MODULE ANNOUNCEMENT

FOR

ADVANCED RESEARCH PROJECTS AGENCY FOR HEALTH RESILIENT EXTENDED AUTOMATIC CELL THERAPIES (REACT)

ARPA-H-MAI-24-01-02

DECEMBER 27, 2023

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ATTACHMENT 1: OTHER TRANSACTION BUNDLE (VOLUME 1)

1. MODULE ANNOUNCEMENT OVERVIEW INFORMATION

FEDERAL AGENCY NAME: Advanced Research Projects Agency for Health (ARPA-H)

FUNDING OPPORTUNITY TITLE: RESILIENT EXTENDED AUTOMATIC CELL THERAPIES (REACT)

ANNOUNCEMENT TYPE: Initial Announcement

FUNDING OPPORTUNITY NUMBER: ARPA-H-MAI-24-01-02

ASSISTANCE LISTING NUMBER: 93.384 Research and Development that accelerates better health outcomes for all Americans.

DATES: (All times listed herein are Eastern Time)

- ***Module Announcement DRAFT release date***: October 26, 2023
- ***Module Announcement release date***: *December 27, 2023*
- ***Frequently Asked Questions (FAQ) release date:*** December 27, 2023
- ***Proposal due date***: January 26, 2024, at 2:00 PM ET

2. OPPORTUNITY DESCRIPTION

The Advanced Research Projects Agency for-Health (ARPA-H) is soliciting proposals for the Resilient Extended Automatic Cell Therapies (REACT) program using the Master Announcement Instruction (MAI) solicitation strategy. For more information, please refer to the attached ARPA-H-MAI-24-01, which aims to provide proposers with the ability to scale the level of effort that they spend developing proposal materials with the magnitude of the effort they plan to propose. The MAI introduces a tiered approach to proposal submission for small scale (BIT / BYTE), mid-scale (KILO/MEGA), and large scale (GIG/TERA) efforts. The REACT solicitation described below is soliciting a Module Announcement at the large-scale GIG Module category level. All awards will be made in the form of an Other Transaction (OT).

Specifically, ARPA-H is soliciting innovative proposals for research and development (R&D) in therapeutic development and affordability and improving the way patients manage their own health. Currently many therapeutics are ineffective, not because they are medically unsound, but because of the barriers faced by patients who need them. Limited access and high costs block many patients from benefiting from the newest treatment regimes. Moreover, many acute and lifelong diseases significantly burden patients with continuous management of their health through pills, injections, blood draws, or even invasive surgery. This burden often leads to low treatment fidelity and poor health outcomes for the patient. Improving health and wellness requires simultaneous resolution of limitations in access and affordability.

The REACT program will address both challenges, limitations in access and affordability, by changing the paradigm in therapeutic development and affordability and improving the way patients manage their own health by developing two platforms—one that automatically produces and delivers patient-specific therapy and one that monitors a disease in real time.

In the first program track, recent advances in synthetic biology, materials, and bioelectronics will be integrated to form an implantable Living Pharmacy. The Living Pharmacy will be a small, implantable bioelectronic device that maintains cellular factories modified to produce and secrete a hormone, cytokine, or other therapeutic molecules at appropriate times from inside of the body. The device will be controlled externally by a patient who would need only to “subscribe” to a treatment for it to be delivered

automatically.

In the second program track, a similar implantable device will be constructed to act as a Living Sentinel. This device will use cells to detect a key biomarker of disease. When a biomarker is detected, the cells will communicate with the bioelectronics to convey a signal to the patient. Patients would require only a quick outpatient procedure to implant the device. Then, the patient could control the therapy and timing within the range set by the clinician.

A. INTRODUCTION

Diseases that span a lifetime require constant vigilance to delay their progression and the associated therapies can be prohibitively expensive. These immense resource burdens on the patient drive health disparities. They also raise public health concerns since medication nonadherence generally results in treatment failure and hence increased morbidity and mortality. Indeed, the rate at which patients can fully complete a course of treatment is low: after one year, up to 50% of US adults no longer adhere to treatment, leading to preventable hospitalizations and costs ranging from $100 to $300 billion every year[1,2,3]. Many factors lead to low adherence including patient financial challenges, forgetting medication, fear of side effects due to impersonalized treatments, complex medication schedules, and the ability to follow up appropriately with clinical care practitioners.

The REACT program will reduce barriers of limited access and affordability by automating the precise dosing of therapies even for complex schedules, driving down the cost of prolonged treatment, and tracking key biomarkers to empower patients to monitor their disease and take greater control of their health. To reduce the time and cost to manage chronic conditions, the REACT program will develop two independently operating platform devices to deliver capabilities currently unavailable to patients. While the technologies could work together for closed loop control, this is not a program requirement. The expectation is that the patient will, for now, interact with the two separate devices independently.

The first device will be an implantable “Living Pharmacy” consisting of cells that produce therapeutic molecules and a bioelectronic carrier that contains the cells and controls the administration of the therapy. From within the body, the device would automatically produce and deliver single or combination therapies tailored to the patient, leading to better efficacy with minimal side effects. Patients would require only a quick outpatient procedure to implant the device. The patient could then control the therapy and timing within the range set by the clinician. Alternately, the patient could simply opt to follow the prescribed therapy automatically.

Building such a device requires a bioelectronic carrier integrated with cellular factories that is small enough to be implanted through minimally invasive outpatient surgery. The cellular factories should be designed to deliver therapies as appropriate to the disease. For instance, delivery could be either in pulses, continuous, or aligned with circadian rhythms. To enable the use of lower cost allogeneic cell lines, the device would be masked from the body. This could be achieved by using cells to secrete immunoevasive molecules or by using a membrane, hydrogel, or other permeable barrier to isolate the device from the immune system. The permeable barrier should enable passage of nutrients from the body to support the allogeneic cell line while allowing systemic release of the therapies, such as hormones or other soluble

[1] Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *The New England journal of medicine*, *353*(5), 487–497.

[2] Iuga, A. O., & McGuire, M. J. (2014). Adherence and health care costs. *Risk management and healthcare policy*, *7*, 35–44.

