

Proposals identified for negotiation are expected to result in Cooperative Agreements or Other Transactions (OTs). Selection of award instrument will be based upon consideration of the nature of the work proposed, the required degree of interaction between parties, and other factors. The Government may request additional necessary documentation, tailored to the individual proposals once it makes the award instrument determination. The Government reserves the right to remove proposals from award consideration should the parties fail to reach agreement on award terms, conditions, and/or cost/price within a reasonable time, and/or if the proposer fails to timely provide requested additional information.

Proposers looking for innovative, commercial-like contractual arrangements are encouraged to consider requesting OTs.

In all cases, the Government's applicable OT and Grants Officer(s) shall have sole discretion to select award instrument type, regardless of instrument type proposed, and to negotiate all terms and conditions with selectees.

[3] In this document, proposal refers both to the abstract and the full proposal unless otherwise indicated.

3. Eligibility Information

3.1. ELIGIBLE APPLICANTS

All responsible sources capable of satisfying the Government's needs may submit a proposal.

3.1.1. Federal Entities and Federally Sponsored Entities

Federal entities and federally sponsored entities (e.g., Government/National laboratories, Federally Funded Research and Development Centers (FFRDC), University Affiliated Research Center (UARC), military educational institutions, etc.) are not eligible for award under this announcement. However, ARPA-H is committed to working with its federal partners. Federal partners interested in working with ARPA-H on this program should contact APECx@arpa-h.gov to discuss supporting this effort.

3.1.2. Other Applicants

ARPA-H will prioritize awards in accordance with 42 U.S.C. § 290c (Section 499A(n) of the PHSA). Without limiting the foregoing ARPA-H will prioritize awards to domestic entities (organization and/or individuals) that will conduct funded work in the US. However, non-US entities may participate to the extent such participants comply with nondisclosure agreements, security regulations, export control laws, and other governing statutes and regulations applicable under the circumstances. Non-US entities are encouraged to collaborate with domestic US entities. 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. § 3059)) or entities suspended or debarred from business with the Government.

3.2. ORGANIZATIONAL CONFLICTS OF INTEREST (OCI)

Proposers are required to submit an OCI mitigation plan that identifies and discloses all facts relevant to potential OCIs involving the proposer's organization and any proposed team member (proposed subproposer). Although the Federal Acquisition Regulation (FAR) does not apply to OTs or Cooperative Agreements, 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 proposers, and as applicable, proposed team members' OCI mitigation plans. 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 and may be included in Volume II.

Agency Supplemental OCI Policy

In addition, ARPA-H restricts performers from concurrently providing professional support services, including, Advisory and Assistance Services or Science, Engineering, and Technical Assistance 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 subproposer) providing the support; and
- An OCI mitigation plan in accordance with FAR 9.5.

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 R&D Solicitation evaluation criteria.

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.

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

4. Application and Submission Information

4.1. ADDRESS TO REQUEST APPLICATION PACKAGE

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 APPLICATION SUBMISSION

NOTE: Non-conforming submissions that do not follow R&D Solicitation 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 R&D Solicitation number, proposer organization, and proposal title/proposal short title.

4.2.1. Abstract Format

Proposers to the R&D Solicitation must first submit an abstract in order to be invited to submit a full proposal.
Based on evaluation of the abstract, ARPA-H may request a full proposal from R&D Solicitation respondents. The cover sheet should be clearly marked "ABSTRACT," and the total length should not exceed four (4) pages in length. The maximum page count excludes the cover page and the Rough Order of Magnitude. The Government will not review pages beyond 4; and any abstract submitted that exceeds four (4) pages will only be reviewed at ARPA-H's discretion. Official transmittal letter is not required.

A. Cover Page

The cover page should follow the same format as the full proposal described in Section 4.2.2.A. The cover page does not count towards the page limit.

B. Concept Summary

Describe the proposed concept with minimal jargon and explain how it addresses the topic area(s) of the R&D Solicitation.

