AMENDMENT ONE (1)

Solicitation Number: PHS 2025-1

Date of Solicitation Issuance: 08/02/2024

Date of Amendment No.1 Issuance: 10/01/2024

Number of Pages: 34

Points of Contact:

Callie Prassinos, Contracting Officer
E-mail: Callie.Prassinos@nih.gov

Julie Rodriguez, Contracting Officer
E-mail: ncioasbir@mail.nih.gov

ISSUING OFFICE OF ACQUISITIONS

National Institute of Allergy and Infectious Diseases (NIAID)
5601 Fishers Lane, Suite 300, MSC 9821
Rockville, MD 20852

PURPOSE OF SOLICITATION AMENDMENT

The purpose of this amendment is to:
- Provide slides, recording, and transcript of the pre-proposal conference; and,
- Respond to Questions received regarding the solicitation.

The hour and date specified for receipt of Offers remains unchanged.
Except as provided herein, all terms and conditions of the solicitation remain unchanged and in full effect.

A recording of the pre-proposal conference and associated materials have been posted on the NIH SBIR/STTR SEED webpage and are also made available below:

- Watch the video.
- Access the slides.
- Access the transcript.

General Solicitation Questions

Question 1: For our SAMs account we selected to focus on grant applications and not governmental contracts. Is this something we can still apply for?

Answer 1: Your company must have an active registration in SAMs that reflects "purpose of registration: All Awards" not "Federal Assistance Awards Only." Please review Section 4.12 of the solicitation for more information.

Question 2: Do we have to provide cost proposal justification other than some details required in Appendix C? In the SBIR grant application there is a budget justification document. For the SBIR contract, where should we justify the expected costs in more detail?

Answer 2: In Appendix C, page 2 under Item Description, there are instructions on what to include for cost/price justification. If more space is needed, please add pages to this appendix and label clearly.

Question 3: Are there any examples of the awarded SBIR contract proposals available? I only found SBIR grant proposal examples on the NIA website.

Answer 3: NIH does not have a copy of a funded SBIR contract proposal as an example.

Question 4: For a Phase II contract, will it still be a firm-fixed price contract, or is it a cost-reimbursable contract?

Answer 4: Phase II funding type will vary among each topic. Therefore, it is important for the proposing firms to review the topics description and reach out to the specific Contracting Officer in the agency for that topic.

Question 5: What percent of the total budget can be allocated to sub-contracts?

Answer 5: In Section 4.2 of the solicitation, it states "For Phase I, a minimum of two-thirds of the research or analytical effort must be performed by the awardee. For Phase II, a minimum of one-half of the research or analytical effort must be performed by the awardee. The percentage of work will be measured by total award dollars."

Question 6: Can a PI/company submit two proposals to a solicitation this time?

Answer 6: Yes, a company is allowed to submit more than one proposal under the same topic or under different topics, if the proposals represent separate and distinct projects.

Note that for proposal submission in eCPS, the company would need to create entirely separate submission packages. The company would go through the eCPS submission process for the 1st submission and then repeat the process for the next submission. If a company is planning to submit more than one proposal under the same topic, it is recommended that the Company differentiates between their different Phase I proposals by using a unique identifier in the file names/naming conventions. For example: if each submission has a different PI, include the PI name in the submission file names, etc., to ensure reviewers will be aware that the

submissions are different proposals from the same vendor not a duplicate submission of the same proposal.

Question 7: What are the timelines (e.g., award notification and project kick-off) after November submission?

Answer 7: The timelines will be different for each agency. Please review the estimated timelines in the solicitation, Section 9, which contains projected dates for when the review and award will take place.

Question 8: What is the process for NIH and CDC to make decisions? Is it the same review process as SBIR grant?

Answer 8: The requirements are identified and described specifically under each of these research topics. The way that the review will be conducted is that each awarding component will assemble a panel of peer reviewers, which is similar to grants review in the sense that it's a peer review. However, the expertise that's gathered for those panels is going to be collected based on the needs and requirements of the specific topic. So, proposals submitted under a topic will be reviewed together by a peer review panel that's reviewing against the criteria that's stated in the Solicitation. Please review section 6 of the solicitation for information.

Question 9: Does "outsource" mean subcontracting?

Answer 9: Outsource can be a subcontractor or any contract/agreement with a third party for activities being conducted in the Statement of Work.

Question 10: Could you please elaborate the criteria for a Fast Track contract?

Answer 10: A Fast Track submission may result in award for Phase I with a contractual option for Phase II. The Government is not obligated to fund the Phase II portion unless and until the awarding HHS Component exercises that option. Performance requirements are specific to each contract and will be addressed by the awarding component's Contracting Officer for proposals identified for negotiation.

Question 11: What if there are multiple PIs? Do all need to be 50% employed by company?

Answer 11: At least one proposed PI must be primarily employed with the applicant, as discussed in Section 4.2 "Offeror Eligibility and Performance Requirements."

Question 12: Are there restrictions on eligibility for SBIR/STTR funding if the applying company is owned more than 50% by a non-profit organization?

Answer 12: Small Businesses must meet the eligibility criteria listed here: https://seed.nih.gov/small-business-funding/small-business-program-basics/eligibility-criteria

Question 13: Are there suggested page lengths for the sections of the proposals? Does this page limit include biosketches? resource pages etc.?

Answer 13: SBIR Phase I Technical Proposals (Item 1) shall not exceed 50 pages. SBIR Phase II Technical Proposals (Item 1) shall not exceed 150 pages. The Technical Proposal shall not exceed the page limits stated, inclusive of all pages, cover sheet, tables, CVs, resumes, references, pictures/graphics, appendices, attachments, etc.

Question 14: Do Phase IIs follow the same due dates listed in the funding opportunity announcement or are awarded Phase I agencies notified of Phase II requirements individually? Do you typically apply for Phase I and Phase II at the same time?

Answer 14: Please refer the solicitation Section 8.4 'Phase II Proposal Instructions', for information regarding Phase II proposal's (either as part of a FAST TRACK or Direct to Phase II). This will depend on the topic and fast track applications.

Question 15: If we are a startup just incorporated, can we use 40% indirect rate for budget?

Answer 15: SBIR offerors who propose a G&A/IDC rate of 40 percent of total direct costs or less will not be required to negotiate Final Indirect Rates with the NIH Division of Financial Advisory Services (DFAS), or other cognizant auditing agency. However, awarding Contracting Officers may require offerors to document how they calculated their IDC rate(s) in order to determine that these costs are fair and reasonable.

Question 16: How should I determine and document indirect rates?

Answer 16: The solicitation allows for small business to charge indirect costs at a rate of up to 40% of total direct costs without requiring that the small business negotiate an indirect rate agreement with the NIH Division of Financial Advisory Services (DFAS). However, this does not mean that an indirect rate of 40% will be acceptable for every business.

After reviewing the DFAS website, https://oamp.od.nih.gov/division-of-financial-advisory-services, if you have further questions, you are encouraged to contact the DFAS staff at dfas-idc@nih.gov for assistance in understanding how to determine an appropriate indirect rate.

Question 17: Can you explain the difference between grants vs contracts?

Answer 17: A contract is a legally binding agreement between the two parties, your organization and the government. There will be specific performance requirements in the statement of work and details of deliverable schedule that will include dated that are expected for performance.

Question 18: Are we required to submit Pricing proposal form other than in Appendix C? Or are there any other detailed forms needed?

Answer 18: Appendix C is the pricing proposals that is required.

Question 19: Are letters of support required? If so, how many and from whom (ex. researchers, doctors, potential end users, etc.)?

Answer 19: When a subcontractor or consultant collaborator is proposed, a letter must be included from each individual confirming his/her role in the project and extent of involvement; when facilities other than those of the applicant are proposed, a letter must be included stating that leasing/rental arrangements have been negotiated and will be available for the use of the SBIR applicant; and, for Phase II proposals under a Fast Track submission, letters should be included in the Finance Plan section of your Commercialization Plan.

In addition, some of the specific Topic Descriptions in Section 12 refer to additional and/or more specialized letter requirements, so check your individual Topic of interest carefully.

All of these letters should be included in your Technical Proposal to ensure that they are reviewed by all reviewers.

In addition, costs associated with collaborators should be addressed in Appendix C of the Business Proposal, and letters that discuss or confirm financial information for collaborators can also be included in the Business Proposal to support the evaluation of the proposed project budget. For NIH Topics, please note that information submitted in the Business Proposal, however, will not be seen by all evaluators, some of whom will only review the Technical Proposal.

Question 20: With SBIR, do you have to be with a university?

Answer 20: You do not have to be affiliated with a university to submit an SBIR.

Question 21: In general, how guaranteed are the funds stated in the topics?

Answer 21: NIH/CDC will not fund a proposal for more than the budget listed for each topic (with the exception of potential Technical and Business Assistance funding, as described in that section of the solicitation). The Agency is under no obligation to fund any proposals or any specific number of proposals in a given topic.

Question 22: Are contracts eligible for Technical and Business Assistance (TABA)?