[3] Viswanathan, M., Golin, C. E., Jones, C. D., Ashok, M., Blalock, S. J., Wines, R. C., Coker-Schwimmer, E. J., Rosen, D. L., Sista, P., & Lohr, K. N. (2012). Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Annals of internal medicine*, *157*(11), 785–795.

factors, produced by the cells. The carrier itself contains circuitry that controls the cells, monitors their functionality, supports their viability, and enables communication with the patient.

To maintain their health, patients should be able to track progression of their disease. To achieve this, the REACT program will also develop a complementary implantable device—a Living Sentinel—that measures key biomarkers within the body. The Living Sentinel will utilize many of the same components as the Living Pharmacy, but instead of the carrier stimulating cells to deliver therapy, the cells will respond to the presence of the target biomolecule by producing fluorescent molecules, changing their membrane potential, or otherwise producing a signal that the carrier can detect and, in turn, convey to the patient. The use of cells for detection will enable real-time monitoring of signaling molecules such as hormones or cytokines for extended periods. The approach requires the integration of several recent advances in synthetic biology, biocompatible materials, and bioelectronics into a robust, implantable system. Since the patient would track their own biomarkers, patient mistrust regarding therapy or dosing would be ameliorated. Such a model would enable constant monitoring of patient disease status, both by the patient and clinician, leading to real-time therapy decisions, protecting patient convenience, and practically eliminating the burden of compliance.

One inspiration for REACT is the recent progress in implanting encapsulated beta cells, which directly detect elevated glucose levels and respond by producing insulin. REACT would build on this capability to develop a platform where cells can deliver a broad range of therapies. Specifically, this program would broaden the number of cellular factories that could be implanted so that many different hormones or other therapies can be produced. Because the goal of REACT is to develop an innovative platform that addresses a broad range of disease, the REACT program is disease agnostic.

NOTE: Any disease that can be treated with the defined release of hormones may be proposed with sufficient justification. This justification should include a short description of the disease, identification of the biomolecule to produce or to track, citations to published research that it is treatable via restoring hormonal or other imbalances, and identification of a patient population that is sufficiently large to enable testing of the devices through all clinical trials. The justification should be approximately one page long. Abbreviated examples of justifications follow:

- For metabolic conditions like obesity, the gold standard treatment include highly invasive gastric bypass surgery followed by lifestyle modifications and significant dietary restrictions. Alternately, recent non-surgical advances in (Glucagon-Like Peptide) GLP-1 agonists are promising but remain expensive, lead to various side effects, and require the patient to take the medicine continually to maintain weight loss. Consequently, the cost of disease management is high, leading to 47% of patients stopping the medication after 12 months and 70% stopping after 24 months[4]. A robust biomarker of obesity is adiponectin, with normal physiological levels (5–37 μg/mL) decreasing as obesity progresses (4–22 μg/mL). Drugs in the GLP-1 agonist class have shown tremendous promise in reducing body weight. Continuous, timed production from within the body could greatly reduce annual costs and the burden of maintaining the therapy.
- For diabetes type 1 and 2 patients, the burden of long-term treatment is well-known, requiring blood draws and injections multiple times a day. The overall medication non-adherence rate in type 2 diabetes was 27% in 2019, and, in 2018, there were 17 million reported visits to Emergency

[4] Weiss, T., Carr, R. D., Pal, S., Yang, L., Sawhney, B., Boggs, R., Rajpathak, S., & Iglay, K. (2020). Real-World Adherence and Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists Therapy in Type 2 Diabetes Mellitus Patients in the United States. *Patient preference and adherence*, *14*, 2337–2345.

Departments to resolve issues related to diabetes[5]. Lack of adherence is up to 29% in patients with type 1 diabetes (T1D)[6], leading to severe complications. One biomarker of non-insulin-dependent Type 2 diabetes is amylin (< 20 pmol/L) whose concentration increases during early phase type 2 diabetes (20–100 pmol/L). Potential therapies to be produced are GLP-1 or glucagon. (Insulin may be produced; however, a compelling rationale on why it would be superior to beta cell implantation must be provided.)

- As a final example, REACT could impact thyroid diseases, such as hypothyroidism, that require daily medication and regular blood testing to adjust the dose for each patient properly. Inadequate treatment results not only from medication non-adherence, but also ensuring dosing at the correct time of day or on an empty/full stomach. This is important for levothyroxine, where optimal absorbance is on an empty stomach 30-60 min before eating. Hypothyroidism results from increased TSH (>4.5 mIU/L) and decreased T4 (< 5.0 µg/dL). Accurate dosing can require multiple rounds of blood testing, often weeks apart, followed by dose adjustment. The ability to automatically measure thyroid biomarkers to track disease status accurately and then dispense the correct dose precisely would radically improve the quality of treatment and life for the patient while also decreasing the burden of testing and medication compliance.

B. TECHNICAL APPROACH AND STRUCTURE

The REACT program will require advances in multiple Technical Areas (TAs). Once key advances have been made, the technology must be integrated using a robust engineering plan described below. The TAs for REACT include:

TA1: **Long-Term Maintenance of Cells *In Vivo*:** Support viability of the engineered cells for a year inside the device once implanted in the host.
TA2: **Improve the Manufacture of Standardized Cell Lines**: Manufacturing process development for the routine engineering of cells to form a standardized cell line that can either deliver therapies or detect biomarkers.
TA3: Implantable Device that Communicates with Patients: Develop an implantable bioelectronic device that houses the living cells along with secure communications between the patient and carrier as well as between the carrier and the engineered cells. Components must be integrated such that recharging is required only once per week.
TA4: Therapy Generation with Stimulated Release: Reliable and accurate release of the therapy for at least one year after implantation.
TA5: Accurate Biomarker Detection: Accurate tracking of a biomarker concentration for at least one year after implantation.

A primary challenge in the REACT program is engineering cells to either produce a therapy when stimulated or to track the concentration of a biomarker. Through synthetic biology, extensive work has been invested in the remote activation of cellular signaling. A range of stimuli—electric fields, light, mechanical forces (via ultrasound), and even magnetic fields—can now induce cells to produce or release previously accumulated compounds on demand. For instance, recent advances have shown a robust system that could be implanted for several weeks and uses cells to deliver insulin whenever they are

[5] Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html.