C. Innovation and Impact

Clearly identify the health 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 the technical challenges posed by the R&D Solicitation. Explain the concept's potential to be disruptive compared to existing or emerging technologies. Describe how the concept will have a positive impact on at least one of ARPA-H's mission areas.

To the extent possible, provide quantitative metrics in a table that compares the proposed technology concept to current and emerging technologies and includes:

- State of the art / emerging technology "baseline"
- Target for proposed technology in its final, commercializable form
- Target for proposed technology at the end of the proposed ARPA-H project

D. Proposed Work

Describe the final deliverable(s) for the project, one (1) or two (2) 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 the scientific and technical literature. The list of citations does not count towards the page limit. Identify commercialization challenges to be overcome for the proposed technology to be successful in the health market.

Describe why the proposed effort is a significant technical challenge and the key technical risks to the project. At a minimum, the abstract should address:

- Does the approach require one or more entirely new technical developments to succeed?
- How will technical risk be mitigated?

E. 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.

F. Rough Order of Magnitude (ROM)

Please include a ROM estimate of timeline and federal funds requested, as well as the total project cost including cost sharing, if applicable. The ROM should also include a breakdown of the work by direct labor, labor rates, subcontracts, materials, equipment, other direct costs (e.g., travel), indirect costs, profit, cost sharing, and any other relevant costs. Cost sharing is neither required nor forbidden and is not considered a factor in evaluation. The below table may be used for this breakdown:

Cost Category	**Amount**
Direct Labor	
Indirect Costs	
Subproposers	
Materials	
Equipment	
Travel	
Other Direct Costs	
Indirect Costs	
Profit	
Total	
Cost Sharing *(if applicable)*	

However, proposers should ensure the ROM encompasses all applicable costs and should modify the above to best reflect the proposer's expected costs. The ROM does not count toward the page limit.

4.2.2. Full Proposal Format

Proposals must be in the format given below. The typical proposal should express a consolidated effort in support of one or more related technical concepts or ideas. Disjointed or unrelated efforts should not be included in a single proposal. Proposals shall consist of two volumes: 1) **Volume I, Technical and Management Proposal (composed of 2 parts),** and 2) **Volume II, Cost Proposal**. The Cover Page shall be no more than one (1) page in length. The page limitation includes all figures, tables, and charts. All pages shall be formatted for printing on 8-1/2 by 11- inch paper. Margins must be 1-inch on all sides, font size should be no less than 12 pt (Arial or Times New Roman), and page numbers should be included at the bottom of each page. Copies of all documents submitted must be clearly labeled with the ARPA-H R&D Solicitation number, proposer organization, and proposal title/proposal short title (in the header of each page). Please use the following Title Format: "Volume I_Lead Org", "Volume II_Lead Org", "Supporting Document_Lead Org". The maximum page count for Volume 1 is thirty (30) pages. This includes sections A-E described below (Executive Summary, Goals and Impact, Technical Plan, Management Plan and Capabilities). Sections F-I below are not included in the page count (Statement of Work (SOW), Schedule and Milestones, Technology Transfer Plan, and References). However, for all sections, ARPA-H encourages conciseness to the maximum extent practicable. No other supporting materials may be submitted for review. Volume I should include the following components:

A. Volume I, Technical and Management Proposal

Section I: Administrative

Cover Page

1. R&D Solicitation number (75N99224R00001);
2. Technical area;
3. Proposal title;
4. Prime Awardee/entity submitting proposal;
5. Type of organization, selected among the following categories: LARGE BUSINESS, SMALL DISADVANTAGED BUSINESS, OTHER SMALL BUSINESS", Historically Black Colleges and Universities (HBCUs), Minority Institution (MI), OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities) (*NOTE:* The Small Business Administration's (SBA) size standards determine whether or not a business qualifies as small.). Size standards may be found here: https://www.ecfr.gov/current/title-13/chapter-I/part-121#121.201
6. Date of submission;
7. Other team members (if applicable), organization and type of organization for each; Example: Jane Doe, ACME, Other Small Business

8. Technical point of contact (POC) to include: salutation, last name, first name, street address, city, state, zip code, telephone, email;
9. Administrative POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, email; and
10. Total funds requested from ARPA-H, and the amount of cost share (if any).

