Request for Proposals
Operation Payload Delivery
Ion-ARPA Program

Description of the funding opportunity
Ion-ARPA, a new program developed by Ionis Pharmaceuticals, will fund multiple teams to create revolutionary new therapeutic technologies. Modeled on the U.S. Department of Defense program known as the Defense Advanced Research Projects Agency (DARPA), the Ion-ARPA approach will facilitate innovation of novel cutting-edge technologies capable of pioneering new markets in healthcare. Ion-ARPA programs will be funded based on high-risk ideas with high-reward potential.

Description of this request for proposals
Selected teams will design and develop a novel, multifaceted, scalable, non-immunogenic strategy to deliver complex macromolecular therapeutic payloads to specific target cells and tissues. The payload must be delivered into the target cells in a biologically active form that can induce phenotypic and/or genotypic changes and enable healing for the patient.

Eligibility
Investigators from academic institutions, companies, national laboratories, nonprofit institutes, and other organizations are welcome to apply.

Funding level
Ionis will invest up to $30M over four years in this program. Annual funding could range from seedlings of $300K to full programs of $1M per laboratory, with appropriate justification. Funding can be used for principal investigator (PI), postdoctoral researcher, and graduate student salaries, relevant travel, laboratory supplies, open access publication costs, small laboratory equipment, vivarium expenses, and institutional indirect costs. Ionis will consider providing unrestricted funding at the seedling level to rapidly initiate programs perceived to be high value that can start during the 2021 calendar year.

How the program works
Ion-ARPA will announce areas of interest and solicit requests for proposals (RFPs). Each announcement will pose a specific technological challenge and outline expected milestones. Programs are intended to run for two years to test bold ideas, with the potential to continue for additional years if encouraging results are obtained.

Proposals will be required to have a structure and content similar to those submitted to other funding agencies (e.g., DARPA, NIH, NSF, BARDA, and BMGF) and must contain a scientific explanation for the proposed concept and goals with quantitative milestones and timelines. Programs will be actively managed by Ionis, and performers will be required to prepare monthly updates (typically a slide deck discussed during a 1-hour video conference) and quarterly reviews (typically, a written report and follow-up video conference). Proposals will be

reviewed confidentially by Ion-ARPA scientific staff and confidentially by selected scientific advisors to the company. Proposers are encouraged to prepare and submit a white paper (see guidelines below) in advance of submitting a full proposal.

Teaming is *highly encouraged* as it is anticipated that responsive solutions will require integration of expertise from diverse disciplines and access to appropriate therapeutic payloads and to animal models. PIs who work on a team with PIs from different institutions will each be funded directly from Ionis but will be reviewed as a team. Teams with PI's from multiple institutions should select one individual to serve as the lead PI for the team. *Teams with diverse skill sets will have an advantage over individual investigators when proposals are ranked for priority.*

Intellectual property

The awardees will retain ownership of intellectual property created during performance of the program. In exchange for its funding, Ionis will receive a paid-up, non-exclusive license and first option to negotiate for an exclusive license.

Key Dates

Program announcement:	July 15, 2021
White papers due:	October 15, 2021
Invitation for full proposals:	November 1, 2021
Full proposals due:	December 15, 2021
Award announcements:	January 15, 2022
Funding start:	Immediately following award announcement and contract

Fast track seeding funding

Because it may be impractical to fund a full proposal before the end of the year, and funds are available that can be used in the 2021 calendar year, particularly attractive white papers can be fast-track funded up to $300K (total cost) in parallel with the full proposal process. Early submission of white papers is strongly encouraged to take advantage of this opportunity.

Background of this request for proposals

A long-standing goal in therapeutics development, that remains for the most part unmet, is the ability to deliver medicines to the tissues and cells where the therapeutic agent will produce a desired benefit. Medicines are often needed only in specific diseased organs, tissues, or even certain cells, but the vast majority of drugs are distributed throughout the body, and the bulk of the administered drug ends up in locations where it is not needed, often producing unwanted side effects. Newer medicines, such as nucleic acid-based therapies (oligonucleotides, DNA, and RNA), proteins, or macromolecular complexes have a much higher degree of specificity than conventional small-molecule drugs, but often fail clinically because these agents do not reach the relevant diseased cells and tissues.

This challenge has been widely recognized and has led to the concept of targeted or "smart drug" delivery. Some of the earliest efforts at targeted drug delivery were based on liposomes.

Liposome encapsulation masks the chemical or physical properties of drugs and changes their biodistribution. As the technology has become more sophisticated, liposome formulations or drugs themselves have been outfitted with targeting ligands that can provide a high degree of delivery specificity. Nevertheless, there have been few major advances in the field of drug delivery for decades. Delivery to target tissue and cell type within that tissue will continue to be the major obstruction to revolutionary therapeutic advances, and therefore a focused program to solve the delivery problem could provide great value for the entire field of therapeutics.