[6] Currie, C. J., Peyrot, M., Morgan, C. L., Poole, C. D., Jenkins-Jones, S., Rubin, R. R., Burton, C. M., & Evans, M. (2013). The impact of treatment non-compliance on mortality in people with type 1 diabetes. *Journal of diabetes and its complications*, *27*(3), 219–223.

stimulated by electrical pulses. REACT seeks to expand upon such interventions to create a platform technology that delivers a broader range of therapies over a longer time period. **NOTE:** REACT proposals should detail the proposed approaches for engineering the appropriate sense and response circuits in the cells in a way that supports long-term cellular viability and stability.

Another major challenge in the REACT program is the development of the technology for high-fidelity signaling between the bioelectronic carrier and its cells to control the detection or production of biomolecules. Significant advances have been made in biocompatible materials, low-power communications protocols, and efficient means of stimulating cells. When combined, these advances produce devices for stimulating cells (e.g., chip-based light sources, integrated piezoelectric elements such as Capacitive Micromachined Ultrasonic Transducers (CMUTs), and conductive polymers), thus tracking production (via microspectrophotometers or coulometers) and recharging implanted devices (via magnetoelectronics). **NOTE:** Successful proposals will detail approaches for integrating advanced bioelectronic capabilities into a device with a small form factor that is conducive to implantation in an outpatient setting.

A third challenge in the REACT program is maintaining the viability and function of the allogeneic cells when implanted for at least a year within the host. Success will require careful engineering of both the external surface— to prevent an immune reaction and fibrosis—and the internal surface to maintain cell phenotype and viability. For the external surface, multiple strategies exist, from porous membranes to hydrogels, that prevent the entry of immune cells and the development of fibrosis. These devices must also permit the ingress of metabolites needed to support cells and the egress of therapies released by the cellular factories. Device surfaces will also need to withstand extended implantation *in vivo.* Similarly, as cells are responsive to their immediate environment, the cell chamber must stabilize cell function. The internally facing surfaces will form a niche around the cells and provide stabilizing signals that promote the maintenance of cell phenotype so that the device maintains function. **NOTE:** Proposals that include cell support strategies such as engineered extracellular matrices, provision of helper cells, or release of engineered metabolites will be welcome with the caveat that cell support strategies must operate for at least one year.

The final challenge in the REACT program is to create a prototype of an implantable device that can accurately release a therapy or track the concentration of a biomarker. Synthetic biology has developed a range of molecular and metabolic reporters detectable by an external electronic device. Each of these transduction strategies has relative strengths and weaknesses in power consumption, robustness of elicited response, production rates, time delay before production, and on/off ratios. Tradeoffs among these factors will be hard to fully resolve until integrated into a complete working system. **NOTE:** Consequently, successful proposals must focus on efficient designs that balance the required extent of cell engineering with the demand on the implanted device (e.g., power, space, timing) to create the stimulus. Similar tradeoffs exist for the Living Sentinel device that will require the engineered cells to be sufficiently sensitive to biomolecules at physiological levels and to produce a detectable signal quickly enough to track fluctuations in the body.

C. TECHNICAL AREAS (TAS)

Performers for the REACT program will create an implantable carrier that houses living cells, maintaining cell viability and function for at least one year. The carrier will establish high-fidelity signaling with the cells either to control production or to transduce the detection of biomolecules by the cell. Each performer will create a fully integrated device that combines these technological advances. Additionally, each performer will develop manufacturing processes (TA2) that enhance scaling.

Proposers will elect to create a Living Pharmacy (Track 1) AND/OR a Living Sentinel (Track 2). Proposers must identify which program track or tracks the proposals will pursue. If both tracks are proposed, **costs must be separated by track**. ARPA-H reserves the right to only fund one track at any point in the program. ARPA-H must be notified of any changes to proposed tracks throughout the duration of the program. Developing either of these devices will require proposers to address all applicable TAs. **Living Pharmacy track proposals must address TAs 1-4**, and **Living Sentinel track proposals must address TAs 1-3 and 5.** The TA titles follow:

TA1: Long-Term Maintenance of Cells *In Vivo*
TA2: Improve the Manufacture of Standardized Cell Lines
TA3: Implantable Device That Communicates with Patients
TA4: Therapy Generation with Stimulated Release
TA5: Accurate Biomarker Detection

Performance metrics and deliverables for all TAs are laid out in and will increase in difficulty and complexity over the course of the REACT program.

NOTE: Living Pharmacy (Track 1) Proposals must clearly indicate which hormones, cytokines, or other therapeutic molecules they will engineer into the system, expected dosing profile, and physiologically relevant concentrations. The proposed platform could deliver therapies for many different indications from thyroid insufficiency (e.g., T4) to obesity (e.g., GLP-1). One compelling disease to be addressed is obesity. Given the significant research into beta cell implantation, proposers are encouraged to include innovations beyond just the production of insulin, and proposals targeting insulin release should describe how the effort would substantially improve over the state of the art (SOTA). Novel cell-based approaches that could address diabetes, such as the production and delivery of GLP-1, glucagon, amylin, etc., are within scope. Note that multiple devices may be used as long as each controls a different hormone. Solutions that use combination therapies to comprehensively treat a disease are of interest, such as a solution that includes an insulin device for hyperglycemia and glucagon device for hypoglycemia.

NOTE: Living Sentinel (Track 2) Proposals must clearly indicate which biomarkers they will track, the physiologically relevant levels, and the expected necessary sampling frequency. The goal of this track is to monitor biomarkers that clearly represent the state of a disease and to convey that information to the patient so that they can readily manage their disease. Performers should clearly state and justify their choice of biomarker. Potential biomarkers for the example diseases are as follows:

Disease	Marker	Healthy Range	Diseased range
Obesity	Adiponectin	5–37 µg/mL	4–22 µg/mL
T2 Diabetes	Amylin	< 20 pmol/L	20–100 pmol/L (Early)
Thyroid Disease	TSH T4	0.5–5 mIU/L 5.0-12 µg/dL	>4.5 mIU/L (Hypo) <5.0 µg/dL

The primary goal for the Living Sentinel effort is the direct detection of a hormone, such as insulin, so efforts for tracking glucose or lactate must justify performance over the SOTA. The direct detection of insulin or other signaling molecules such as those mentioned above would be within scope.