Section II: Detailed Proposal Information

A. Executive Summary: Provide a synopsis of the proposed project, including answers to the following questions:

- What is the proposed work attempting to accomplish or do?
- How is it done today, and what are the limitations?
- What is innovative in your approach?
- What are the key technical challenges in your approach, and how do you plan to overcome these?
- Who or what will be affected, and what will be the impact if the work is successful?
- How much will it cost, and how long will it take?

B. Goals and Impact: Clearly describe what the team is trying to achieve and the difference it will make (qualitatively and quantitatively) if successful. Provide an overview of the current and previous R&D efforts related to the proposed research and identify any challenges associated with such efforts, including any scientific or technical barriers encountered in the course of such efforts or challenges in securing sources of funding, as applicable. Describe the innovative aspects of the project in the context of existing capabilities and approaches, clearly delineating the uniqueness and benefits of this project in the context of the state of the art, alternative approaches, and other projects from the past and present. Describe how the proposed project is revolutionary and how it significantly rises above the current state-of-the-art. Describe the deliverables associated with the proposed project and any plans to commercialize the technology, transition it to a customer, or further the work.

C. Technical Plan: Outline and address technical challenges inherent in the approach and possible solutions for overcoming potential problems. This section should provide appropriate measurable milestones (quantitative if possible) at intermediate stages of the program to demonstrate progress, a plan for achieving the milestones, and a simple process flow diagram of the final system concept. The technical plan should demonstrate a deep understanding of the technical challenges and present a credible (even if risky) plan to achieve the program goal. Discuss mitigation of technical risk.

D. Management Plan: Provide a summary of expertise of the team, including any subproposers, and key personnel who will be doing the work. A PI for the project must be identified, along with a description of the team's organization, including the breakdown by TA. All teams are strongly encouraged to identify a Project Manager/Integrator to serve as the primary POC to communicate with the ARPA-H PM, IV&V team, and OT/Grant Officer's Representative equivalent for each award instrument (e.g., Grants Management Specialist), coordinate the effort across co-

performer, vendor, and subproposer teams, organize regular performer meetings or discussions, facilitate data sharing, and ensure timely completion of milestones and deliverables.

Provide a clear description of the team's organization including an organization chart that includes, as applicable: the programmatic relationship of team members; the unique capabilities of team members; the task responsibilities of team members, the teaming strategy among the team members; and key personnel with the amount of effort to be expended by each person during each year. Provide a detailed plan for coordination, including explicit guidelines for interaction among collaborators/subproposers of the proposed effort. Include risk management approaches. Describe any formal teaming agreements required to execute this program.

E. Capabilities: Describe organizational experience in relevant subject area(s), existing intellectual property, specialized facilities, and any Government-furnished materials or information. Describe any specialized facilities to be used as part of the project, the extent of access to these facilities, and any biological containment, biosafety, and certification requirements. Discuss any work in closely related research areas and previous accomplishments.

F. Statement of Work (SOW)[4]: The SOW should provide a detailed task breakdown, citing specific tasks for each TA, and their connection to the milestones and program metrics. Each Phase of the program should be separately defined. The SOW must not include proprietary information. The SOW will not be evaluated as part of the technical evaluation.

For each task/subtask, provide:

- A detailed description of the approach to be taken to accomplish each defined task/subtask.
- Identification of the primary organization responsible for task execution (prime awardee, subproposer(s), by name).
- A measurable milestone, i.e., a deliverable, demonstration, or other event/activity that marks task completion. Include completion dates for all milestones. Include quantitative metrics.
- A definition of all deliverables (e.g., data, reports, software) to be provided to the Government in support of the proposed tasks/subtasks.