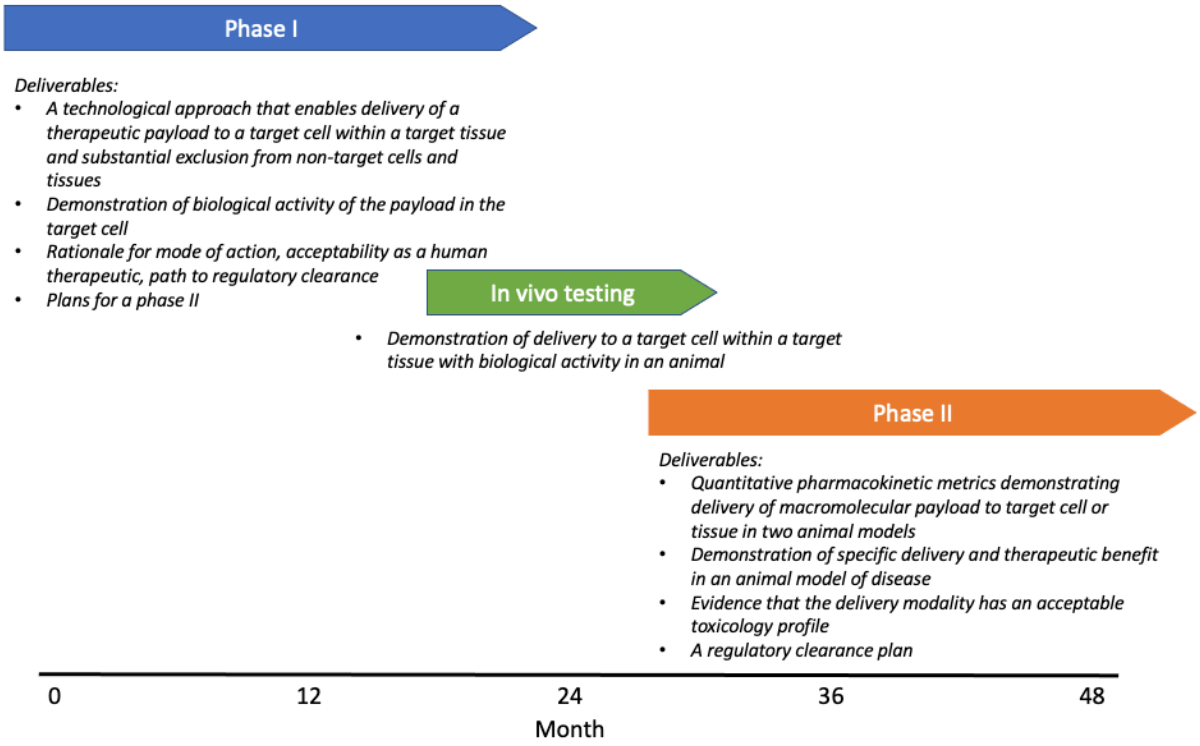
Overview of Operation Payload Delivery

This RFP is intended to stimulate revolutionary advances in the delivery of therapeutic products to specific target cells within target tissues based on foundationally new mechanisms. *Exceptional novelty with a credible research path toward the envisioned outcome will be the most important factor in funding decisions.* Incremental advances grounded in existing strategies are specifically excluded.

Operation Payload Delivery is organized in two phases: Phase I (24 months) is intended to demonstrate proof of principle that the new modality will enable delivery of complex macromolecular payloads to specific target cells within a selected target tissue. Proof of concept can be accomplished initially with use of reporter molecules that demonstrate delivery to specific target cells and substantial exclusion from non-target cells. An even more compelling scenario would be delivery of a payload with more than one component (e.g., a combination of an oligonucleotide and protein) that produces a measurable biological change in the target cell. If sufficiently encouraging results are obtained to justify experimentation in an animal, additional funding will be provided after the 24-month phase I period. If the team achieves the phase I goals sooner than 24 months, funding will be provided to accelerate testing in an animal or animal disease model without delay, and proposers may include the animal studies in their phase I budget if they believe this can be achieved within the phase I period. Proposers must provide a mechanistic rationale for why the new modality will ultimately be acceptable for human therapeutic use (e.g., it will not generate an undesired immune response, obstruct blood vessels, leave behind toxic materials, or initiate other pathological sequelae).

Phase I will culminate in a *plan* for a capability demonstration to be carried out during phase II. In phase II, the performing team must provide evidence that the component parts of their proposed solution can be assembled to package their chosen payload and must select a challenging target cell or tissue type and two appropriate animal models, at least one of which is disease relevant. A brief *look ahead* description of the performer's preliminary thoughts on their phase II plans will make a more compelling phase I proposal.

The goal of phase II (24 months) will be to demonstrate successful delivery of a performer-chosen macromolecular therapeutic payload in animal models. Targeting to specific target cells within a selected target tissue must be achieved *and* anticipated effects must be observed. During phase II, an acceptable toxicology profile should be demonstrated, and a regulatory clearance plan should be prepared.