Answer 22: Section 4.16 provides guidance on State Assistance and Technical Assistance. NIH offers distinct technical assistance programs to NIH SBIR and STTR Phase I and Phase II awardees. These programs offer specialized, strategic business training and provide access to a vast network of industry experts which is made possible by the efficiencies of scale accomplished through providing this service through the Government.

Note for CDC offerors: CDC does not participate in the NIH TABA Program. If you are a CDC offeror and wish to utilize your own technical assistance provider, you are required to include these costs in your budget and to provide a detailed budget justification. You may request up to $6,500 per year for a Phase I and up to $50,000 per Phase II project (across all years) for assistance.

Refer to Section 8 for how to include this in your Pricing Proposal. Please note, if funds are requested to utilize your own technical assistance vendor and an award is made, the awardee is not eligible to apply for the NIH-provided technical assistance program for the phase awarded.

Question 23: Can a new corporation apply for a direct-to-phase II contract using the results of the previous LLC? The team and resources remain the same, the company structure and name are the only changes.

Answer 23: There should not be an issue with changing company structure.

https://www.sbir.gov/faqs/all states:
What happens if we change our corporate structure and change our EIN or DUNS number, are we considered new company or existing company?

If you change your corporate structure, EIN, or DUNS, you will add a new record to the already existing company for data and recordkeeping purposes.

Question 24: Are you able to provide the contact information for the program managers/contract officers for the different Topics?

Answer 24: All inquiries must be addressed to Contracting Office personnel, as set forth in Section 10 of the solicitation.

Question 25: Are the contract topics ever repeated? In case a company is unable to apply before the deadline, would there be another opportunity to apply for a similar topic?

Answer 25: An SBIR contract topic may or may not be repeated in future years. If the topic of interest is not repeated, applicants may consider applying for the SBIR/STTR Omnibus solicitations. Link:
https://seed.nih.gov/sites/default/files/HHS_Program_Descriptions.pdf.

Question 26: Could you briefly outline the criteria used to assess the 'best overall value" as stated in the solicitation?

Answer 26: *Best value* means the expected outcome of an acquisition that, in the Government's estimation, provides the greatest overall benefit in response to the requirement. As stated in section 6.2 Award Decisions; the Awarding Component will make awards to the offerors who provide the best overall value to the Government, considering ratings resulting from the technical evaluation, areas of high program relevance, program balance (i.e., balance among areas of research),

availability of funds, Cost/Price, ands security risk as assessed by the HHS Due Diligence Program.

Question 27: Are all SBIR disbursements done by invoice, or can it be done by drawdowns from a PMS account? Would the invoices be submitted based on the completed milestones, or on a regular basis?

Answer 27: All SBIR payments will be made by invoice method only. Invoice submission and payment will be outlined in contract and might be different per each awarding competent. Please reference Section 4.17 Payment and discuss with specific Topic's Contracting Officer.

Question 28: Are late submissions possible for this program?

Answer 28: Late proposals will not be accepted. Section 7.4 Submission, Modifications, Revision, and Withdrawal of Proposals states that, "Any proposal, modification, or revision, that is received after the exact time specified for receipt of proposals is "late" and will not be considered for award."

Question 29: Should a company receive the award, can funds from the award be allocated to equipment purchases?

Answer 29: Equipment purchases may be allowed. Any equipment specifically proposed as a cost to the contract must be justified in the proposal as well as detailed in the budget.

Question 30: Please clarify general purpose office furniture or equipment regardless – to mean things like telephones, computers – etc., but not specialized equipment that might be used in the actual research, such as lab equipment?

Answer 30: General purpose equipment, such as office chairs, are generally unallowable (see solicitation page 37). However, Section 8.8 has directions regarding the proposal requirements for listing any specialized equipment needed to complete the work proposed under "Resources." Section 8.13 further discusses special tooling and test equipment.

Question 31: I do see we have the contract pricing template (Appendix C) that needs to be completed and the budget excel as optional. We are proposing a 2-year project; will we need to complete 2 of the contract pricing templates?

Answer 31: Please submit one contract pricing sheet for the project. This will include all costs for the two-year duration.

Question 32: What would be the project start dates?

Answer 32: Project start dates will be determined during negotiations. Your organization will work with the CO/COR to determine these dates.

Question 33: I created an external account on eCPS. Does that mean I am registered? The solicitation said it could take several days but I could create an account immediately. Just want to make sure I have done this correctly.

Answer 33: If you have questions regarding an eCPS account, please contact eCPSAdministrator@niaid.nih.gov.

Questions: Section 12 Component Instructions and Technical Topic Descriptions

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

NCATS Topic 025: Development of a versatile small footprint benchtop device to perform batch evaporation

Question 1: Solicitation asks for automating 4 evaporations simultaneously. Is there value to the NIH to expand beyond 4 evaporations simultaneously?

Answer 1: There is value to expand to 8 vials at a time as it'll cover the entire rack of High Recovery Vials, making the batch evaporator easier to integrate with other processes. However, in the testing performed at NCATS, expanding to 8 vials has proven unwieldy regarding the performance of the evaporation; hence it's recommended to stick to 4 vials for now.

Question 2: The solicitation lists 8 solvents (including water). Are these the common solvents that we should be focusing on, or are there other solvents of interest?

Answer 2: The 8 solvents listed are the most common solvents used in synthesis. The design should be modular to support other solvents, if necessary, but for now, the 8 solvents are sufficient.

Question 3: Can there be some user input, for example needing to attach lids, or entering in the type of solvent being used in each vial, or does every step need to be automated?

Answer 3: Yes, there will need to be user input through a Python/C# based UI that allows a user to enter evaporation conditions and operate the evaporator physically, like closing the lids if needed. The intended use is for a user to provide the conditions/parameters for the evaporation and press Start, after which the batch evaporator will perform the necessary steps in an automated fashion: Seal Lid Open/Close, Vacuum/ Nitrogen/ Heating On & Off.

Question 4: Along those lines, we are intending to have individual sample temperature and vacuum pressure control. Are there any other types of control over evaporation conditions that the NIH would like?

Answer 4: Vacuum, Nitrogen, and Temperature control. Seal Open/Close control. Evaporation Time control. These controls, except for the "Time" parameter, apply to all 4 vials in the evaporator; there won't be individual parameters set for each vial.

Question 5: The initial prototype was designed for 8 mL samples. Is that an appropriate sample volume for an updated system? In other words, what is the range of volumes you would like the batch evaporator to operate under (minimum and maximum expected volumes)?

Answer 5: 8mL was selected based on the upstream and downstream chemistry requirements. However, the idea is that upon leaving the batch evaporator, the total volume in the vial should be less than 8mL. The starting pre-evaporation volume can be up to 10mL and a minimum of 1mL. Anything beyond these values will likely result in inefficient evaporation behaviors.

Question 6: The solicitation mentions "90% dryness" within 10 minutes. Is that the desired final state of the sample, or are you looking to dry the sample to completeness, or have the option to do both?

Answer 6: The desired use for this system is to bring it down to 90% dryness and never to full dryness because that can lead to losing valuable samples. The expected time doesn't necessarily need to be 10 minutes. Recent findings show that some solvents take up to 15 minutes for 90% dryness, and this number changes based on the solvent type. The goal should be to reach 90% dryness within 15 minutes.

Question 7: With regards to integrating the device with an existing ACS workflow, is there a specific ACS workflow or system that can be referenced for integration with the proposed evaporation system?

Answer 7: Yes, the most direct integration would be with the Biotage V10 evaporator, which performs evaporation to full dryness in a controlled environment. The idea is to use the Batch Evaporator to evaporate up to 90% using the Batch Evaporator and finish the rest in the Biotage V10. This process will reduce the overall time it takes for evaporating a single vial compared to just using the V10 for evaporation.

Question 8: Is the product in the reaction mixture expected to be non-volatile? In other words, we only need to worry about eliminating high vapor pressure solvents and reagents, and will not need to be concerned about losing product?

Answer 8: There is a risk of losing product if the batch evaporator is used in an uncontrolled, fully manual setting where the evaporation is run beyond the expected time range. However, the batch evaporator being developed needs to have safeguards in place to cut off evaporation upon reaching the intended evaporation time to prevent this from happening.

Question 9: Will we have access to more data from the NCATS prototype if awarded the grant? What makes the NCATS version unsuitable for commercialization? Is your preference for someone to try to improve that design or design a completely new system?

Answer 9: Yes, data can be provided if required. The NCATS version is just a basic prototype which needs to be improved upon by following industry-standard manufacturing guidelines. From a design perspective, the system is capable of

commercialization, but the expectation is to improve on the current design by manufacturing with robust guidelines.

Question 10: Does the unit need to consider air-sensitive compounds (e.g., capability to backfill with N2 after releasing vacuum)?

Answer 10: There can be two approaches here: either the vials are backfilled with Nitrogen, or the Seal remains in place until the user is ready to extract the vials from the evaporator. Both options ensure protection for air-sensitive samples.

Question 11: Are there any restrictions on what the vials can look like? Is it expected to be able to concentrate directly in the reaction vessel, or if there is a post-reaction work-up step, in that vial? Could the solution be transferred into a specialized vial?

