ENDOCRINE SOCIETY
Hormone Science to Health

Representative Diana DeGette
2111 Rayburn House Office Building
Washington, D.C. 20515-4329

Representative Fred Upton
2183 Rayburn House Office Building
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July 16, 2021

Dear Representatives DeGette and Upton,

The Endocrine Society appreciates the opportunity to comment on the establishment of the new Advanced Research Projects Agency for Health (ARPA-H). Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization dedicated to research on hormones and the clinical treatment of patients with endocrine diseases. Our members include basic and clinical researchers advancing our understanding of endocrine systems and developing new therapies and innovative devices, as well as clinicians who apply new discoveries in endocrine science to improve patient care. We welcome the Biden Administration and Congress' efforts to drive transformational innovation to improve public health, and we appreciate your engagement as the ARPA-H initiative takes shape. In our comments we address several of the questions posed in the RFI, and we also propose additional considerations that Congress, the National Institutes of Health (NIH) and the Office of Science and Technology Policy (OSTP) should evaluate as ARPA-H takes shape.

1. **Which aspects of DARPA should ARPA-H include?**

The Defense Advances Research Projects Agency (DARPA) model is recognized for its ability to bring together groups of experts to solve otherwise intractable problems or questions, in particular for engineering projects where multiple approaches with several potential solutions may exist. DARPA projects also excel when there are well defined near- and mid-term objectives and interim deliverables to track progress. Replication of similar frameworks to establish partnerships among different stakeholders in public health and biomedical research could in principle drive new solutions to certain problems in medicine and biology, and we expect that intramural and extramural researchers funded by NIH and other agencies will be involved in many projects funded by ARPA-H.

However, there are features of the DARPA model that may create barriers to the effective recruitment and engagement of NIH-funded researchers. DARPA grants involve a great deal of administrative work, including detailed compliance and reporting requirements. Academic scientists already manage significant administrative workloads, and the integration of a DARPA-like grant management system may be insurmountable for many academic scientists and unintentionally limit the pool of candidates to a select group of researchers at well-resourced institutions. Program officials will be able to better foster collaboration among experts in different settings by implementing a more flexible compliance scheme with funded support for administrative

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requirements. We also note that biological problems we expect to be investigated by ARPA-H will necessarily require different approaches than the engineering problems typically investigated by DARPA and may result in unanticipated discoveries and new biological knowledge that require a change in direction or additional work in a new direction. Program officials should therefore understand and support a measure of freedom and flexibility for the unique complexities of biological research such as the importance of sex differences and gene by environment interactions.

2. On what areas should ARPA-H focus?

It will be important for leadership at ARPA-H to clearly communicate whether project deliverables are preferred to have specific, demonstrable effects or potential for broad impact. However, opportunities exist to bring together research teams with diverse expertise and professional backgrounds for both specific and targeted projects with near-term deliverables, as well as broader high-risk/reward projects that address cross-cutting priorities.

Several specific, targeted advances could be prioritized by ARPA-H to the benefit of patients with a variety of endocrine diseases, including diabetes which affects millions of Americans and drives substantial medical expenditures of over $230 billion per year, of which over half is paid by Medicare, Medicaid, and military healthcare programs. Teams of researchers devising better ways to measure the amounts of hormones and other analytes present in small concentrations could create a pathway towards real-time measurement of parameters used to diagnose and treat diseases or identify changes in hormonal levels due to disrupted signaling and accelerate the use of machine learning and for acute care of endocrine disorders. Advances in diabetes treatment specifically could be made by bringing computer scientists together with researchers and clinicians to improve the electronic security of the increasingly complex ecosystem of disease management devices such as continuous glucose monitors and insulin pumps, as well as improvements to the underlying mathematical equations driving these devices. Cheaper, safer, and more effective drug delivery systems (e.g., insulin and other hormones) could also have a significant impact on patient care. Importantly, successful advances in these areas may also drive broader solutions for medical devices used in the management of critical care patients and/or patients with chronic diseases that require vigilant management.

ARPA-H could also foster the development of more advanced technological solutions that build on the fundamental research supported by NIH. For example, innovations in healthcare systems could be achieved by accelerating development of point-of-care testing technologies to monitor biological responses to hormone replacement therapies. High-throughput systems could be developed using induced pluripotent stem cell technologies to identify new regenerative medicine-based therapeutic approaches to correct congenital abnormalities.

Finally, ARPA-H can foster interagency efforts related to the often-underappreciated role of the environment in health and disease. Environmental factors have significant influence on the development and severity of nearly all diseases including cancer, diabetes, reproductive disorders,

and neurodevelopmental disorders. ARPA-H could drive transformative change by fostering collaborations between researchers funded by FDA, NIH, EPA, and industry to develop better public health interventions to reduce hazardous exposures to carcinogens and endocrine-disrupting chemicals that are present across all regulated sectors, such as per- and polyfluoroalkyl substances (PFAS), which we are exposed to via food packaging materials, contaminated water, and other sources. Better models that integrate a variety of environmental factors along with lifestyle and social determinants of health to estimate health consequences of environmental exposures would advance public health goals through a focus on primary prevention; such work also has the strong potential to address health disparities. Near-term objectives for projects could include setting up the research infrastructure to collect and evaluate environmental data, with downstream objectives focusing on health outcomes pending successful development of the necessary research infrastructure.