It is recommended the SOW be developed so that each TA and Phase of the program is separately defined.

G. Schedule and Milestones: Provide a detailed schedule showing tasks (task name, duration, work breakdown structure element as applicable, performing organization), milestones, and the interrelationships among tasks. The task structure must be

[4] **F** through **I** do not count towards the 30-page limit of Volume 1.

consistent with that in the SOW. Measurable milestones should be clearly articulated and defined in time relative to the start of the project.

H. Technology Transfer Plan: Provide information regarding the types of partners (e.g., government, private industry) that will be pursued and submit a timeline with incremental milestones toward successful engagement.

I. References: Add a list with the cited literature

B. Volume II, Cost Proposal

(1) All proposers must submit the following:

Cover Page

1. R&D Solicitation number (75N99224R00001);
2. Technical area;
3. Prime Awardee/entity submitting proposal;
4. Type of organization, selected among the following categories: LARGE BUSINESS, SMALL DISADVANTAGED BUSINESS, OTHER SMALL BUSINESS", Historically Black Colleges and Universities (HBCUs), Minority Institution (MI), OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities)
5. Proposer's reference number (if any);
6. Other team members (if applicable) and type of organization for each;
7. Proposal title;
8. Technical POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, email;
9. Administrative POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, and email;
10. Award instrument requested: Cooperative Agreement or OT;
11. Place(s) and period(s) of performance;
12. Total proposed cost separated by base and option(s) (if any);
13. Name, address, and telephone number of the proposer's cognizant auditor (as applicable);
14. Date proposal was prepared;
15. Unique Entity Identification (UEI) number;
16. Commercial and Government Entity (CAGE) Code;
18. Proposal validity period (Minimum of 120 days).

Cost Proposal Information

The Government requires proposers use the provided MS Excel ARPA-H Standard Cost Proposal Spreadsheet in the development of cost proposals[5]. All tabs and tables in the cost proposal spreadsheet should be developed in an editable format with calculation formulas intact to allow traceability of the cost proposal. This cost proposal spreadsheet should be used by the prime organization and all subproposers. In addition to using the cost proposal spreadsheet, the cost proposal still must include all other items required in this announcement that are not covered by the editable spreadsheet. Subproposer cost proposal spreadsheets may be submitted directly to the Government by the proposed subproposer via email to the address in the Part I *Overview Information*.

NOTE: Non-conforming submissions that do not address the TAs as outlined under Section 1.2.1 and/or do not follow instructions herein may be rejected without further review.

Cost Breakdown Information and Format

Detailed cost breakdown to include[6]:

1. **Total Program Costs**
    a. Broken down by major cost items (e.g., direct labor, including labor categories; sub-agreements; travel; materials; other direct costs; overhead charges, etc.). For materials exceeding $5,000, a backup (screenshot, quote, etc.) is required.
    b. Further broken down by task and phase
2. **Major Program Tasks by Fiscal Year**
3. **An Itemization of Major Sub-agreements**
    a. In the same detail as the total program cost breakdown, and equipment purchases.
4. **Equipment**
    a. Documentation supporting the reasonableness of the proposed equipment costs (e.g., vendor quotes, past purchase orders/purchase history, detailed estimates from technical personnel, etc.) shall be provided.
5. **Itemization of Any Information Technology (IT) Purchases** (as defined by FAR 2.101)
    a. Documentation supporting the reasonableness of the proposed equipment costs (e.g., vendor quotes, past purchase orders/purchase history, detailed estimates from technical personnel, etc.) shall be provided.
6. **Summary of Projected Funding Requirements**
    a. By month
7. **Any Industry Cost-Sharing (if applicable)**
    a. Include the source, nature, and amount
8. **Identification of Pricing Assumptions**
    a. Use of Government Furnished Property/Facilities/Information, access to Government Subject Matter experts, etc.