Answer11: The vials need to be standard 20mL High Recovery Vials with a conical bottom. The vials need to be 1D and 2D barcoded. After the Batch Evaporation step, the vials will be taken to the Biotage V10 evaporator for final evaporation. There will be no work-up steps required between these processes. There can be work-up steps after V10, but it is beyond the scope of this grant.

Question 12: Will there eventually be a need to remove higher boiling solvents like toluene, etc., or mixtures containing large quantities of water?

Answer 12: We have identified water as an edge case for high boiling point solvents, which should cover those types of solvents in general.

Question 13: Are there any expectations for the User Interface or the controls platform used?

Answer 13: There aren't any UI expectations for a Manual Batch Evaporator; instead, it'll need a push-button to operate and a display to show temperature, pressure, etc. However, for an automated Batch Evaporator, we will need a Python/C# based UI to control the system as well as integrate with ChemDash-like application.

Question 14: Is there more definition on the information that the API needs to be able to handle?

Answer 14: The API will need to handle system information such as Nitrogen and Vacuum pressure, Temperature, Vial Presence, Vial Barcode, and operational information such as Handshakes with other integrated systems.

Question 15: What is the desired behavior upon completion of the cycle?

Answer 15: Desired behavior upon completion is a complete automatic shutdown of utilities: nitrogen, vacuum, and heating. Seal to be removed upon manual input from the user to avoid letting the vials sit without a covering.

Question 16: Is there a risk of "over-processing" the vials? If so, are controls needed to monitor and prevent this?

Answer 16: There is a risk of over-processing vials; the sample material can go dry if the evaporation exceeds the desired time of evaporation. To help mitigate this, the evaporation utilities will cut off automatically once the desired evaporation time is reached, which will allow it to get to 90% dryness, the goal of the Batch Evaporator. The time of evaporation is determined based on the performance metrics collected during testing for a variety of solvents used in chemical synthesis.

NCATS Topic 026: Scalable Generation of Liver and Brain Organoids Derived from Human iPS Cells.

Question 1: Is it necessary to establish both liver and brain organoids using 8 iPSCs provided by NCATS for the Phase I SBIR Contract? Given budget constraints, can we generate either liver organoids or brain organoids in Phase I SBIR Contract?

Answer 1: Yes, we are looking for both liver and brain organoids as part of the same contract. We would like brain organoids generated from 4 iPSC lines (2 NGLY patient derived lines and 2 healthy donor control lines) and liver organoids from 4 iPSC lines (2 ALGS patient derived lines and 2 healthy donor lines). We would like to have improved methods with increased efficiency and reduced costs.

Question 2: Assuming the total number of organoids to be generated is 60,000 (= 10,000 organoids/batch in 3 batches in months 1 – 6 and 10,000 organoids/batch in 3 batches in months 7 – 12), with 8 iPSCs (4 patient-derived iPSCs and 4 control iPSCs) used, is it correct to calculate that the total number of organoids generated per iPSC is 7,500 (= 60,000 organoids/8 iPSCs)?

Answer 2: We are looking for 60,000 organoids (in 6 batches of 10,000) per iPSC line.

Question 3: The count of the pillar plates with organoids to be generated can be a bit confusing. If we use a 144PillarPlate with a 12 x 12 array of pillars, and each pillar accommodates one organoid, we need to manufacture 416 of the 144PillarPlates for 8 iPSCs (= 8 iPSCs x 7,500 organoids/144 pillars). Conversely, if 10 organoids are loaded on each pillar, only 42 of the 144PillarPlates would be required. Given budget constraints, can we load multiple organoids on each pillar and manufacture smaller number of the pillar plates with organoids?

Answer 3: We leave the details of organoid generation up to the CRO, as long as the organoids are differentiated from human iPSCs, and that the cells self-organize and differentiate to allow modeling of disease phenotypes. The liver organoids should have cells expressing albumin (hepatocytes) and CK7 (cholangiocytes) markers. The Midbrain organoids should have cells expressing tyrosine hydroxylase (TH), FOXA2, EN1, and EN2 markers. Biological relevance to brain and liver tissues are critically needed.

Question 4: Given the challenges of cryopreserving mature liver and brain organoids, it is a viable option to ship frozen early hepatic progenitor cells and neuroectoderm in the pillar/perfusion plates, which can then be matured through one or two differentiation steps at NCATS. Does NCATS have robust cryopreservation protocols for mature liver and brain organoids?

Answer 4: We are looking for cryopreserved mature organoids that are readily used for experiments such as testing drug efficacy. We currently have successfully cryopreserved liver organoids.

Question 5: What is the required Technology Readiness Level (TRL) for a company to begin working with this technology?

Answer 5: In the proposal, the company should convincingly show that they have the resources and expertise in the field of 3D tissue models and organoid development to be able to carry out the work required under the contract.

Question 6: Could we access more information about the i3D-RARE pilot projects through a provided link to better align our proposal?

Answer 6: There was a workshop held on this topic in September last year, and here is a recording- https://www.youtube.com/watch?v=T6J9ox8pCCA Additional workshop information can be found here- https://site.corsizio.com/event/64dd17cd42fb65a6bae73f62

Question 7: Which rare genetic diseases is NCATS particularly interested in, to help us clarify our future objectives and commercialization strategy?

Answer 7: NCATS is disease agnostic and therefore we do not have a special emphasis panel of diseases. For more information about NCATS' Rare Disease Programs, please visit- https://ncats.nih.gov/research/research-activities?related_office%5B%5D=2#research-activities-at-NCATS

NCATS is interested in Alagille Syndrome (ALGS) for liver organoids and NGLY1 deficiency for midbrain organoids. NCATS will provide 4 iPSC lines for liver organoid generation (2 healthy donor lines, 2 ALGS lines) and 4 iPSC lines for midbrain organoid generation (2 healthy donor lines and 2 NGLY1 lines).

Question 8: There is a requirement of Generation of 10,000 organoids/batch in three batches over the first six months. NCATS will be provided total 8 cell lines, which means we have to generate 80,000 organoids, in 3 batches in cell lines 240,000 organoids. Is this one of the goals for this topic?

Answer 8: Yes, this is correct. To clarify, the 8 iPSC lines will be divided into 4 lines for liver organoid generation and 4 lines for midbrain organoid generation. In the first 6 months, we are looking for 10,000 organoids/batch in 3 batches for each of the 8 iPSC lines. So, 120,000 liver organoids from 3 batches from 4 lines in the first 6

months, and 120,000 midbrain organoids from 3 batches from 4 lines in the first 6 months.

Question 9: Is the goal to generate both liver and midbrain organoids, or just one? I would worry that most submitters may have a strong solution for one but may not have something for both.

Answer 9: The goal is to generate both liver and brain organoids. For each organoid type, we are looking for 10,000 organoids/batch in 3 batches for each of the 4 iPSC lines. For a total of 120,000 organoids per type in months 1-6 of the contract.

Question 10: Is that 10,000 organoids/batch of each type (so 20,000 organoids/batch with three batches per cell line for each six-month period)?

Answer 10: For midbrain organoids: 10,000 organoid/batch for 3 batches for each of 4 iPSC lines in months 1-6. Then, 10,000 organoid/batch for 3 batches for each of 4 iPSC lines in months 7-12.

For liver organoids: 10,000 organoid/batch for 3 batches for each of 4 iPSC lines in months 1-6. Then, 10,000 organoid/batch for 3 batches for each of 4 iPSC lines in months 7-12.

NATIONAL CANCER INSTITUTE (NCI)

NCI Topic 466: Novel Delivery Systems for RNA-based Cancer Vaccines

Question 1: Would we be competitive for a Direct to Phase II proposal? Or do we need to have Phase I equivalent data for the mRNA vaccine coupled with the delivery system for Phase II, in which case we should develop a Phase I proposal instead? Is there a requirement to focus on one cancer indication for the proposal, or can we target multiple indications (in either a Phase I or Phase II proposal)?

Answer 1: The focus of this topic is on the development of RNA delivery systems to develop novel RNA delivery systems that will improve the safety, efficacy, and availability of RNA-based cancer vaccines. Thus, if the offeror has already optimized the RNA delivery platform/system and has demonstrated already accomplished results equivalent to the proof-of-concept studies outlined by the Phase I deliverables, then it would be appropriate to apply for a direct to phase II. If these have not been done, then a phase I or Fast-Track proposal would be a better fit.

Question 2: Can we submit an STTR proposal for this topic, or must it be an SBIR? (I found no explicit statements addressing this in the solicitation.)

Answer 2: This contract solicitation utilizes SBIR set-aside funds, thus only SBIR proposals are accepted.

Question 3: We have completed all mandatory Phase I requirements in an academic setting, so we'll submit a "Direct to Phase II" proposal. One of the Phase II requirements is benchmarking against an FDA-approved LNP system. We

prefer to do a comparison in an academic setting to avoid potential LNP licensing issues. Would that be acceptable?