3. What is the best way to ensure ARPA-H operates differently than the status quo?

For ARPA-H to truly be unique and different from the status quo, it will be critically important for ARPA-H to not compromise the excellent work that is conducted by NIH intramural and extramural investigators. For example, the diabetes-related projects described in the sections above should complement work already done at NIDDK without eroding yearly increases in NIDDK's annual appropriation. Funding decisions at ARPA-H should avoid excessive overlap with NIH projects, and NIH ICs should not be required to contribute significant financial resources to ARPA-H projects to preserve the investigator-initiated basic and clinical research pipelines that generates fundamental physiological discoveries and leads to new biomedical opportunities. Leadership at ARPA-H should prioritize projects, outcomes, and goals that are not typically funded through existing grant mechanisms, and officials at other research funding agencies, in particular NIH, will therefore need to be involved in the identification of projects.

An effort should be made to identify entire research domains and demographics that could benefit from innovative approaches and new partnerships. Populations that are typically underrepresented in clinical research, including pediatric patients, pregnant and lactating people, and minority populations, would benefit immensely from new, inclusive approaches to research that meets their needs. Biological transitions such as puberty and menopause offer tremendous opportunity to understand fundamental mechanisms that drive complex changes in the human body. All of these research domains would benefit from targeted basic research using animal models for health and disease as well as clinical research. ARPA-H can build on the previous successes of other research endeavors; for example, meta-analyses of research published following the implementation of the NIH Sex as a Biological Variable (SABV) policy could lead to new opportunities to improve women's health, and therapeutic interventions driving increasing cancer survivorship require us to develop long-term solutions to deal with endocrine and other complications due to cancer treatments.

In addition to funding different projects and using more flexible funding mechanisms, ARPA-H is also an opportunity to work with new partners. The role of academic investigators in projects should be clarified and project managers should be encouraged to explore partnerships with academic institutions and investigators that do not typically receive substantial federal funding. We also note that younger researchers, including those individuals interested in entrepreneurship or engaged in the NIH Small Business Innovation Research or Small Business Technology Transfer Research (SBIR/STTR) grant mechanisms often generate innovative research ideas and ARPA-H could create opportunities through proactive outreach to these scientists. Leadership and project managers should also design ARPA-H to incorporate diverse perspectives, with particular attention to groups that have been historically underrepresented in biomedical research, throughout the planning and execution of projects to maximize the benefit to society.

4. **How should ARPA-H partner with the private sector?**

While we appreciate that the private sector will need to be involved in ARPA-H projects where the anticipated deliverables will result in new cures and treatments, private companies should be encouraged to invest financial and human resources in projects. Project managers should establish transparent decision-making structures that prioritize scientific objectives over commercial success. We encourage HHS, NIH, and OSTP to further define potential partnership modalities and anticipated boundaries with the private sector so that we and other stakeholders can more knowledgeably comment on how such partnerships could be most effective.

5. **Additional Considerations**

We appreciate that many details regarding the operation of ARPA-H remain to be determined, and we welcome this effort to involve stakeholders early in the process. In addition to the questions posed in the RFI, we urge Congress, NIH, and OSTP to continue to explore the following considerations as ARPA-H takes shape to ensure that stakeholders are prepared to effectively contribute to project goals.

- The existing academic tenure and promotion process for biomedical researchers is heavily biased towards standard NIH grant mechanisms. Academic institutions should be engaged so that they can not only help reduce administrative burdens for researchers involved in ARPA-H, but also so that these projects are recognized in tenure and promotion decisions.
- The process to prioritize and fund projects will need to be carefully thought through and grounded in science – we urge Congress, NIH, and OSTP to build in safeguards to prevent undue influence from limited stakeholder groups, including political influence.
- While DARPA represents one model to fund biomedical research in a new way, we encourage Congress, the NIH, and OSTP to also examine outcomes from other approaches to biomedical research that have been funded e.g., through the Department of Defense or private foundations such as the Gates Foundation.

- Congress, NIH and OSTP will need to consider how success will be measured – it may be more practical to consider different approaches involving incremental achievements that may lead towards goals, for example understanding why cancer cells do not undergo apoptosis to generate pathways leading to new therapeutic approaches for cancer.
- ARPA-H represents an opportunity to design a biomedical research agency with foundational principles that incorporate diversity, equity, and inclusion. ARPA-H should ensure that diverse perspectives are heard throughout decision-making processes and researchers from all backgrounds, career/life stages, and professional settings, are empowered to participate in projects.

Our members are excited about the opportunities to advance biomedical research and address pressing public health priorities through ARPA-H, and there are many outstanding issues in endocrine science that would benefit from new research funding models. We look forward to continuing to engage with OSTP, NIH, and the Congress as this new initiative moves forward, and thank you for soliciting stakeholder input at this early stage. If we can be of further assistance, please contact Joe Laakso, PhD, Director of Science Policy at jlaakso@endocrine.org.

Sincerely,

Carol H. Wysham

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President, Endocrine Society