[5] Proposers and any subproposers requesting a Cooperative Agreement do not need to use the Standard Cost Proposal Spreadsheet. Instead, Cooperative Agreement applicants must the MS Excel SF-424A Budget Worksheet Research provided via https://www.grants.gov.

[6] While cost and pricing data is required, certified cost and pricing data is not required for any award instruments resulting from this R&D Solicitation.

Tables included in the cost proposal must be in editable (e.g., MS Excel) format with calculation formulas intact.

NOTE: If PDF submissions differ from the Excel submission, the PDF will take precedence.

C. Supporting Cost and Pricing Data

Respondents to the R&D Solicitation should include supporting cost and pricing information in sufficient detail to substantiate the summary cost estimates and should include a description of the method used to estimate costs and supporting documentation. For other direct costs (ODCs) (e.g., equipment, IT) greater than $5,000, please provide screenshots/quotes. For indirect costs, if one has been negotiated with the federal government, please provide the most current indirect cost agreement (e.g., Colleges and Universities Rate Agreement, Forward Pricing Agreement, Provisional Billing Rates, etc.). The proposer must provide the point of contact (email and phone number) for the rate agreements (FPRA or Provisional Billing rates).

Subproposer Proposals

The awardee is responsible for compiling and providing all subproposer proposals for the Grants or OT Officer as applicable. Subproposer proposals should include Interdivisional Work Transfer Agreements or similar arrangements between the awardee and divisions within the same organization as the awardee. Where the effort consists of multiple portions which could reasonably be partitioned for purposes of funding, these should be identified as option periods with separate cost estimates for each. A cost workbook is required for ALL subproposers.

All proprietary subproposer proposal documentation, prepared at the same level of detail as that required of the respondent's proposal and which cannot be uploaded with the proposer's proposal, shall be provided to the Government either by the proposer or by the subproposer when the proposal is submitted. Subproposer proprietary proposals may be submitted directly to the Government. See Section 4.2.4. of this R&D Solicitation for Proposal Submission information.

D. Other Documents

Proposers should include any other required documents, as applicable, in Volume II. This should include, as applicable, OCI disclosures, OCI mitigation plans, Human Subjects and Animal Subjects Research documentation, intellectual property representations and assertions, etc.

4.2.3. Additional Proposal Information

Proprietary Markings

The government will protect any submissions marked as proprietary. 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."

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.

Human Subjects Research (HSR)

All entities applying for funding that involves 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 (https://www.hhs.gov/ohrp/index.html). All human subjects research must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46. The 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 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 personnel directly involved with the contemplated human subjects research. Funding cannot be used toward human subjects research until ALL approvals are granted.

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[7] , which incorporates the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training,"[8] and "Guide for the Care and Use of Laboratory Animals" (8th Edition).[9]

For all proposed research anticipating animal use, proposals should briefly describe plans for Institutional Animal Care and Use Committee (IACUC) review and approval. Proposers must also submit the Vertebrate Animals Section (VAS) as required by the NIH Office of Laboratory

[7] olaw.nih.gov/sites/default/files/PHSPolicyLabAnimals.pdf
[8] olaw.nih.gov/policies-laws/gov-principles.htm
[9] olaw.nih.gov/sites/default/files/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf

Animals Welfare. See here for requirements for the VAS: https://olaw.nih.gov/guidance/vertebrate-animal-section.htm).

Section 508 of the Rehabilitation Act (29 U.S.C. § 749d)/FAR 39.2

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

Cooperative Agreement Summary

Proposers requesting Cooperative Agreements awards must submit a Project Abstract Summary (use current version in Grants.gov). The one (1) page summary may be publicly posted and explains the program or project to the public. The proposer should sign the bottom of the summary confirming the information in the abstract is approved for public release. Proposers are advised to provide both a signed PDF copy, as well as an editable (e.g., Microsoft word) copy. Summaries contained in Cooperative Agreements proposals that are not selected for award will not be publicly posted. The document will only be requested if a full proposal is requested.