Answer 3: Offerors should provide justification that the benchmarking experiments are relevant and enable demonstration of equivalent or superior performance to approved LNP systems. Where the work is performed is not specified and offerors may choose to work with academic partners to perform this work.

Question 4: We would like to propose the development of a method to deliver chemotherapeutics and adjuvants as a potential treatment for melanoma. Can we use pneumatic biolistic particle delivery to disperse materials? By controlling the compressed gas, we would like to propose the delivery of chemotherapeutics.

Answer 4: Please refer to the deliverables outlined in the contract solicitation: https://sbir.cancer.gov/small-business-funding/contracts/current-solicitation/466. Note, the solicitation states that "Strategies to optimize therapeutic response that do not involve RNA delivery" are NOT responsive to this topic. The solicitation does not specify any cancer type/indication, melanoma is acceptable, but the approach must be focused on delivering RNA.

NCI Topic 468: Synthetic Microbes (Excluding Oncolytic Viruses) for Immuno-Oncology Therapies

Question 1: We are developing an engineered live bacterial therapy designed to engraft the gut of Familial Adenomatous Polyposis (FAP) patients and continuously express Bile Salt Hydrolase (BSH). In Phase 1, we intend to confirm in vivo anti-tumor efficacy using appropriate cancer models and controls including measuring tumor growth, quantifying metastases, and monitoring the survival of tumor-bearing mice. My question: Would this be responsive to NIH/NCI 468 - Synthetic Microbes (Excluding Oncolytic Viruses) for Immuno-Oncology Therapies?

Answer 1: Yes, the described BSH engineered microbe technology is responsive to NIH/NCI topic 468 - Synthetic Microbes (Excluding Oncolytic Viruses) for Immuno-Oncology Therapies

Question 2: I'm wondering if you have a format for the content of technical element. I know there are Appendix A and B for the cover sheet and abstract, but I'm wondering if you have a format for "content of technical element" as well. If yes, would you please let me know where I can find it?

Answer 2: Please section 8.8 in the solicitation for the format of the Content of Technical Element (Item 1). Please see also note proposal preparation and instructions under section 8 of the solicitation as well.

NCI topic 469: Development of Novel Therapeutics for HPV-related Precancer

Question 1: If a company uses the same compound for two different types of development programs (e.g. a topical pre-cancer and an oral/IV cancer program), does this fall under the "essentially equivalent work"?

Answer 1: No.

Question 2: If a company includes the required information in Appendix A and C about their recent SBIR Phase II grant submission (PA-24-245), is the company still allowed to submit a contract application since the SBIR grant funding decision would not be known until Q1 2025?

Answer 2: Yes, provided that the submissions do not have overlapping aims. Example above (Question 1) is allowed-same compound for two different types of development programs.

Question 3: In Section 8.13 of the solicitation, disclosure of pending support of similar proposals requires certification in Appendix A, which is the cover page for a Phase I submission. Do we still use Appendix A if the contract submission is for a Direct to Phase II?

Answer 3: Yes.

Question 4: Can two business entities working on a project can apply? Specifically, one entity is responsible for conducting the R&D experimentation, while the other provides most of the scientific guidance and expertise. Both companies are actively involved in the project and have a unique synergy, and we have a joint patent filing with inventors from both businesses.

Answer 4: One business would need to be the main contractor, and the other one can be a sub-contractor. How they assign each business entity is a business decision that they would need to decide internally.

NCI Topic 470: Precision Nutrition Interventions to Reduce Cancer-Related Symptoms

Questions 1: We are considering partnering with an academic institution to access patients and do a study. Are we allowed to use funding for a study as part of Topic 470?

Answer 1: Partnering with an academic institution is allowed.

Question 2: Can the NCI be flexible with allowing more than 33% to be outsourced? Our business is as a wholesaler of the food product, not as the product manufacturer, at least while we are still a small business concern. This expense, coupled with our academic partnership, would exceed $132K, but our Phase 1 could be done within $400K.

Answer 2: For Phase I, NCI allows up to 33% to be outsourced. For Phase II, NCI allows up to 50% to be outsourced. Please note that CRO or Fee for Service are different from a subaward: https://seed.nih.gov/faqs#11782

Question 3: If CRO or Fee for Service are different from a subaward, does this mean that the funds we use to study the product with the academic partner and/or the product development costs we need to pay the manufacturer would not be

considered "outsourced?" Can you clarify the definition of outsourced funds?

Answer 3: A CRO or Fee for Service provider provides goods or services within normal business operations and operates in a competitive environment providing similar goods and services to a variety of customers. CROs or Fee for Service providers not operating in the capacity as a subaward or subrecipient may not be calculated in the total amount of all consultant and contractual arrangements to third parties for portions of the scientific and technical effort.

NCI Topic 471: Drug-Loaded Carrier Particles for Improved Oral Delivery for Colon Cancer Prevention

Question 1: Would less conventional carrier-particles, such as engineered bacteria for delivery be considered for this topic?

Answer 1: Yes, if you can demonstrate that the engineered bacteria can act as carrier particles for delivering drugs (small molecules or biologics) orally to prevent colon cancer. Please refer to the project goals outlined in the contract topic solicitation for further details.

Question 2: Is a display of efficacy in an IBD animal model required/necessary for Phase I of this proposal topic?

Answer 2: It is important to note that the activities and deliverables outlined for Phase I in the solicitation are provided as examples and are generally expected in a Phase I research proposal. However, these activities and deliverables can be adjusted based on the stage of product development. Your proposal will be evaluated on your ability to justify your research approach effectively. A key deliverable for Phase I is demonstrating the initial effectiveness of agent-loaded carrier particles in preventing colon cancer.

Question 3: We specialize in engineered microbial cell factories designed to express and release cargo within the intestine. While not a classical "carrier-particle", as I read the topic description many of the requirements fit our technology quite nicely. Our technology provides sustained, controlled, reproducible delivery of therapeutic compounds past biological barriers, such as the stomach acid; many of the features called for by the topic description. So, my question is would less conventional carrier-particles, such as engineered bacteria for delivery be considered for this topic?

Answer 3: Yes, if you can demonstrate that the engineered bacteria can act as carrier particles for delivering drugs (small molecules or biologics) orally to prevent colon cancer. Please refer to the project goals outlined in the contract topic solicitation for further details.

Question 4: Does the selected agent for particle formulation specifically need to have shown preclinical efficacy in models of IBD and/or CRC, or can applicants propose to test novel agents within the same drug classes as those previously tested?

Answer 4: It depends upon which funding phase you plan to apply to. The key deliverable for Phase I is demonstrating the initial effectiveness of agent-loaded carrier particles in preventing colon cancer. Yes, you can propose testing novel agents within the same drug classes as previously tested. Your proposal will be evaluated based on how effectively you justify your research approach.

NCI Topic 472: Antibody-Drug Conjugates as Radiopharmaceutical Theranostics for Cancer

Question 1: Does this topic consider a 'tumor antigen binding protein domain-drug conjugate' which has a much smaller molecular weight (smaller size), better tumor penetration, tunable blood circulation, and could work better than ADC from the point of view of TRT.

Answer 1: Yes, adding radioisotopes to "tumor antigen binding protein domain-drug conjugate" for diagnostic and/or therapeutic purposes would be responsive under Topic 472. You will see in the solicitation under "Project Goals," the following sentence: "Although this solicitation is written to highlight conventional ADCs and therefore conventional antibodies, other types of binding reagents (e.g., antibody fragments, peptides, and peptide nucleic acids) used to target tumor antigens for delivery of cytotoxic drugs may be proposed by offerors."

Question 2: Does "ADC for radio-conjugation" in this solicitation refer to: (a) a construct that includes both a chemotoxic payload and a radionuclide (simultaneously), or (b) a targeting moiety previously validated as an ADC, which will now be developed as a theranostic/therapeutic TRT agent?

Answer 2: Part "a" is correct. We are looking for constructs that include both a chemotoxic payload and a radionuclide simultaneously.

Question 3: The solicitation talks about *Antibody*-Drug Conjugates specifically, but are other non-antibody-based targeting strategies still acceptable?

Answer 3: Yes, the Topic 472 solicitation supports using targeting ligands other than antibodies (e.g. aptamers, peptides, antibody fragments).

Question 4: Is this solicitation only for the SBIR? Is STTR OK?

Answer 4: Unfortunately, this solicitation is only for SBIR proposals, and we are not able to award STTRs from this funding mechanism.

Question 5: What stage of development should the ADC projects be in to be considered for this topic? Are you looking for clinical-stage projects only, or are preclinical-stage projects also eligible?

Answer 5: See the solicitation, where it reads, "To be responsive to this solicitation, the proposed ADC for radionuclide conjugation must have already been validated by the offeror with in vivo biodistribution and pharmacokinetics studies showing that it targets cancer-specific antigens, does not accumulate in normal tissues, and

has well-defined clearance kinetics." This can be clinical stage or preclinical stage.

Question 6: Is biodistribution data absolutely required before we can submit a proposal, or can this be addressed during the Phase I activities? As you know, biodistribution studies are rarely done as a part of IND enabling studies.