TECHNICAL AREAS (TA) ONE (1) THROUGH FIVE (5):

TA1 – LONG-TERM MAINTENANCE OF CELLS IN VIVO

A key feature of these hybrid devices is that the engineered cells stably function *in vivo* either as a drug delivery platform or as a biomarker sentinel for at least a year. (Systems functioning for multiple years are permitted but beyond the scope of this proof-of-concept demonstration.) Stability is a necessary criterion for the technology because otherwise the sensor would drift out of calibration, or the pharmacy would not maintain reproducible delivery even with feedback. Successful completion of this TA requires stability both in the number of cells (viability) and in the function of those cells (phenotype). While 70% cell viability goal is proposed, lower viability is acceptable if performers can demonstrate the requisite production rate despite cell loss. Proposers must provide alternative metrics, with demonstrated production, if 70% viability is not met. Consequently, the TA's central goal is to create a stable niche for the cells. Generating the niche may include (1) encapsulation of the allogeneic cells in a chamber that is permeable to nutrients but impermeable to immune cells, (2) engineering of a well-defined extracellular matrix that maintains cell phenotype and viability, and (3) other strategies such as helper cells or enhancement of metabolism via local delivery of O_2.

NOTE: Complementary efforts may exist in TAs 2, 4, or 5 to edit cell pathways that lead to differentiation and those requirements should be considered in the approach addressing TA1. Proposers should balance the extent of leveraging synthetic biology against the extent of niche creation (e.g., elastic modulus, biochemical functionalization, etc.) to achieve their goals. Cells typically remodel their local environment, so the proposed niche design should account for this factor. Finally, the methods used to achieve the goals of this TA must also be compatible with manufacturing techniques using GLP/current Good Manufacturing Practices (cGMP) standards and eventual regulatory approval.

TA2 – Improve the Manufacture of Standardized Cell Lines

The REACT program will only be a success if the technology platform can be used broadly. This goal will be undercut if each new cell line must be designed *ad hoc* or requires significant reengineering for additional applications. Consequently, the second goal is to reduce the cost of treating a range of diseases by advancing rapid and reproducible engineering of cells. A fixed design choice is that only allogeneic cell lines will be used for production to allow for expansion and banking. The immunogenicity impact will be ameliorated by the membrane isolating cells from the immune system developed under TA1.

REACT welcomes proposals that advance both hardware and software approaches to mammalian cell line engineering at an industrial scale. Hardware approaches may include integrated microfluidics that reduce the number of handling steps by humans while also processing thousands of cells per second. This would enable multiple cell lines to be assessed for functionality. Proposals should describe their approach and the number of cell lines to be screened. Software approaches may include generating a safe harbor integration site in a mammalian cell line to enable the introduction of synthetic genes for sensing or therapy production under the control of an optimized and responsive promoter. These advances, especially in a commercial setting, should lower the entry costs for subsequent disease targets by creating an advanced starting point towards commercialization.

Proposals should justify how their approaches will lower future costs for cell-based production of therapeutics. Moreover, the proposals should delineate how the streamlined step is currently a significant expense in generating cell lines.

TA3 – Implantable Device that Communicates with Patients

The carrier serves both as housing for the engineered cells and a communications hub, connecting the patient with cells that produce therapies or track the disease state. Beyond accessing new treatments, patient uptake of this technology will likely hinge on the ease of participating in a therapy, which principally consists of reducing the time spent interacting with the device. The desired set-and-forget feature necessitates that the device works reliably as designed and that it is sufficiently small to enable

implantation through minimally invasive surgery. **NOTE: Performers must describe the extent of surgery required, the region of implantation, and the expected recovery period.** A central goal is to balance demands for infrequent interactions, assured power, and minimal size of the device. This will be achieved by jointly engineering the power management, transduction, and communications to ensure continuous operation for ≥1 week with reserves for a second week in standby mode. Proposals must describe the actions that a patient will need to perform to operate the device and the frequency with which they will need to take those actions. A key design choice is the method of communication between the carrier and cells. Examples include but are not limited to optogenetic and electrogenetic communication circuits. Consequently, proposals must clearly define a communication strategy and delineate downstream tradeoffs in size and power associated with this choice. Performers will need to successfully demonstrate secure, two-way communication between the implanted device and the patient. Proposals must describe how communication will be secured through highly local fields (ultrasound, magnetics), encryption, or other approaches.

For TA3, performers will be collectively developing software for a new class of therapeutic devices. Long term, it would be beneficial for this class of devices to share common application programming interfaces (API) and mechanisms for interacting with electronic health records systems or other digital mechanisms for communicating patient information to clinicians. To provide a foundation for future integration with digital health systems, performers will need to work together to develop common, open application programming interfaces and data standards that generalize across all REACT devices. Proposers should indicate any data standards or open APIs that they could leverage to serve as a foundation for open software standards for Living Pharmacies and Living Sentinels.

TA4 – Therapy generation with Stimulated Release (Living Pharmacy Track)

By the end of the REACT program, prototype Living Pharmacy devices (i.e., the cells integrated with a bioelectronic carrier) must accurately deliver a therapeutically useful dose. Acceptable error in accuracy will be dictated by the therapeutic index of the selected therapeutic output. Given the potential fluctuations in cell count or functionality, the system must have a feedback mechanism, a calibration method, or some other technique that maintains accuracy. In addition, proposals may choose to have the therapies delivered either locally or distally within a specified timeframe with respect to the intended site of action. For the latter, the device may be designed for implantation into a region of the body, such as subcutaneously, where therapies have not been historically administered or where the therapies are not traditionally released. In this case, performers will need to demonstrate that the produced therapy is delivered to the target site with the target dosage. This can be achieved using animal models or PK/PD modeling tools. By program completion, prototype devices must deliver from 4/5ths to 5/4ths of the target dose unless greater accuracy is warranted for the chosen therapeutic. **NOTE: Proposals must clearly indicate the therapy to be produced and the Physiologically Relevant Rate (PRR) of production.**

TA5 – Accurate Biomarker Detection (Living Sentinel Track)

The ability to accurately transduce biomarkers at physiologically relevant levels would be a gamechanger for continuously tracking a patient's health. Currently, continuous biomarker tracking requires blood draws or other invasive sampling that limits patient compliance. While sensors based on molecular probes are significantly advanced, they generally fail for continuous *in vivo* monitoring in that biochemical specificity requires tight binding between the target and probe molecule, meaning that the probe molecules saturate and must be regenerated. In the REACT program, the key sensing agents will be living cells. The presence of the target molecule will be detected by cell surface receptors and transduced by the cell as a whole into a signal detectable by the carrier. Example signals include fluorescent molecules, membrane potential, or microbubbles. Using cells enables the probe molecule to regenerate or reset with spatiotemporal dynamics that are physiologically relevant to *in vivo* interactions. **NOTE: As noted**

above, proposals should clearly identify the target molecule or molecules associated with the disease and define the time scale at which it must be tracked. As noted above, glucose monitoring is not of interest unless it substantially improves on the SOTA. Some biomarkers may require tracking with a sufficiently high temporal resolution that is incompatible with common approaches built upon transcription and translation. In this case, proposals must include strategies for rapid signaling likely built upon protein-protein interactions or the release of vesicles.