Note: This does not apply to OTs.

Intellectual Property

All proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all intellectual property that will be utilized under the proposed effort. The information will be requested as part of a full proposal request.

Proposers responding to this R&D Solicitation requesting a Cooperative Agreement or OT shall follow the applicable laws, rules, and regulations governing these various award instruments, but, in all cases, should appropriately identify any desired restrictions on the Government's use of any Intellectual Property contemplated under the award instrument in question. This includes both noncommercial items and commercial items. Respondents are encouraged to use a format similar to that shown in the table below. If no restrictions are intended, then the proposal should state "NONE."

Technical Data Computer Software To be Furnished With Restrictions	**Summary of Intended Use in the Conduct of the Research**	**Basis for Assertion (e.g., developed exclusively at private expense, developed exclusively with mixed funds, etc.)**	**Asserted Rights Category (e.g., Unlimited, Limited, Restricted, or negotiated, as defined in FAR 27.401)**	**Name of Person Asserting Restrictions**
(LIST)	(NARRATIVE)	(LIST)	(LIST)	(LIST)

System for Award Management (SAM) and Unique Identifier Requirements

Regardless of award type, all proposers must be registered in SAM before submitting a proposal. Entities that are not currently registered in SAM are advised that the process can take time and are encouraged to begin the registration process as soon as possible. International entities can register in SAM by following the instructions in this link: https://www.fsd.gov/sys_attachment.do?sys_id=c08b64ab1b4434109ac5ddb6bc4bcbb8.

4.2.4. Submission Information for Abstracts and OT Proposals

Proposers are responsible for submitting abstracts and proposals for OTs to the electronic Contract Proposal Submission (eCPS) website at https://ecps.nih.gov/ and ensuring receipt by the date and time specified. Proposers must use this electronic transmission method. No other method of abstract submission is permitted. Instructions on how to submit a proposal into eCPS are available at https://ecps.nih.gov/howtosubmit. Proposers may also reference Frequently Asked Questions regarding online submissions at https://ecps.nih.gov/faq.

For each of the requested files, please create a new business PDF and submit as new business document. If unable to do so, please consolidate these documents and include them to the end of "Supporting Document - Lead Org".

Be advised that registration is required to submit an abstract into eCPS and registration may take several business days to process. It is highly recommended offerors plan to register through eCPS well in advance of the abstract submission deadline, late abstract submissions resulting from delays with eCPS registration will not be accepted or considered.

This R&D Solicitation is open and in effect until the R&D Solicitation Closing Date outlined in Part I., Overview Information of this R&D Solicitation.

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

A. Abstract Submission

Refer to Section 6.1.1 for how ARPA-H will notify proposers to submit a full proposal.

B. Proposal Submission

Refer to Section 6.1.2 for how ARPA-H will notify proposers as to whether their proposal has been selected for potential award.

(1) Solely For Proposers Requesting Other Transaction Agreements

Proposers requesting an OT must provide a document describing Current and Pending Support. The document is mandatory for all Senior/Key Personnel including the PD/PI. This document should include the following information:

- A list of all current projects the individual is working on, in addition to any future support the individual has applied to receive, regardless of the source.
- Title and objectives of the other research projects.
- The percentage per year to be devoted to the other projects.
- The total amount of support the individual is receiving in connection to each of the other research projects or will receive if other proposals are awarded.
- Name and address of the agencies and/or other parties supporting the other research projects
- Period of performance for the other research projects.

The document should be included in the Cost Proposal volume.

(2) Solely For Proposers Requesting Cooperative Agreements

Full proposal applications must be submitted in https://www.grants.gov/. In addition to the volumes requested elsewhere in this R&D Solicitation, proposers submitting a requested full proposal must also submit the three (3) forms listed below. The forms do not count toward the page limitations.

Form 1: SF 424 *Research and Related (R&R) Application for Federal Assistance*, available on the Grants.gov website at https://www.grants.gov/web/grants/forms/r-r-family.html. This form must be completed and submitted.