Answer 6: The expectation is that biodistribution studies have already been completed. See quote from solicitation in response to Question 5 immediately above.

Question 7: Is pharmacokinetic (PK) data also absolutely required for submission? If so, what species do you need the PK data from (e.g., rodents, non-human primates)?

Answer 7: The expectation is that pharmacokinetic studies have already been completed. See quote from solicitation in response to your question 5 above. The choice of animal species used for pharmacokinetic studies should be driven by discussions with FDA (is not stipulated in the solicitation).

Question 8: Is there particular interest in specific linker-payload ADC platforms older auristatin-based payloads qualify? What would you like to see explored in proposals for this topic?

Answer 8: We have no preference for specific antibody-drug conjugate platforms.

NCI Topic 473: Point of Care Detection of Antibodies Against HPV16/18 E6 and E7 Oncoproteins in Oropharyngeal Cancer

Question 1: For a primary care setting, do you have a recommended price point?

Answer 1: No, we do not recommend a price point. You need to determine it based on your market research.

Question 2: For a primary care setting, can some reagents be refrigerated?

Answer 2: This is the offeror's decision.

Question 3: Please confirm whether or not the expectation for a primary care setting instrument would be to provide different information (e.g., ID of protein and concentration) from that of an at-home device (e.g., a protein is presence yes/no).

Answer 3: You need to provide enough information for the intended users regardless of a primary care setting or an at-home setting.

Question 4: What is the allowable footprint for the primary care device?

Answer 4: It can be defined by your own research.

Question 5: What is the anticipated start date for projects funded under PHS 2025-1 Topic NIH/NCI 473?

Answer 5: The solicitation states that the NIH/NCI Scientific and Technical Merit Review: March-May 2025 and the Anticipated Award Date: August-September 2025 (see page 73 of the solicitation).

Question 6: Is this contract intended for a doctor's office solution, i.e. looking for a 15-minute assay, or a clinic / hospital setting that can run the assay with results in 24 hours? We utilize PCR and Next-generation sequencing for our multiplexed immunoassay.

Answer 6: As published, "The goal of this topic is to support the development and validation of a rapid, point-of-care (POC) device for HPV-related OPCs; the device should be capable of separate detection of antibodies against HPV16 and HPV18 E6 and E7 oncoproteins." As long as your device/test fits that setting, you are responsive.

Question 7: Is there a Budget for this topic?

Answer 7: As published, Phase I budget is up to $400,000 for up to 12 months; Phase II budget is up to $2,250,000 for up to 2 years.

Question 8: If I submit both a Phase 1 and a Phase 2 now and if the Phase 1 is acceptable and funded while a Phase 2 is not acceptable, will I still be invited to submit a Phase 2 after completion of Phase 1?

Answer 8: Yes.

Question 9: The Phase 1 activities and deliverables includes the following statement: "In the Final Report, commit to a specific timeframe for a pre-submission/IND meeting with FDA, which must take place before the Phase II proposal is submitted." Just to clarify, this is not required in the proposal, but when we are executing the project, correct?

Answer 9: Yes, this refers to a requirement during execution of the Phase I project, if funded. If you submit a Fast-Track proposal, you should include in your proposal a commitment to meet with FDA before the Phase II portion of the project begins.

Question 10: Do we get a summary statement for Phase 1 & Phase 2s separately even if the Phase 2 is considered unacceptable? Or do we need to request debriefing to get feedback?

Answer 10: You will receive feedback on your phase I proposal if it is not selected for award. If the phase II is not reviewed because the phase I is determined to be unacceptable, unfortunately you would not receive feedback on that proposal.

Question 11: Can we use 177-Lutetium for the diagnostic – since that can be used as both a diagnostic and therapeutic?

Answer 11: You can use any radioisotope of your choice. Examples are provided for both diagnostic and therapeutic uses in the solicitation. You will be judged on how well you defend your choices.

Question 12: Do we need to apply for I-Corp at the time of Phase 1 or will we be asked after Phase 1 has kicked off?

Answer 12: You need to include I-Corps at the time of proposal. You will not have this option later.

Question 13: Are the I-Corp workshops virtual?

Answer 13: The NIH I-Corps course includes in-person meetings at the front and back ends (location varies), and virtual weekly meetings in the intervening eight weeks. It is an 8-10 week course typically.

Question 14: If we do not have an industry expert, can one be assigned from the National Innovation Network? I could not see a list of experts from the link in the solicitation.

Answer 14: You will be working very closely with the industry expert on your I-Corps team over the 8 weeks of the course. It is in your best interests to choose your own industry expert. That said, feel free to reach out to the contact listed in the last-published NIH I-Corps solicitation (https://grants.nih.gov/grants/guide/notice-files/not-od-23-188.html) to ask their expert opinion.

Question 15: For the I-Corp program, is the 25 hrs./week cumulative for the 3 team members or is it each team member?

Answer 15: Each team member.

Question 16: What does "Demonstration of the manufacturing scale-up scheme" mean? Do we have to actually scale up or show how we will scale up?

Answer 16: It means to show in a pilot at small scale how you perform large scale up of manufacturing.

NCI Topic 474: Point of Care Technologies for GI Cancer Prevention and Early Detection

Question 1: What are you looking is it a device or a test?

Answer 1: The technology developed should effectively screen for precancerous conditions and early cancers in the GI tract, and it should be affordable, scalable, and usable at point-of-care. The solicitation Phase I deliverables' states, "Using end-user co-design principles, develop the prototype diagnostic test, assay, method, technology and/or device (here onwards referred to as device/test) with the following characteristics:

- Ease of use: the device/test must be suitable for use by local caregivers in its operation and maintenance.

- Operable in locations with limited clinical infrastructure (i.e., design for use outside of laboratory settings).
- Designed for use at the community level and in non-traditional healthcare settings.

Question 2: Could you elaborate the definition of "point-of-care tests (POCTs)" in the contract solicitation?

Answer 2: The POCTs should be affordable and able to screen for precancerous/early cancers in the GI tract. In addition, please see the following details from the solicitation regarding the characteristics of the POCT developed.

Using end-user co-design principles, develop the prototype diagnostic test, assay, method, technology and/or device (here onwards referred to as device/test) with the following characteristics:

- Ease of use: the device/test must be suitable for use by local caregivers in its operation and maintenance.
- Operable in locations with limited clinical infrastructure (i.e., design for use outside of laboratory settings).
- Designed for use at the community level and in non-traditional healthcare settings.

Question 3: Is the priority on the device or the software component?

Answer 3: The priority of this topic is to develop an affordable POCT that can effectively screen for precancerous conditions/early cancers in the GI tract. Supported work under this topic includes both development of a device and integration of the POCT with healthcare monitoring/delivery systems (e.g., utilizing linkages to mobile health/telemedicine tools to communicate results in real-time). At the end of the Phase I, it is envisioned that a working prototype has been developed and that it has been tested to establish analytical performance (sensitivity, specificity, limit of detection, reproducibility, etc.).

Question 4: To effectively screen for precancerous conditions and early cancers in the GI tract at a Point of Care Operable in locations with limited clinical infrastructure (i.e., design for use outside of laboratory settings). Would a clinic or doctor's office/urgent care center be acceptable? Is there any limitation on restriction on the method / assay to be used?

Answer 4: The POTC should be designed for use at the community level and in non-traditional healthcare settings. Technologies should be affordable by local providers and operable in locations with limited clinical infrastructure. The method/assay developed should align with these restrictions listed in the solicitation.

Question 5: As this SBIR is to first develop a working prototype POC assay method and initial analytical performance to be determined, and the actual field clinical testing would follow after further development before IRB, etc., which would follow into Phase II, what is the purpose of: *Demonstrate a working*

relationship with the site(s) where the clinical validation study will take place? **How would this "working relationship" be considered in the proposal evaluation?**

Answer 5: Ideally, the offeror will provide a letter of support in the Phase I proposal that demonstrates a future collaboration/partnership with a group that can provide relevant patient access to test the prototype in the Phase II proposal.

Question 6: I helped my client submit a Phase I SBIR to NCI for the September 5th deadline. We saw the PHS 2025-1 contract solicitation and would like to propose an overlapping scope of work from our recently submitted SBIR. Can we have a grant and contract with an overlapping scope of work under review at the same time? We understand that we would not be able to accept both awards if offered.

Answer 6: No. In the solicitation, please see section 4.14 Prior, Current, or Pending Support of Similar Proposals or Awards: "A small business concern may not submit both a contract proposal and a grant application for essentially equivalent work (see definition in Section 3.1) in response to multiple NIH/CDC SBIR solicitations and funding opportunity announcements. The only exception is that a grant application is allowed to be submitted after a contract proposal has been evaluated and is no longer being considered for award. […] It is unlawful to enter into contracts or grants requiring essentially equivalent effort."

NCI Topic 476: Digital Twin Software for Optimization of Cancer Radiation Therapy

Question 1: For budgeting purposes, we intend to do 1/3 of the work as the prime with consultants doing 1/3 and a subcontractor doing 1/3 based on the budget. Could you please confirm if this Phase I budget allocation is acceptable?