D. PROGRAM METRICS

The below program metrics are minimum requirements appropriate for all proposers and serve to bound scope of the effort while still affording maximal flexibility, creativity, and innovation of the proposed solutions. **NOTE: Proposers should propose additional quantitative metrics appropriate to their specific approach for each Step of the program.** Achievement of all metrics, as agreed to by ARPA-H, is the basis for initiation of the optional Steps.

STEP I (MONTHS 1-36)

Step 1 will comprise development of an appropriate cellular niche, manufacturing process development, and design of an implantable induction device. At the end of Step I, performers must demonstrate that at least one cell type is viable and stable *in vivo* after 6 weeks. Animal models must demonstrate appropriate transduction and genetic design in the cell type of choice. To accomplish this, performers will demonstrate *in vitro* and *in vivo* production of cell-released therapeutics of interest (Table 1).

Goal: Creation of genetically engineered cells that remain viable and produce physiologically relevant levels of proteins of interest. Demonstrated transduction reproducibility within a large animal model.

TABLE 1. STEP I METRICS ACROSS TECHNICAL AREAS

TECHNICAL AREAS	STEP I: MONTHS 1-36
TA1: Long-Term Maintenance of Cells *In Vivo*	□ Biocompatibility of optimized immune-isolation membrane or coating tested for 4 weeks (12 months) □ Demonstrate *in vivo* viability of >70% after 2 weeks (24 months) □ ≥70% cell viability with ≥50% of viable cells having maintained function after 8 weeks *in vivo* (36 months)
TA2: Improve the Manufacture of Standardized Cell Lines	□ Manufacturer consults on optimal chassis with performer (6 months) □ Screen ≥5 cell types for performance trade-offs (18 months) □ Perform high throughput screening of ≥100 microenvironmental conditions to optimize cell viability and stability (24 months) □ Determine ≥10 potential safe harbor sites for gene insertion (24 months) □ Demonstrate that at least 5 different genes can be stably integrated using the safe harbor. Only one transgene is integrated at a time, but ≥2 must produce protein at physiologically relevant rates (36 months)
TA3: Implantable Device that Communicates with Patients	□ Demonstrate optimization of transduction mode *in vitro* (12 months) □ Demonstrate communications power is within specification in an appropriate phantom or animal model (12 months) □ Demonstrate *in vivo* testing with cells for 6 months (36 months)

TA4: Therapy Generation with Stimulated Release	□ Demonstrate ≥10% production rate of therapeutic molecule *in vitro* relative to physiologically relevant rate (12 months) □ Demonstrate modeling or animal studies confirming target dose of therapeutic to be delivered (18 months) □ Demonstrate physiologically relevant production rate with an on/off ratio of ≥10 (24 months) □ Demonstrate device can confirm release of therapy (24 months)
TA5: Accurate Biomarker Detection	□ Demonstrate that cells transduce the target *in vitro* and routinely produce detectable signal from the expected cell population (12 months) □ Demonstrate LOD <10x of therapeutic range (24 months) □ Demonstrate LOD below therapeutic range *in vitro* (36 months) □ Demonstrate measurement at Nyquist frequency or as appropriate to the biomarker dynamics (36 months)

STEP II (MONTHS 37-66)

Step II, *30-months*, will cover the integration of the technologies developed under the TAs into a coherent implantable device followed by refinement of capabilities. By the end of Step II, progress will be made in all TAs towards an integrated system demonstrating therapeutic efficacy or biomarker sensing.

Goal: Production of two classes of devices that target human health. *Pharmacy Projects (Track 1):* a bioelectronic carrier will be created that releases therapeutics at physiological levels accurately for at least 3-months and maintains a charge for ≥1 week. *Sentinel Projects (Track 2):* ≥ 70% of engineered cells remain viable and maintain function after 12-months *in vivo*. These cells will have ≥2 proteins of interest produced at physiologically relevant levels.

TABLE 2. STEP II METRICS ACROSS TECHNICAL AREAS

TECHNICAL AREAS	STEP II: MONTHS 37-66
TA1: Long-Term Maintenance of Cells *In Vivo*	□ Demonstrate >70% cell viability with ≥50% of viable cells having maintained function after 4 months *in vivo* (48 months) □ *In vivo* testing of cells in encapsulation membrane for 12 months (48 months) □ Demonstrate encapsulation membrane can be fabricated using scalable processes compatible with commercialization (60 months) □ Demonstrate ≥70% cell viability with ≥70% of viable cells having maintained function after 12 months *in vivo* (60 months)
TA2: Improve the Manufacture of Standardized Cell Lines	□ Demonstrate production rates sufficient for Phase I clinical trial (48 months) □ Demonstrate production rates sufficient for Phase II clinical trial (66 months)
TA3: Implantable Device that Communicates with Patients	□ Demonstrate that the system can function on a single charge for one week *in vivo* with reserves for a standby week (48 months)
TA4: Therapy Generation with Stimulated Release	□ Confirm PK/PD via device *in vivo* (48 months)

TA5: Accurate Biomarker Detection	□ Demonstrate LOD below therapeutic range *in vivo* (48 months) □ Demonstrate detection remains accurate *in vivo* for 3 months (54 months) □ Demonstrate detection remains accurate *in vivo* for 1 year (66 months)

STEP III (MONTHS 67-72)

The final Program Step consists of a Phase I clinical trial to test the safety of the device and any side effects. It will also inform the strategy for the dosing profile and timing of the therapy. In addition to the meticulous monitoring and recording of side effects, as well as insights into preliminary efficacy, performers will be required to collect usability feedback from both patients and physicians. This feedback will be used to assess potential product viability and market adoption. When designing the clinical trial, performers will propose an appropriate method of feedback collection (e.g., existing or novel usability scoring systems, written surveys, interviews, etc.), that will be discussed and subject to ARPA-H's approval.

