Request for Proposals
Novel Therapeutic Payloads
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 will fund researchers who have high-risk ideas with high-reward potential.

Background of this request for proposals
Aberrant gene expression caused by genetic or epigenetic variation underlies many human diseases. A long-standing goal in therapeutic development is to correct such defects by developing tools to modulate gene expression in disease-associated cells. New technologies, such as mRNA- or CRISPR-based therapeutics, show tremendous promise for the treatment of previously intractable human diseases. Despite these advancements, however, expression of many disease-causing genes cannot be regulated via existing technologies -- for known or unknown reasons -- highlighting the critical need for the development of non-conventional approaches. *Our program aims to identify and support completely novel technology concepts that go beyond existing strategies and that could provide great value for the future of therapeutics.*

Objectives of Novel Therapeutic Payloads Program
The Ion-ARPA program is intended to stimulate revolutionary advances in foundationally new mechanisms of therapy. *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 already described in the literature are specifically excluded. This funding opportunity is exclusively to develop and test new ideas.

Description of this request for proposals
The program seeks proposals that detail strategies to develop non-conventional technologies to modulate the expression of mammalian genes to overcome a disease state. The strategy could leverage inherent or synthetic molecular mechanisms. Approaches could be tunable, auto-regulatory (e.g., respond to the context of the specific cells being treated), or controlled with a physical method (e.g., ultrasound or magnetic fields).

General areas of interest include, but are not limited to, novel strategies for silencing or activating genes, targeted RNA modification, and gene editing *beyond* existing CRISPR/Cas9- or deaminase-based approaches. The scale of the approach can range from the modulation of a single gene to that of an entire chromosome.

It is *not* required that the proposal detail a strategy to deliver a macromolecular complex to the target cells, as this is the subject of a separate request for proposals.

Success criteria for funding

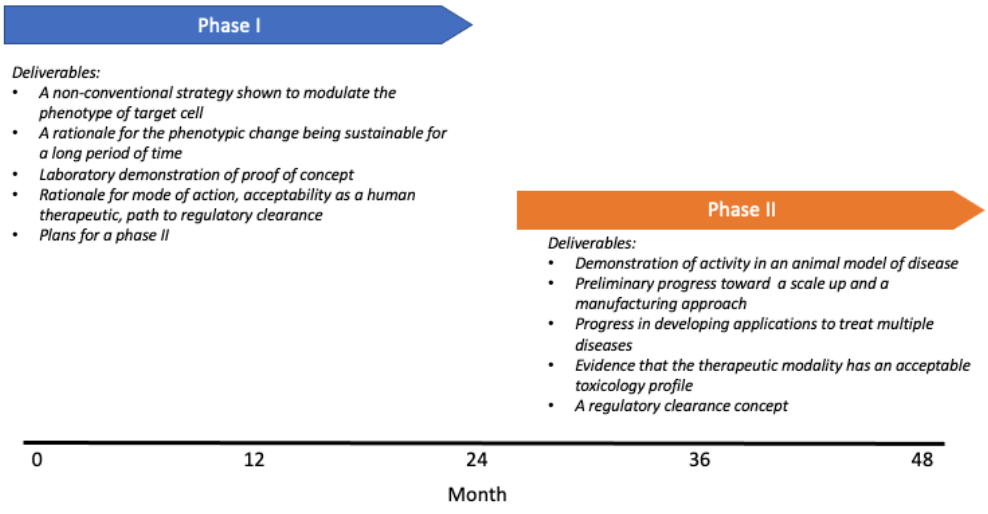
Exceptional novelty of the concept and the quality of the experimental design will be the primary factors considered in scoring proposals in addition to the traditional metrics of investigator and team qualifications, relevant experience, research setting, and milestones.

Key dates

Program announcement:	November 15, 2021
White papers due:	March 1, 2022
Invitation for full proposals:	March 30, 2022
Full proposals due:	May 15, 2022
Award announcements:	June 15, 2022

Organization of the Novel Therapeutic Payload Program

The program will be organized in two phases: Phase I (24 months) is intended to demonstrate proof of principle for the new modality for regulating the phenotype of a cell. Phase I will culminate in proof of concept for the novel approach and a *plan* for a capability demonstration to be carried out during phase II. In phase II, the performing team must select a challenging target cell or tissue type and appropriate animal models of a disease process. 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 a successful anticipated outcome in animal models and an acceptable toxicology profile.



Modalities *within* the scope of proposals *could* include:

- Silencing specific gene expression through novel approaches, such as piRNA re-purposing
- Approaches that allow dosing the patient infrequently, potentially annually or longer
- Turning on or off genes from multiple loci or even from an entire chromosome at a time.

- Engineering chromatin or topologically associated domain structures to alter gene expression
- Moving and anchoring a chromosome to a specific nuclear location to regulate chromosome-wide transcription
- Phase separating DNA, RNA, or protein to regulate gene expression
- Inserting cell-type specific enhancers into specific locations in the genome for gene activation
- Altering RNA activities via modulating 3D RNA structures
- Manipulating the epigenome to regulate transcription
- Expressing inheritable replicons to enable stable expression of exogenous genes throughout cell divisions
- Editing the genome using methods completely different from CRISPR or deaminases

Mechanisms specifically *excluded* include:

- Incremental improvements of methods already well-established in the literature
- Previously well-defined gene regulatory technologies
- Small molecule approaches
- Open-ended "research"
- Anything already fully described in the literature or patented

Proposers are expected to establish their own metrics to measure success and to provide justification for their choice of metrics. How progress will be assessed and how midcourse corrections will be made should be explained. Examples of success metrics might include:

- Demonstration of xx% silencing or activation of one or a group of genes
- Demonstration of the capability to direct a chromosome to desired location in the nucleus with xx efficiency
- Demonstration of altered boundaries of topologically associated domains
- Demonstration of the formation or destruction of xx% of cellular condensates via microscopy
- Demonstration of insertion of a regulatory element into a specific genomic locus with at least xx% efficiency
- Demonstration of genome editing and quantification of on-target to off-target ratios
- Demonstration of inheritable changes in cell division through five cell divisions

Eligibility

Investigators from academic institutions, companies, national laboratories, nonprofit institutes, and multi-institutional teams 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 per year or more with appropriate justification. Funding can be used for principal investigator (PI), co-principal investigator, staff scientist, 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.

How the program works

Ion-ARPA funded programs run initially for two years (Phase I) to test bold ideas, with the potential to continue for additional years if encouraging results are obtained. Proposals must have a structure and content equivalent 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 consultants to the company. Potential applicants are required and submit a white paper (see guidelines below) in advance of submitting a full proposal.

Development of collaborative teams from the same or multiple institutions is *highly encouraged* as it is anticipated that responsive solutions will require integration of expertise from diverse disciplines. PIs who work on a team with PI's from different institutions will each be funded directly from Ionis but will be managed and 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.

White papers

Recognizing that preparation of a full proposal is time consuming, Ion-ARPA requires submission of 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.

Full proposals

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

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 will 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.