Answer 2: For budget allocation, a small business (contract offeror) may outsource up to 1/3 of the total cost of the budget to third parties for a Phase I. The small business has to do at least 2/3 of Phase I research.

The payment for the two consultants with 1/3 of the total budget could be a concern. If the two consultants are hired as company's employees, the SBIR budget rules should be satisfied. If not, the contract offeror could violate the SBIR budget rule in terms of allocating at least 2/3 of the total cost within the small business.

NCI Topic 477: Wearable Technologies to Facilitate Remote Monitoring of Cancer Patients Following Treatment

Question 1: I believe that our wearable sensor fits within the scope of NIH/NCI 477 by enabling novel insights for evaluating the toxicity impact related to chemotherapy treatments by capturing the temporal dynamics of tissue electrical properties. Our wearable sensor provides sensing beyond current commercially available fitness trackers to address the project goals. Also, we are developing deep learning approaches for signal denoising to minimize the noise artifacts from the raw bioimpedance measurements.

Answer 1: The wearable sensor described fits Topic 477 provided the offeror proposes a combination of their wearable sensor, with sophisticated analytical approaches and user interfaces that allow patients to be remotely monitored for cancer- or treatment-related adverse events (e.g., acute chemotherapy-induced toxicities). They need to propose a complete solution (e.g., hardware and software) to allow healthcare providers the ability to monitor a patient in real-time and preemptively mitigate adverse events when needed.

Question 2: For the budget, only 33% can be allocated to subawards and contractors. Does this also include consultants?

Answer 2: Yes, it includes consultants.

Question 3: Can the demonstration include individuals (non-patients) only?

Answer 3: The demonstration deliverable for Phase I should include testing with at least 5 individuals/patients. This statement refers to patients.

Question 4: For the demonstration, with whom and where will the demonstration take place? NIH or another designated location?

Answer 4: Virtual meeting with CO, COR, and other NCI scientific personnel who developed the topic.

Question 5: Do we need to include travel in our budget to attend the demonstration?

Answer 5: No.

Question 6: Could we apply to the contract if the deliverable is to provide biochemical measurements in interstitial fluid in a controlled setting rather than a patient setting?

Answer 6: This would be considered nonresponsive as stated in the solicitation: “Tools that don’t focus on an identified clinical cohort and associated treatments with at least some assessment of adverse event risks relevant to those patients that could be monitored with the identified wearable technology(s) proposed”.

Question 7: The contract refers to biophysical and passive monitoring—would biomarker-level data from passive, interstitial fluid wearables be applicable?

Answer 7: Yes, but it must be focused on “a well-defined cancer treatment scenario with documented adverse event risks, where effective remote monitoring is enabled through an appropriate user interface that serves the needs of both patients and clinical care teams, to actively monitor cancer patients during sensitive periods of their care”.

Question 8: If the last deliverable was a standard curve in interstitial fluid, would we be eligible for the contract?

Answer 8: All published Phase I deliverables must be met.

Question 9: Given that we are validating our sensor technology in buffers, blood, and interstitial fluid, would these validation efforts align with the contract requirements?

Answer 9: All published Phase I deliverables must be met.

Question 10: Since we are in the early stages of development and focused on feasibility of our electrochemical biosensor, does this fit within the scope of the contract?

Answer 10: All published Phase I deliverables must be met.

Question 11: Would it be possible to clarify if only SBIR applications are acceptable or if STTR applications are also allowed?

Answer 11: Unfortunately, this solicitation is only for SBIR proposals, and we are not able to award STTRs from this funding mechanism.

NCI Topic 478: Advanced Biomaterials to Improve Cancer Modeling for Research

Question 1: I noticed that the solicitation does not include a section for "references" or "citations" in the proposal requirements? Can these be included? And if so, what is the appropriate location within the technical proposal?

Answer 1: You can add the reference at the end of your proposal.

Question 2: Is the primary goal here to develop synthetic tissues that can be used to encompass and experiment with tumor cells? (For example, new substrates to help culture difficult cells or 3D matrices on which to grow cells that are more realistic than 2D cell cultures).

Answer 2: In reference to the Project Goals as stated on NIH/NCI 478, projects considered responsive to this solicitation include, but are not limited to: biomaterials that enable the culture of cancer cells that are difficult or can't currently be cultured, or the long-term culture and manipulation of cancer tissue or organoids that are free from xenogeneic contaminants and are chemically defined, biomaterial that mimic aspects of the immune system, biomaterials that enable dynamic remodeling of the tumor or its microenvironment.

Question 3: "Hydrogels" are listed under "traditional biomaterials" as having problems, but most of the examples of advanced synthetic biomaterials are also hydrogels or components of hydrogels – is the goal to improve over the functionality of past hydrogels with new hydrogel materials? Would it be hydrogels made of materials that are biological in origin (proteins, polysaccharides, etc.) so that they are more compatible than what exists today? In other words, it's not that hydrogels are the problem, it's that they're made of the wrong material.

Answer 3: Yes, a responsive proposal could be improving the functionality of past hydrogels with new materials as long as the improvements lead to a product/technology that fall into one of the following three areas:

1) kits and reagents that are user-friendly (no specific skills or non-standard/expensive lab equipment required);
2) biomaterials allowing researchers (if kits and reagents) or the small business (if services) to program or tune the biomaterial for specific cancer applications;
3) biomaterials with the capacity to change or adapt in response to tumor initiation, progression, or metastasis to probe the mechanisms of cancer biology or for passive diagnostic readout.

Question 4: Are any of the three topic areas preferred? (ex. User friendly kits/reagents, tunable biomaterials, adaptable biomaterials)?

Answer 4: Each area is equally important.

Question 5: Is there a desire to embed the biomaterial with living healthy tissue cells, or just the cancer cells?

Answer 5: Depending on the intended cancer-relevant use or application, the material needs to be biocompatible and modulate or mimic the cancer environment and/or the surrounding tissue. The biomaterials in development need to allow the study of cancer (tumor, microenvironment, or host-response, drug efficacy or toxicity). Materials that are not biocompatible, biomaterials intended solely for drug delivery or therapeutic use (e.g. microneedles, nanovesicles, etc.), biomaterials used in static phantoms intended solely for advancing imaging capabilities, technologies not directly applicable to cancer, and services not applicable to cancer are not considered responsive to this solicitation.

Question 6: What is envisioned with "AI" inclusion? Is that focused on employing AI in design or implementation of the biomaterial? Or on the backend data-analysis with biostats or imaging analysis?

Answer 6: AI inclusion is not required. Your biomaterial (that falls within the 3 areas under projects goals) may enable integration (if at all) with cutting-edge sensors, AI, microfluidics, 3D/4D bioprinting, and other biomaterials for a variety of cancer-relevant applications.

Question 7: Does the statement "biomaterials with the capacity to change or adapt" mean that they respond independently to microenvironmental changes, or these adaptations would be triggered by the scientist (e.g., should the material change in stiffness due to a natural change in pH or does the researcher decide they want a stiffer tissue and initiate that themselves either through chemical reactions or remote electrical control). Is this related to a later statement about "biomaterials that enable dynamic remodeling of the tumor or its microenvironment"?

Answer 7: This could be either. Materials that adapt to tumor or microenvironmental changes and/or user defined on-demand initiated changes are acceptable. Dynamic remodeling refers to whether these changes are reversible or programmable over time.

Question 8: Does the reference to microfluidics mean mimicking vasculature of a tumor or ability to transport nutrients, drugs, other things into a tumor, etc.? Or is it some other application?

Answer 8: Microfluidics are not required but are permitted. Your biomaterial (that falls within the 3 areas under projects goals) may enable integration (if at all) with cutting-edge sensors, AI, microfluidics, 3D/4D bioprinting, and other biomaterials for a variety of cancer-relevant applications.

Question 9: Is the idea of a fluorescent readout to look for the presence of certain biomarkers? Would it be something like a chemoresponsive dye chosen by the user and mixed into the formulation when they are casting their material, or would it be something we decide on and integrate into the formulation?

Answer 9: This could be either. This could be integrated into your formulation or have a base biomaterial that allows for user customization on-demand with each customization having well-characterized properties and behavior over time.

Question 10: Can you expand on what you mean by "biomaterials that mimic aspects of the immune system". Does that mean a simple release of molecules in response to something the tumor cell does, or would it be a scaffold upon which you could grow cells to make a synthetic organ like the thymus where cells of the immune system are produced?

Answer 10: Materials should not simply be used to reproduce components of the immune system like the thymus or bone marrow. However, there could be many biomaterial-based approaches that mimic aspects of the immune system (e.g., neutrophil extracellular traps, immunomodulatory molecules or tertiary lymphoid structures). The proposed system may involve release of biologically active molecules, but it should be tied to immune processes and outcomes relevant to the studying the tumor microenvironment. For example, biomaterials could enable the clustering of immune cells, initiate or resolve inflammation, or prompt immune infiltration in a cancer-relevant context.

Question 11: What would be a good indicator of success? For example, showing cells can grow on a new material (somewhat simple), running a full experiment on a generated tumor (more complicated), just showing properties like ability to stiffen in response to a stimulus like pH (simple) etc.