The enrollment and execution of the REACT clinical trial must also meet the program's equity requirements, described in Section 2.G.

i. PROGRAM STRUCTURE AND INTEGRATION

REACT is a 72-month program developed over a three Step process, as illustrated in Section 2.D. During Step I (36-months), performers will establish each of the foundational capabilities laid out in the TAs. During Step II (30-months), performers will integrate the developed components into a refined system, carry out validation or testing in a large animal model, and successfully apply for a pre-IDE/pre-IND (Investigational Device Exemption (IDE); Investigational New Drug (IND)) approval(s). Step III (6-month Option) efforts will focus on human trials to demonstrate safety, side effects, best dose, and timing of a new treatment.

ARPA-H anticipates funding multiple technical approaches for Track 1 and 2. A proposer must submit a single proposal for TA1-TA4, the Living Pharmacy, **or** TA1-TA3 and TA5, the Living Sentinel. Team formation is the sole responsibility of the prime proposer. Applicants applying to both tracks must submit one technical proposal encompassing all aspects necessary for completing both tracks.

INTEGRATION

All components developed under the TA must be integrated into a single system that delivers secure and accurate therapy or biomarker tracking. **NOTE: Proposals must identify a team member as the primary integrator** of the different TA components; this person does not need to be the Principal Investigator (PI). Additionally, teams must include milestones for an Initial Design Review and Critical Design Review (CDR) by the end of Step I (Month 36). The IDR should at minimum discuss the targeted therapeutics or molecule(s) to be tracked; describe device materials, design, and plans for system integration; and review risks and mitigation strategies. The CDR should update and solidify plans provided in the PDR. Performers must have a successful pre-IDE/pre-IND submission for the integrated device to execute the Step III Option.

INDEPENDENT VERIFICATION AND VALIDATION (IV&V) OF THE TECHNOLOGY

Throughout the program, the performers will work with an independent verification and validation

(IV&V) team established by ARPA-H. The IV&V team will consist of subject matter experts from the Government, Federally Funded Research and Development Centers (FFRDCs), academia, and/or other relevant domains. The IV&V team will test and validate the technology to confirm the performer's progress. Further, the IV&V team will test the ability of the REACT technology to respond accurately to the appropriate external communications/activation and elicit a relevant physiological response in large animal models by the end of Step II. During Step I, proposals should budget for monthly interactions with the IV&V team, at least one weeklong visit to key performer laboratories for familiarization with the techniques, and the provision of a sufficient number of devices to verify the key metrics for Step I.

TESTING OF BIOCOMPATIBILITY AND SAFETY BY A CONTRACT RESEARCH ORGANIZATION (CRO)

For this technology to be adopted, the end user must be assured that the technology is safe, will provide sufficient benefit to justify usage, and is under the user's control. Proposals must include plans and a budget for contracting third party groups to test carrier and intervention biocompatibility such as acute and subacute toxicity, biofouling, and safety during Steps I and II. Proposals must describe the type and number of tests necessary for regulatory evaluation and transition of the technology into humans. **Proposers should request the necessary funds to engage with CRO and IV&V teams.** To avoid potential conflicts of interest, performers for REACT will not be allowed to compete for the IV&V contract. REACT is not soliciting proposals for IV&V.

Low-cost initiatives to improve patient access to therapy: The proposers must prioritize strategies that reduce cost of the final product throughout the various TAs. The proposal should include a section outlining key strategies, such as the use of allogeneic cell lines, reusability of the device for multiple therapies, or innovations in low-cost cGMP device manufacture. The use of intrinsically expensive material or technology by the performers must be adequately justified by improved efficacy or clinical outcome. This initial cost reduction strategy should also outline the current cost of the therapy.
User Interface Design. To enhance ease of use and accessibility for REACT device users, performers will be required to describe an intuitive user interface in the initial design of the software during Step I. Clear patient messaging and control, in real time, is a requirement of software design and a critical design review should be accomplished by month 36. All modules should be designed to simplify the user experience and will be assessed during the clinical trials to ensure that the interface is uncomplicated, consistent, and accurate.

Procedure Difficulty and Implementation Assessments. Complicated in-patient procedures can be costly and cumbersome, resulting in limited access for some patients. Consistent with ARPA-H's mission to create affordable therapeutics for all Americans, REACT will prioritize solutions that only necessitate minor, out-patient procedures. Additionally, REACT performers will be required, regardless of the chosen track, to complete at least two procedure difficulty and implementation assessments. In these assessments, performers should provide as much detail about the procedure(s) necessary to implant and use REACT devices.

The first assessment will be in the full proposal, where proposers must include a written section that describes what procedures for implantation and usage are intended to be required. Proposers should provide as much detail as possible, but at a minimum must include descriptions and approximate durations of the procedure(s), whether the procedure(s) is inpatient or outpatient, and if there are any specialty personnel or equipment required that are not generally available in an outpatient setting.

The second assessment will be due to the REACT team before the onset of Step II or before any *in vivo* study in a large animal model, whichever comes first. It is expected that the second assessment should

describe the procedure(s) as closely as possible to what will be implemented in the Step III Phase I clinical trial (i.e., what would be submitted for regulatory approval). Therefore, the second assessment should include all details about the procedure, including step-by-step instructions for the healthcare staff and the patient for implanting and using the device. The REACT program will allow performers to present this information in the way the performers best see fit (e.g., a written report, slides, computer simulation, etc.) and will meet with the performers at either one of the regularly scheduled check-in meetings or a separate additional meeting (to be determined by ARPA-H and the REACT team) to discuss the procedure(s) in full.