Modalities *within* the scope of this proposal could include:

- Synthetic biology/chemical constructs
- Approaches that use directed evolution
- Genetically or physically engineered extracellular vesicles
- Nanoparticles based on entirely new modes of delivery/action
- Biomimetic strategies (e.g., phage or bacterial conjugation-like mechanisms)
- Engineered self-assembled or self-delivering nucleic acids and RNA-protein complexes
- Physical methods or strategies linked to advanced imaging
- Novel combinations of advanced technologies (e.g., nanocarriers that respond to external stimuli, on-site triggered delivery and/or activation of genetic circuits, viral vectors and optogenetics)
- Autonomous RNA-protein complexes or nano-lipid containers with non-deleterious longevity in a host that adapt to disease progression
- Genetically modified amoeboid cells that are attracted to a signal and can be loaded with therapeutic extracellular vesicles for release at a target site based on a trigger
- A two-tier approach where the first tier opens 'the right door' (i.e., open the endothelial barrier at tissue-specific site) and the second tier delivers the payload to the target cell
- Mechanisms to target cells that express receptors
- Implantable cellular bioreactors that can produce adaptable disease-specific therapeutic extracellular vesicles in response to the uptake by target cells

Specifically *excluded* mechanisms include:

- Conventional liposome-based formulations, micelles, or dendrimers
- Ligands attached to drugs or conventional liposomes
- Previously well-described formulations of vesicles
- Incremental improvements of methods already well-established in the literature
- Liver targeting

Proposers are expected to establish their own metrics to measure success and justification for their choice of metrics. Examples of success metrics might include:

- Demonstration of loading a payload vehicle with a single-type molecule where X% (or a specific amount) of the vehicle content is delivered to the target cell
- Demonstration of loading a vehicle with multiple macromolecular components (e.g., one nucleic acid and two proteins)
- Demonstration of the capability to create a nanoparticle/vesicle/vehicle that causes a recipient cell to produce a biological effect
- Demonstration of a cell with a gene circuit that can be introduced into an animal to create an ongoing, regulatable supply of biologics like vesicles (as the liver does)
- Demonstration of delivery of a cargo into the nucleus or other cell compartments in the targeted cell type affected in the disease
- Demonstration of four key components: 1. production of delivery vehicles, 2. loading cargo into vehicles, 3. delivery and controlled release of cargo into target cells in vivo, and 4. potential compatibility with human therapeutics
- Demonstration of a novel strategy for delivery of cargo to specific cells and functional utility within target cells in vivo
- Demonstration of remote control delivery of a payload vehicle to a specific target tissue (e.g., by putting magnetic particles into vesicles and controlling localization with magnetic fields, by using acoustic or optical guides for cells or nanoparticles, by engineering chemotropic gradients and differentiation signals modeled after cell guidance in development)
- Demonstration of an ability to monitor the release of payload in real time or close to real time
- Demonstration of a novel strategy of escape from immune surveillance and endosomal-lysosomal degradation to deliver cargo
- Demonstration of a strategy for self-amplification of payload in the target cell
- Creation of a payload with an internal energy source to power and enable movement of the delivery vehicle, with possible external guidance
- Creation of a device that produces payload vehicles in a continuous supply for the necessary period in connection with the bloodstream or other biofluids that perfuse the target cells/tissue
- Demonstration of a strategy for simultaneous monitoring of targeted delivery and phenotypic readout
- Demonstration of immune compatibility in healthy controls or no adverse effects in animal models of disease

It is anticipated that successful solutions will ultimately be agnostic of the chosen therapeutic payload and easily re-configurable to target a variety of different cells and tissues. Strategies to penetrate the blood-brain barrier are not specifically encouraged unless the proposed solutions are radically different from methods currently described in the literature. A plausible path to manufacturing must be described and there must be no obvious showstopper to approval by the Food and Drug Administration (FDA).

White papers
Recognizing that preparation of a full proposal is time consuming, Ion-ARPA accepts short (up to 5 pages) white papers. Following review of the white paper, an Ion-ARPA program manager will provide guidance on recommendations for a full proposal. Guidance for preparation of a white paper can be found here.

Success criteria
Exceptional novelty of the concept and the quality of the experimental design will be the primary factors considered in scoring proposals in addition to the traditional metrics of investigator and team qualifications, relevant experience, research setting, and milestones.

Full proposals
Guidance for preparation and submission of a full proposal can be found here.

Informational webinar
Ionis will conduct an informational webinar at a date that will be announced shortly.

Further questions
The Ion-ARPA program is a new initiative, and potential performers may have questions before embarking on preparation of a white paper. An Ion-ARPA program manager would be happy to discuss your interest and answer your questions. Please send inquiries to Ion-ARPA@ionisph.com with contact information, and we will arrange for a discussion.