Answer 11: Offerors should clearly state what their product/service will be, how it falls into the 3 responsive areas listed under project goals (i.e. its user-friendliness, its tunability and its capacity to adapt, etc.), how superior to current products on the market used in cancer research and its potential impact in cancer research/how it will help advance cancer research.

NATIONAL INSTITUTE ON AGING (NIA)

NIA TOPIC 011: Digital Technologies as Tools to Screen and Monitor Alzheimer's Disease (AD) and Related Dementias (ADRD)

Question 1: Are biomarkers required in the research?

Response 1: The objective of this contract solicitation is to develop digital tools to assess the effectiveness, safety, or performance of medical devices to be used for i) screening, ii) early detection, iii) enrollment in clinical trials, iv) monitoring, and v) evaluation of the treatment effectiveness in Alzheimer's Disease (AD) and AD-related dementias (ADRD). A tool can be a method, material, or measurement to assess medical devices subject to regulation by CDRH. A biomarker test can be a tool but there is no requirement to have a biomarker test.

Question 2: Can you give some background on why a Phase 1 is not allowed? I believe it said somewhere that if FastTrack application was submitted, it is possible to receive only the phase-1 part of the research?

Response 2: A Fast-Track application includes both Phase I and Phase II. The Phase I deliverables for this topic include submitting an MDDT Proposal to FDA for determining the suitability of the proposed MDDT based on its ability to facilitate regulatory decision making. This topic addresses the need of validating the tools already developed or being developed for specific devices for their wider utility to assess the performance of other medical devices that are to be used in a similar context. Since a significant research and development activity must have already taken place before being considered for this contract topic, it fits the Fast-Track mechanism. It is possible to receive only the Phase I if the MDDT Proposal or the Qualification Plan is not accepted by the FDA.

Question 3: Why is there a Phase I budget listed in the solicitation if Phase 1 is not allowed?

Response 3: The Phase I and Phase II budgets are referring to the Fast Track budgets. Fast Track proposals must contain both a Phase I and Phase II.

Question 4: **In order to be responsive to this topic, it is *required* that the device being developed under this topic be able to monitor disease progression? Put another way, could a wearable device that provides a therapeutic benefit to AD/ADRD populations but does not independently monitor disease progression also be responsive to the topic?**

Response 4: The objective of this contract solicitation is to develop digital tools to assess the effectiveness, safety, or performance of medical devices to be used in the context specified in the solicitation, not to develop a device. A digital tool that could assess the effectiveness, safety, or performance of medical devices that provide therapeutic benefit to AD/ADRD populations would be responsive to this solicitation.

Question 5: The list of assessment types (e.g., sleep, gait) included in this contracting solicitation did not include neurocognitive measures. Can NIA confirm that

the contract offering would also consider neurocognitive measures as a viable approach and that it would be potentially fundable?

Response 5: The assessment types listed in the contract solicitation are a few examples of potential measurements. Digital neurocognitive measurements would be considered for this topic.

Question 6: It appears that the "deliverables" of Phase I will be the preparation of the MDDT Proposal, etc. How much of this pre-proposal preparation needs to be included in the contract solicitation submission due on Closing Date: October 18, 2024, 5:00 PM Eastern Daylight Time?

Response 6: The submissions that include greater relevant details would be more competitive.

Question 7: To what extent are the funds in PHS 2025-1 intended to be used exclusively toward qualifying an existing device/technology through the MDDT program? By contrast, to what extent is it expected that the funds will be used for device/technology R&D in addition to creating an MDDT qualification package?

Response 7: The funding is intended to be used exclusively for the activities performed for the development of an MDDT for qualification, which include collecting initial evidence for preparing a strong MDDT Proposal and generating evidence to support qualification of the tool for the defined context of use.

Question 8: The solicitation says, "Please note that the MDDT process phases are separate from the SBIR phases". What are the main differences? Is it expected to already have a completed SBIR before doing a MDDT?

Response 8: The MDDT qualification process consists of two phases, Proposal Phase and Qualification Phase. The SBIR Phase I includes collecting initial evidence for preparing a strong MDDT Proposal, submission of the MDDT proposal to the FDA for acceptance, followed by submitting an MDDT Qualification plan to FDA. The SBIR Phase II activities include collecting evidence to support qualification of the tool for the defined context of use as described in the MDDT Qualification plan and preparing and submitting a Full MDDT Qualification Package to the FDA. There is no requirement of previously having completed an SBIR program.

Question 9: Is it considered responsive to propose a wearable device with custom software which utilizes precise positional tracking to measure dementia-related gait changes?

Response 9: The objective of this contract solicitation is to develop digital tools to assess the effectiveness, safety, or performance of medical devices, which may include devices that measure dementia-related gait changes.

Question 10: Is it recommended that Phase I in the MDDT process perform preliminary testing with human subjects, or is this not justified until after qualification (Phase 2)?

Response 10: The necessity of performing preliminary testing with human subjects would depend on the nature of the proposed MDDT.

Question 11: If we have an existing prototype that can be extended with additional functions for the proposed MDDT, would it be acceptable to request for funding to build and test the extended prototype with the new diagnostic features, with a group of study participants?

Response 11: Developing an existing method, material, or measurement into a tool to assess medical devices subject to regulation by CDRH and as described in this solicitation is acceptable.

Question 12: Regarding the MDDT submission for FDA, would that be based on the verified, final iteration of the prototype, with acceptable performance for the diagnosis?

Response 12: The MDDT qualification process consists of two phases, Proposal Phase and the Qualification Phase. The goal of the proposal phase is to determine if the MDDT is suitable for qualification consideration through the MDDT Program. The goal of the Qualification Phase is to determine whether, for a specific context of use, the tool is qualified based on the evidence and justifications provided. The data collected according to the Qualification Plan is submitted as the Full Qualification Package and reviewed by FDA for qualification decision.

NIA Topic 012: Modeling Aging through Microphysiological Systems

Question 1: What is the required Technology Readiness Level (TRL) for a company to begin working with this technology?

Response 1: The solicitation does not specify a TRL. However, it does require that the contractor benchmark the performance of the MPS, demonstrate that the MPS can be mass produced in a cost-effective manner and with a modular assembly (where appropriate), and conduct pre-market and end-user testing. The process of FDA qualification should also be initiated for proposed MPS already in advanced staged of development.

Question 2: This topic mentions the technology as a "self-contained system" in the project goals. Does a self-contained system refer to a device such as a microfluidic device that is a closed system, or can it include MPS such as scaffolds in a well that is an open system?

Response 2: Self-contained refers to a system in which all cell/tissue components are housed and functional within the same unit over a period of time. That extends to constructs that may be maintained in microwells.

Question 3: Does the NIA have a preferred schedule for milestones for research contracts, e.g. Monthly/Quarterly/Yearly quantifiable milestones for statement of work completion? This would aid us when writing the proposal to structure work in such a way that we could meet regular milestones. For example, on another award we have 6-month milestones with monthly meetings.

Response 3: Phase I milestones must be completed in one year. Phase II milestones must be completed in two years.

Question 4: Is the solicitation aiming to produce systems which can maintain models without user input? The solicitation talks about "self-contained systems" and "precise thermal and environmental control, fluid pumping, and sampling". Is this point made to promote ease of use in extended culture times or is it in the mind of the NIA a standalone requirement for any proposed system, would a non-automated user-friendly system suffice?

Response 4: Partial or full automation of the MPS is desirable but it is not required for this solicitation. "Precise thermal and environmental control, fluid pumping, and sampling" indicates the requirement to clearly specify those technical parameters that determine the experimental conditions tested and would influence the outcomes.

Question 5: Can milestone details be modified during the award if the experimental data/scientific progress suggests other milestones of progress should be used, or should milestones be written such that there is some flexibility around the exact details? E.g. A milestone says we will track gene X as a marker of aging, but newly published literature shows gene Y is a more reliable marker.

Response 5: Minor modifications such as substituting one genetic marker of aging for another can be made, with sufficient justification and NIA approval, provided that the changes are still within scope and do not increase the overall cost of the contract**.**

NIA Topic 013 - Leveraging Multimodal and Generative Artificial Intelligence to Advance the Application of Social Robotics in Caregiving

Question 1: Do you need/require actual robots for the application?

Response 1: The primary deliverable is a generative-AI based framework that can be used to enhance existing assistive care social robots. While the development work will be primarily on the software side for both Phase I and II, access to a functional product will likely be necessary to test and demonstrate enhance functionalities in real world testing if the offeror is applying for fast-track funding. Moreover, given that the goal is to deploy this in an existing product, in an exclusively Phase I application, the software to be developed is intended to be informed by gaps in functionality of an existing product. So, it would be difficult to target and develop phase I deliverables without existing products or collaborations that provide access to the same.

Question 2: Is it considered responsive to propose a virtual (not physical) robot who appears to the PwD and caregiver to "navigate the physical environment of an ALF" because it is aware of the physical surroundings via augmented reality room mapping?