PRE-COMMERCIALIZATION COLLABORATION

(OPTIONAL SUB-SECTION THAT DOES NOT COUNT TOWARDS PAGE NUMBER)

ARPA-H will work with an external organization to establish a collaboration for pre-commercialization work among all performers. The goal would be to accelerate the development of cell lines as well as regulatory approval. Potential tasks would be (1) to establish a systematic, platform approach to cell characterization to speed regulatory approval and commercialization, (2) define the Critical Quality Attributes (CQAs) and Quality Control specifications necessary to ensure safe and efficacious delivery, and (3) improve production systems for bioengineered cell-based products. Proposers may suggest additional opportunities for collaboration to be supported by ARPA-H; however, **proposers retain sole responsibility for achieving all program metrics**. Work associated with this effort is not being competed under this announcement.

COMMERCIAL TRANSITION SUPPORT

(OPTIONAL SUB-SECTION THAT DOES NOT COUNT TOWARDS PAGE NUMBER)

Proposers who are selected for an ARPA-H award may, at their discretion and at the government's cost, appoint a team of non-government advisors known as Entrepreneurs in Residence (EIR) or Experts in Residence (XIR). In coordination with the Program Manager, the EIR/XIR will provide commercial transition support to the awardee. The goal is to offer complementary capabilities to the team; therefore, the extent of the work is flexible. Examples of tasks may include cost modeling, end-user engagement, market analysis and mapping, competitive analysis, techno-economic analysis, manufacturing and scale-up strategy, intellectual property (IP) securement strategy, and financial plan creation. All commercialization and transition activities should align to the technology's stage of maturity. EIRs/XIRs will work closely with ARPA-H's Project Accelerator Transition Innovation Office (PATIO) team to leverage that Office's extensive network of U.S. investors, strategic partners, and mentors.

Proposers wishing to participate must:

- Briefly (<1 page) describe a strategy for transitioning the technology from its expected state at the end of Step I into a product or
- Itemize EIR/XIR tasks, with their proposed costs, for developing a viable Go-to-Market Strategy over the course of the program (<1 page; example tasks are listed above)

Participation in the program is voluntary but recommended. Participants are not expected to form a new company or leave their current research positions to pursue transition; instead during the program, they should identify appropriate partners for enabling transition.

E. SCHEDULE/MILESTONES

NOTE: Successful proposals will describe a clear plan to meet these milestones in the program Steps. While milestones should be met in all TAs, each track will have key goals routinely spaced in the Steps that are directly aligned with the target disease. **Proposals should include milestones for their specific disease.** Potential key milestones for the three example diseases are as follows:

LIVING PHARMACY TRACK:

Time (Months)	*Example Disease*	Goal
24	*All*	Demonstrate physiologically relevant production and secretion rates from encapsulated cells *in vivo*. Physiologically relevant levels must be in line with animal model used. Constitutive expression is allowed.
36	*Obesity*	Implanted cells should lower an animal model's weight by at least 5% relative to a control after 8 weeks.
	Diabetes	Cells implanted into a model should restore normoglycemia within 1 hour from both hypo- and hyper-glycemia. Two different engineered cells may be used.
	Thyroid	Implanted cells should restore at least 20% of the target hormone levels within 8 weeks
48	*Obesity*	The implanted device should lower the weight of a large animal model by at least 10% by the end of 16 weeks.
	Diabetes	The implanted device must restore normoglycemia in < 1 hour after implantation in a large animal model and maintain it for 6 weeks.
	Thyroid	The implanted device should release therapy in <1hr that restores 80% of target hormone levels `by the end of 8 weeks.
66	*Obesity*	The implanted device must have achieved and maintained weight loss in a large animal of at least 20% at the end of 1 year.
	Diabetes	The devices must restore normoglycemia in < 1 hour from both hypo- and hyper-glycemia after implantation in a large animal model and maintain it for one year.
	Thyroid	The implant should release therapy in<1 hr, restore ≥80% of target hormone levels and maintain them for 1 year.

LIVING SENTINEL TRACK:

Time	*Example Disease*	Goal
24	*All*	Demonstrate a limit of detection (LOD) <10x the Therapeutic Range (TR) for the chosen biomarker, with validation in a spiked clinical sample or other matrix in vitro or in vivo.
36	*All*	The limit of detection of the cells should be less than or equal to the Therapeutic Range (TR) for the chosen biomarker *in vitro.* Achieving the metrics *in vivo* will obviate achieving them *in vitro*. Reproducible functionality is expected.
48	*All*	The limit of detection for the sensor should be less than or equal to the Therapeutic Range (TR) for the chosen biomarker after four weeks of implantation.
66	*All*	The sensors must meet all previous specifications and remain accurate for 1 year *in vivo*.

ARPA-H will meet with REACT performers at least monthly to review progress towards the metrics defined below.

An expected schedule for key engineering and regulatory events is below. **Performers may propose an alternate timeline with justification.**

Month	**Engineering of Carrier**	**Engineering of Software**	**Other Research**	**Regulatory**
6	Complete Initial Hardware Design	• Complete Initial Software Design and establish architecture. • Specify all major modules. • Work with other performers to develop baselines for open data standards and open APIs.		
12	Testing of all components/ Risk Analysis	Coding		
18	• Initial Design Review • All materials should be stable through sterilization	• Code Inspection or Walkthrough • Periodically update the program-wide open data standards and open APIs as needed.		
24	• Assembly of Initial Prototypes. • All materials must have established biocompatibility. (New materials must be tested for biocompatibility.)	Software tested in prototypes	• In vitro testing of assembled device	
30	• Testing for environmental stability, reliability, and safety. • Preliminary preclinical work as needed. • Informal design reviews with contract GMP manufacturer	• Revisit code as needed. • Periodically update the program-wide open data standards and open APIs as needed.		
36	Critical Design Review	Critical Design Review	• Confirm PK/PD *in vivo* from direct injection or with device if ready • Establish necessary cellular Production Levels	Discuss APIs with ONC
42	Devices built under manufacturing control			
48		Refine GUI based on patient and clinician feedback	Preclinical Pilot Efficacy	**INTERACT**
54	• All additional environmental and reliability testing • Biocompatibility of assembled device		• Preclinical Pivotal Efficacy • Safety & Toxicology • Confirm PK/PD via device in vivo	
60				**Pre-IND**
66	Manufacturing Build Review			**File IND**
72	**Phase I Clinical trial**			

F. POLICY CONFORMANCE, AGILE DEVELOPMENT, OPEN STANDARDS, EQUITY REQUIREMENTS, AND INTELLECTUAL PROPERTY

OPEN SOFTWARE STANDARDS

Performers should plan to interact with one another and ultimately with the Office for the National Coordinator of Health IT to lay the foundation for open data standards and open APIs for REACT devices. These open standards should create a path toward integration with health records systems and other types of digital health interfaces.