To evaluate compliance with Title IX of the Education Amendments of 1972 (20 U.S.C. § 1681 et seq.), HHS is collecting certain demographic and career information to be able to assess the success rates of women who are proposed for key roles in applications in science, technology, engineering, or mathematics disciplines. HHS is using the forms below to collect the necessary information to satisfy these requirements. Detailed instructions for each form are available on Grants.gov.

Form 2: The Research and Related Senior/Key Person Profile (Expanded) form, available on the Grants.gov website at https://www.grants.gov/web/grants/forms/r-r-family.html, will be used to collect the following information for all senior/key personnel, including Project Director (PD)/PI and Co-Project Director/Co-PI, whether or not the individuals' efforts under the project are funded by HHS. The form includes 3 parts: the main form administrative information, including the Project Role, Degree Type and Degree Year; the biographical sketch; and the current and pending support. The biographical sketch and current and pending support are to be provided as attachments:

- Biographical Sketch: Mandatory for PDs and PIs, optional, but desired, for all other Senior/Key Personnel. The biographical sketch should include information pertaining to the researchers:
    - Personal Statement

  - Positions and Honors
  - Contributions to Science
  - Additional Information: Research Support and/or Scholastic Performance

- Current and Pending Support: Mandatory for all Senior/Key Personnel including the PD/PI. This attachment should include the following information:
  - A list of all current projects the individual is working on, in addition to any future support the individual has applied to receive, regardless of the source
  - Title and objectives of the other research projects
  - The percentage per year to be devoted to the other projects
  - The total amount of support the individual is receiving in connection to each of the other research projects or will receive if other proposals are awarded
  - Name and address of the agencies and/or other parties supporting the other research projects
  - Period of performance for the other research projects

Additional senior/key persons can be added by selecting the "Next Person" button at the bottom of the form. If ARPA-H receives an application without the required information, ARPA-H may determine that the application is incomplete and may cause your submission to be rejected and eliminated from further review and consideration under this R&D Solicitation. ARPA-H reserves the right to request further details from the applicant before making a final determination on funding the effort.

Form 3: Research and Related Personal Data, available on the Grants.gov website at https://www.grants.gov/web/grants/forms/r-r-family.html. Each applicant must complete the name field of this form, however, provision of the demographic information is voluntary. Regardless of whether the demographic fields are completed or not, this form must be submitted with at least the applicant's name completed.

4.3. FUNDING RESTRICTIONS

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

4.4. QUESTIONS

Interested entities may submit questions to the R&D Solicitation Coordinator. 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

Abstracts will be evaluated based on Evaluation Criteria #1 and #2. Abstracts will undergo an initial review for responsiveness.

Abstracts that are outside the scope of the R&D Solicitation will not be evaluated further. In addition, Abstracts that do not meet the submission requirements or do not contain one or more of the required items listed above may be deemed nonresponsive 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, achievable, 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.

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

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 entities.

5.1.3. Evaluation Criteria #3: Potential Contribution and Relevance to the ARPA-H Mission

Potential future R&D, commercial, and/or clinical applications of the project proposed, including whether such applications may have the potential to address areas of currently unmet need 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.

5.1.4. Evaluation Criteria #4: Cost Realism

Cost realism will be performed to ensure proposed costs are realistic for the technical and management approach, accurately reflect the technical goals and objectives of this R&D Solicitation, are consistent with the proposer's SOW, and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach. The costs for the prime proposer and subproposers will be substantiated for realism by the details provided in the proposal (e.g., the type and number of labor hours proposed per task, the types and quantities of materials, equipment and fabrication costs, travel and any other applicable costs and the basis for the estimates). In addition, the evaluation will take into consideration the extent to which the proposed intellectual property (IP) rights structure will potentially impact the Government's ability to transition the proposed technology.

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.