Response 2: This topic aims to advance the area of physical robotics. However, since navigating physical environments is a critical research area in robotics, demonstrating: (i) collaborations that inform module development based on

identified needs in an existing robot and (ii) transferability to existing products, are acceptable.

Question 3: Can a proposal be responsive if it is for a conversational model for our virtual, augmented robots with potential for future porting to physical robots?

Response 3: Please see sub-points (i) and (ii) in response to #2.

Question 4: Phase I appears to not require human subjects. Is this accurate? Would we still be responsive if our feasibility criteria are all technical?

Response 4: New human subjects data/testing in Phase I is not a requirement. However, please note that a deliverable is to include stakeholder engagement to inform iterative development. Secondly, a deliverable is evidence of real-world and AI-generated training data repositories. The former will depend on the application to be developed and may involve some human data collection. However, the use of existing datasets is acceptable as well, i.e., the need for new real-world human datasets is not a requirement.

Question 5: Is it considered responsive to propose a virtual robot leading a PwD in movement exercises trained from exercise physiologists using motion-capture algorithms?

Response 5: Please see sub-points (i) and (ii) in response to #2.

NATIONAL INSTUTITE ON ALCOHOL ABUSE AND ALOCOHOLISM (NIAAA)

NIAAA Topic 021: Data science tools for accelerating alcohol research

Question 1: Will a list of datasets related to alcohol use disorder research be provided?

Response 1: In addition to the examples given in the topic description, addition datasets can be found by searching NIH Reporter or the NIAAA website.

Question 2: Will the types of data that would be considered eligible, e.g. electronic health records, sequencing data be clarified?

Response 2: The type of data is not limited.

Question 3: Will researchers working on this contract have access to these datasets for quality evaluation and analysis, and what kind of data access permissions will be provided? E.g. Can the data be uploaded to a cloud virtual machine for processing?

Response 3: The offerors are expected to work with NIAAA supported researchers or data repositories for data access.

Question 4: Which topic would receive greater attention for this specific topic: analysis tools for alcohol use disorder or a tool designed for data quality control, cleaning, annotation, and categorization?

Response 4: Priority is given to the need for the tool with respect to the stakeholder context. The offeror is encouraged to collaborate with NIAAA supported investigators and

datasets and repositories. Either approach is acceptable. The approach depends on the collaboration between the contractor and the NIAAA supporter researcher and the needs of the research program.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

NIAID Topic 137: New Drug Classes with Novel Mechanisms of Action for HIV, Hepatitis B, and Tuberculosis

Question 1: Is a newly developed human gamma/delta T cell mouse platform to isolate TCR clones that can treat HIV, HBV, or Mtb be considered "compatible with current antiretroviral regimens"?

Answer 1: Given the limited information provided, we assume that the human gamma/delta T cell mouse platform for isolating TCR clones would be compatible with current antiretroviral regimens. However, a definitive determination can only be made once the complete proposal is submitted."

NIAID Topic 140: Adjuvant Discovery and Down-Selection for Vaccines against Infectious and Immune-Mediated Diseases

Question 1: Tolerogenic adjuvant discovery is complicated by a lack of knowledge about which biomarkers on antigen presenting cells (APCs) indicate immune tolerance. Would a phase I proposal that performs a high throughput assessment on APCs to identify novel tolerogenic biomarkers that could guide future HTS discovery assays be responsive to NIH/NIAID topic 140?

Answer 1: An example of acceptable activities for a Phase I project under Topic 140 as cited in the solicitation is the optimization of screening assays to identify new potential adjuvant candidates. The identification of appropriate markers of tolerogenic APCs to be included in a subsequent screening assay falls under "assay optimization" and, thus, such an activity is responsive to the solicitation.

Question 2: Would a proposal to develop an antagonistic antibody as an adjuvant be responsive to Topic 140?

Answer 2: NIAID uses the FDA-definition of adjuvants and has also recently clarified in a publication (PMC9892189) that the unifying feature of immunostimulators is the "adjuvant effect", not their chemical or physical nature. Therefore, any molecules (including antibodies) that enhance (or, in the case of tolerogenic adjuvants, suppress) adaptive immune responses to a co-delivered antigen are defined as 'adjuvants', including antibodies.

Question 3: The RFP states that "…the proposal must include assays to demonstrate the effect of the treatment with an adjuvant on specific allergens or autoantigens." We propose to use an antigen-specific tolerogenic vaccine for EAE – does this satisfy the requirement of the solicitation?

Response 3: This requirement in the solicitation for Topic 140 underscores the fact that the program only supports the discovery of novel vaccine adjuvants, but not stand-alone immunomodulators. Any model in which the adaptive immune response to specific antigens (foreign or self) is either enhanced or suppressed (tolerogenic vaccine) is acceptable.

Question 4: **We previously discovered a large panel of cell surface molecules that, when over-expressed, lead to activation of immature dendritic cells. Is it responsive to the RFP if we plan on characterizing the biology and therapeutic potential of this panel further in order to down-select which one(s) may be best developed or targeted in the future as part of an adjuvanted vaccine?**

Response 4: The proposed approach to follow-up on previously identified adjuvants (in this case over-expressed surface antigens as non-classical adjuvants) in a Phase II project is responsive to the solicitation for two reasons: 1) Phase II activities include "confirmatory in vitro screening of hits" and 2) the solicitation allows for the "down-selection of adjuvants for subsequent vaccine development in side-by-side comparisons".

Question 5: **As no tolerogenic adjuvanted vaccines are currently FDA approved, is it acceptable for us in Phase 2 to test potential adjuvants with clinical or preclinical stage tolerogenic vaccines?**

Response 5: The solicitation does not specify at what stage of development the vaccine/vaccine-antigen that is used to evaluate must be and both, the use of preclinical-stage or clinical-stage (tolerogenic) vaccine candidates is acceptable.

Question 6: **Is the evaluation of different adjuvant combinations, to identify a suitable combination adjuvant for further vaccine development, allowable?**

Response 6: Topic 140 supports the discovery of novel adjuvants as well as the down-selection of adjuvants for further vaccine development. This includes the development and evaluation of combination adjuvants.

Question 7: **Would a study of an adjuvant panel in combination with two different vaccines be acceptable?**

Response 7: The solicitation does not limit the number of antigens that novel adjuvants can be tested with. Offerors should, however, keep the following in mind: a) the budget of SBIR projects is capped and evaluating the responses induced against different antigens/the use of different disease models will reduce the depth of the analyses that can be conducted with each antigen/vaccine. b) the purpose of evaluating a panel of adjuvants is "the down-selection of adjuvants for subsequent vaccine development" (see Program Goal of the solicitation). Unless the objective of an adjuvant-antigen matrix experiment is the subsequent development of multiple vaccine candidates, or the selection of the most appropriate vaccine antigen from the same pathogen, such an approach may be criticized as being unfocused.

Question 8: **Is it acceptable to screen a panel of adjuvants against a particular antigen to generate empirical data without an extensive rationale for the adjuvant combinations?**

Response 8: Adjuvant selection for a vaccine continues to be a highly empirical process and to de-risk the process of identifying a suitable adjuvant for a specific vaccine, Topic 140 supports the side-by-side comparison (and down-selection) of adjuvants.

Empirical data for the selection of specific adjuvants (or adjuvant combination) for a specific antigen may not be available yet, and Topic 140 specifically supports the generation of such data for subsequent vaccine/adjuvant development. Offerors are, however, encouraged to reference any potentially relevant studies (if available), such as the identification of immune profiles associated with protection against a pathogen, to support the selection of particular adjuvants (i.e., those that have been shown to promote the induction of such immune profiles.

NIAID Topic 147: Software or Web Services to Assess Quality and Reproducibility of Data and Information about Therapeutics and Vaccines

Question 1: Will a list of datasets related to Therapeutics and Vaccines research be provided? Additionally, will clarity be given of the types of data that would be considered eligible and whether researchers, e.g. the PI for this contract, will have access to these datasets for quality evaluation and reproducibility assessment, and whether the data can be uploaded to a cloud virtual machine for processing.

Answer 1: NIAID does not provide a specific list of datasets related to therapeutics and vaccines research. However, your proposal can consider all publicly available data relevant to topic 147. You may also use private data or data with a license, provided that the method is validated and ensures reproducibility of the analysis. Therefore, data should be made available for future re-analysis.

Please note that relevant data may reside in both controlled access repositories (e.g., dbGaP and accessclinicaldata@niaid) and open access repositories. Additional sources of data include:

- NIH recommended domain-specific repositories: NIH Domain Specific Repositories
- NIH recommended generalist repositories: NIH Generalist Repositories
- NIAID Data Ecosystem Discovery Portal: NIAID Data Ecosystem
- Peer-reviewed publications: PubMed
- Additionally, other specific biological domains might be of interest, such as:
    - For COVID-19: N3C Data Sets
    - For TB: TB Portals
    - For AIDS: DAIDS RSC

Since all data from these resources resides in the public domain, subsequent analyses are encouraged. For datasets with a license, please ensure that your analysis adheres to any restrictions associated with the specific license.