EQUITY REQUIREMENTS

ARPA-H is committed to equitable health care access irrespective of race, ethnicity, gender/gender identify, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. To that end, we will follow the United States Food and Drug Administration's (FDA) guidance titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials".

A key aspect of equitable access is ensuring that the population participating in clinical trials matches the patient population impacted by the disease. Proposers should indicate how their clinical enrollment strategy fulfills that goal. For instance, a road map to equity for the diabetes clinical trial would include enrolling, with reasonably (±5%) tolerances, a patient profile matching that of the affected population: American Indians and Alaska Natives (27%), followed by non-Hispanic Blacks (22%), people of Hispanic origin (21%), non-Hispanic Asians (16%) and non-Hispanic Whites (14%). Similarly, enrollment in the obesity clinical trial should reflect the affected population: Non-Hispanic Black adults (32.6%) Hispanic adults (29.8%), non-Hispanic White adults (27%) and non-Hispanic Asian adults (10.5%). The enrollments must be equally divided between men and women (50% ± 5%) and the socioeconomic status of the patients will be recorded. Robust risk mitigation strategies will be implemented and the enrollment for the clinical trials will serve as an accurate demonstration of the correlation between race and metabolic diseases in the US.

3. AWARD INFORMATION

Multiple awards are anticipated under this announcement; however, the number of awards selected for award will depend on the quality of the proposals received and the availability of funds. Awards will be in the form of OTs.

See Section 1.4 of the MAI, ARPA-H-MAI-24-01 for additional information on award information.

4. ELIGIBILITY

See Section 2 of the MAI, ARPA-H-MAI-24-01 for eligibility requirements.

5. MODULE ANNOUNCEMENT RESPONSES

A. PROPOSAL CONTENT AND FORMAT

This Module Announcement is soliciting Stage 1 Volume 1 proposals. Stage 1 Volume 1

proposals must contain the following document submissions:

- TECHNICAL & MANAGEMENT
- BASIS OF ESTIMATE (BOE)
- TASK DESCRIPTION DOCUMENT OR RESEARCH DESCRIPTION DOCUMENT
- ADMINISTRATIVE & NATIONAL POLICY REQUIREMENTS

ARPA-H anticipates GIG Module category proposals for the REACT program. Strong proposals will select a cost point that is commensurate with the scale and complexity of the proposed approach. ARPA-H expects that proposals for larger efforts will include more thorough technical descriptions, more ambitious milestones, and more detail regarding metrics. Larger efforts should also create more mature or comprehensive capabilities that are more thoroughly tested and evaluated. Smaller efforts may be more exploratory or focus on a subset of the overall technical area, and they will be selected based on the uniqueness of the proposed effort within the overall portfolio.

If a Stage 1 proposal is selected for potential award, a proposer will be notified by the Government that they are eligible to submit a Stage 2 price/cost proposal for further consideration.

All proposals submitted in response to this announcement must comply with the content and formatting requirements of the bundle of attachments. Proposers must use the templates provided in the bundle associated with this announcement. Information not explicitly requested in the MAI or this announcement and bundle, may not be evaluated.

All submissions, including proposals, must be written in English with font type not smaller than 12-point font. Smaller font may be used for figures, tables, and charts. Content and formatting are disclosed in the bundle of attachments. Below is the page restriction:

- **GIG Module** is > $25,000,000 ≤ $50,000,000: Volume 1 shall be limited to **40** pages.

NOTE: A proposer must submit a single proposal for TA1-TA4, the Living Pharmacy, **or** TA1-TA3 and TA5, the Living Sentinel. Team formation is the sole responsibility of the prime proposer.

B. Proposal Submission Instructions

Proposal submissions against this Module Announcements shall be submitted to the electronic Contract Proposal Submission (eCPS)[7], ensuring receipt by the date and time specified in Sectionand 5.E of this Module Announcement.

Proposers should consider the submission time zone and that some parts of the submission process may take from one business day to one month to complete (e.g., registering for a SAM Unique Entity ID (UEI) number or Tax Identification Number (TIN); see Section 5.2.1 of the MAI for information on obtaining a UEI and TIN).

C. Proposal Due Date and Time

Proposals in response to this notice are due no later than 2:00 PM ET on January 26, 2024. Full

[7] electronic Contract Proposal Submission (eCPS) is a component of an integrated, secure system for electronic submission, capture, tracking and review of contract proposals. Be advised eCPS requires user registration to submit a proposal response.

proposal packages as described in Section 5.B must be submitted per the instructions outlined in this Module Announcement and received by ARPA-H no later than the above time and date. Proposals received after this time and date may not be reviewed.

Proposers are warned that the proposal deadline outlined herein is in ET and will be strictly enforced. When planning a response to this notice, proposers should consider that some parts of the submission process may take from one business day to one month to complete.

6. Proposal Evaluation and Selection

Proposals selected and evaluated in accordance with Section 4 of the MAI, ARPA-H-MAI-24-01.

7. Administrative and National Policy Requirements

Section 5.2 of the MAI, ARPA-H-MAI-24-01 provides information on Administrative and National Policy Requirements that may be applicable for proposal submission as well as performance under an award.

The requirement listed in the MAI to register and submit invoices in the Invoice Processing Platform does not apply to awards made as a result of this Announcement. Performers will be required to register and submit invoices for payment in the Payment Management Services (PMS) system.

8. Point of Contact Information

Questions should be directed to:
REACT@arpa-h.gov
ATTN: ARPA-H-MAI-24-01-02

9. Frequently Asked Questions (FAQs)

All questions regarding this notice must be emailed to the point of contact noted in Section 8. Emails sent directly to the Program Manager, or any other address will be **discarded**.

All questions must be in English and must include name, email address, and the telephone number of a point of contact. ARPA-H will attempt to answer questions in a timely manner; however, questions submitted within 10 business days of the proposal due date listed herein may not be answered. In addition to the FAQ specific to this notice (ARPA-H-MAI-24-01-02), proposers should also review the MAI General FAQ list found at SAM.gov.