5.2. REVIEW OF ABSTRACTS AND FULL PROPOSALS

5.2.1. Review Process

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

ARPA-H will conduct a scientific/technical review of each conforming abstract/proposal. Conforming abstracts/proposals comply with all requirements detailed in this R&D Solicitation; abstracts/proposals that fail to do so may be deemed non-conforming and may be removed from consideration. Abstracts/proposals will not be evaluated against each other since they are not submitted in accordance with a common work statement. ARPA-H's intent is to review abstracts/proposals as soon as possible after they arrive; however, abstracts/proposals reviews may be delayed.

Award(s) will be made to proposers whose abstracts/proposals are determined to be the most advantageous to the Government, consistent with instructions and evaluation criteria specified in the R&D Solicitation.

5.2.2. Handling of Source Selection Information

ARPA-H policy is to treat all submissions as source selection information (see FAR 2.101 and 3.104), and to disclose their contents only for the purpose of evaluation. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by support contractors for administrative purposes and/or to assist with technical evaluation. All ARPA-H support contractors performing this role are expressly prohibited from performing ARPA-H sponsored technical research and are bound by appropriate nondisclosure agreements. Subject to the restrictions set forth in FAR 37.203(d), input on technical aspects of the abstracts/proposals may be solicited by ARPA-H from non-Government consultants/experts who are strictly bound by the appropriate non-disclosure requirements.

Information may also be provided to Courts and the U.S. Government Accountability Office, to the extent that the information is necessary for compliance with federal law or a court order.

5.2.3. Federal Awardee Performance and Integrity Information (FAPIIS)

Per 41 U.S.C. § 2313, as implemented by 2 CFR § 200.205, prior to making an award above the simplified acquisition threshold, ARPA-H is required to review and consider any information

available through the designated integrity and performance system (currently FAPIIS). Entities can comment on any information about themselves entered in the database, and ARPA-H will consider any comments, along with other information in FAPIIS or other systems, prior to making an award.

6. Award Administration Information

6.1. SELECTION NOTICES AND NOTIFICATIONS

6.1.1. Abstracts

ARPA-H will respond to each abstract. At that time, the proposer will be notified and informed of one of the following decisions:

1) ARPA-H has not selected the proposer to move forward with the submitted abstract;
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 abstract in order to determine whether the abstract will be selected or not.

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

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;
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, select and enter into negotiations, or require proposal revisions prior to making a selection decision.

6.2. ADMINISTRATIVE AND POLICY REQUIREMENTS

6.2.1. Meeting and Travel Requirements

There will be a program kickoff meeting after award and all awardees are required to attend. Performers should also anticipate regular program-wide PI Meetings and/or periodic site visits at the PM's discretion.

6.2.2. Award Clauses, Terms and Conditions

Specific terms and conditions will be negotiated for each OT. Cooperative Agreement terms and conditions will be as required by applicable regulation and policy and as supplemented by unique requirements of the project.

6.3. 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 to 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. If applicable based on funding amount, reporting requirements specified in 45 CFR Part 75 Appendix XII will be incorporated into a Cooperative Agreement.

6.4. ELECTRONIC SYSTEMS

6.4.1. Payment/Funding Receipt

The Government anticipates performers will be required to register in the Payment Management Services (PMS) system at https://pms.psc.gov.

6.4.2. 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://public.era.nih.gov/iedison).

7. Agency Contacts

Points of Contact:

The R&D Solicitation Coordinator for this effort may be reached at APECx@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. https://arpa-h.gov/engage/programs/apecx/teaming/

8. Other Information

ARPA-H will host a Proposers' Day in support of the APECx Program on the date listed in Part I., *Overview Information* of this R&D Solicitation. The purpose is to provide potential proposers

with information on the APECx program, promote additional discussion, and encourage team networking.

Interested proposers are not required to attend, and 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 abstracts/full proposals. To participate in the event, proposers must complete the online registration form located at https://arpa-h-apecx.powerappsportals.us/.

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