ASTRO
TARGETING CANCER CARE

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July 16, 2021

The Honorable Diane DeGette
2111 Rayburn House Office Building
Washington, DC 20515

The Honorable Fred Upton
2183 Rayburn House Office Building
Washington, DC 20515

Dear Representatives DeGette and Upton,

The American Society for Radiation Oncology (ASTRO), on behalf of our 11,000 members of the radiation oncology team, appreciates your bipartisan leadership on 21st Century Cures 2.0 and the opportunity to respond to your request for information on Sec. 501 Advanced Research Projects Agency for Health (ARPA-H).

Radiation oncology is a central modality in the treatment of cancer, with approximately two-thirds of cancer patients receiving radiation for cure and palliation of pain. Investments in cancer research, such as those you have spearheaded, have led directly to several critical improvements in cancer outcomes, including the development of advanced technologies that increase cure rates and reduce side effects among cancer patients. ASTRO is eager to partner with you and the Biden Administration to advance ARPA-H for the benefit of cancer patients. To that end, please find below our responses to your RFI questions:

(1 of 7) In calling for the creation of ARPA-H, President Biden has cited the success of the Defense Advanced Research Projects Agency (DARPA) and expressed his belief that ARPA-H should be similar. Please provide specific details on which aspects of DARPA ARPA-H should replicate and why this would lead to similar success.

DARPA has served to develop a large number of informatics/information transfer/data standards that allowed transformative communications (i.e. ARPANET, 1st wide-area packet switching network that became the Internet). Creating information standards could lead to a future where data is published within publications (as opposed to summaries of data), leading to massive fair and re-usable capacity that would transform healthcare.

(2 of 7) To ensure it has the biggest impact, on what activities or areas should ARPA-H focus? What activities or areas should ARPA-H avoid?

ARPA-H should focus on activities that are technology driven, rather than hypothesis-driven (e.g. NIH). This means an approach that favors collaborative/collective multi-PI efforts over single-site or single-PI projects. Open-ended developmental approaches should be favored over linear project timelines. ARPA-H should focus on projects that involve direct development of transferable annotation/informatics standards, so data sharing is an inherent component of projects, for both Findable, Accessible, Interoperable, Reusable (FAIR) and "real-time" science. ARPA-H should avoid priorities that are focused on a single hypothesis or "blockbuster breakthrough" mindset, and instead fund efforts that will result in new tools that scale across multiple disease states. For example, research that is focused on cancer should include integration of locoregional therapies that are used across multiple cancers, such as surgery, radiotherapy, and also include systemic approaches, rather than a single mechanism of action drugs designed for a single targeted use-case. ARPA-H should also include radiation therapy modifiers,

such as radiation sensitizers or protectors, in its portfolio and find ways to reduce radiation toxicity and genetics.

(3 of 7) Some assert ARPA-H's ability to operate independently and transparently will be essential to its success. Do you agree? If so, what is the best way to design ARPA-H in order to accomplish this?

Yes, we agree and believe that rigorous peer review should be a component; however, data has shown that peer review processes can be overly conservative. A transparent process also realizes that peer review is fraught with variability (viz. PMC5866547). Data suggest that a modified lottery system (PMC4959526), especially if paired with mandatory publication of both positive and negative results (PMC6689639), can represent a transparent scientific system, as it accounts for randomness, while still providing an initial peer-review threshold to ensure baseline rigor. We also suggest creating an External Advisory Board and resource team that reviews and transparently posts progress and failures, as well as proactively makes recommendations to mitigate conflict of interests. Term limits are another possible approach.

(4 of 7) How should ARPA-H relate to, and coordinate with, existing federal entities involved in health care-related research and regulation?

We suggest that ARPA-H be somewhat independent and work within the NIH in collaboration with NCI. Ideally, projects should be triaged in such a manner that, without undue reformatting, unfunded projects could be independently considered by the National Science Foundation (NSF) or National Institutes of Health (NIH) (similar to the joint NSF-NIH Smart Connected Health program). Additionally, dedicated DOE/DOD computational or "cloud core" support provision as a "data hub" that provides oversight and data sharing through a central data governance/central data & computational repository/central IRB would save considerable effort and regulatory burden. NIH/NCI could also direct projects to ARPA-H.

(5 of 7) What is the best way to ensure ARPA-H has a mission, culture, organizational leadership, mode of operation, expectations, and success metrics that are different than the status quo?

The ARPA-H leadership should include a diverse and inclusive leadership team, not only of senior scientists, but also "young guns". DARPA's major innovations were often sparked by junior team members. A leadership culture that selects diverse teams should include early-stage researchers as project leads, and senior personnel as facilitators, rather than a typical "leader-followers" or "PI-trainee" model. An innovative cultural approach predicated on a standardized communication/prioritization/dispute resolution practice (e.g. the classic Dutch "poldermodel", viz https://doi.org/10.1093/eurpub/ckz185.724 or the RAND corporations Delphi or "Estimate-Talk-Estimate" model, viz. PMID: 31335812) might be considered across all ARPA-H components. We also recommend APRA-H measure what matters, including the mode of operation and culture and team function. ARPA-H should consider a mechanism to file complaints and remove team members.

(6 of 7) How should ARPA-H work with the private sector?

ARPA-H should be protected from concerns regarding reimbursement, profitability or intellectual property (IP). Congress should consider how intellectual property issues that may arise in connection with ARPA-H projects will be addressed. Congress should also consider how Americans will be ensured

access to the products developed through ARPA-H projects. ARPA-H should work with the private sector, but balance industry's interest in making a profit.

(7 of 7) What is the appropriate funding level for ARPA-H? How do we ensure ARPA-H funding does not come at the expense of traditional funding for the National Institutes of Health?

The current NIH budget should not be reduced or impinged upon in any way, as it already represents a huge value to the entire nation. NIH/NCI funding should continue to increase at least at the rate of biomedical inflation. Funding for ARPA-H must be substantial and sustainable and separately funded.

Thank you for considering ASTRO's responses to the RFI, and we look forward to working with you on this important and promising effort. Please contact Margarita Valdez at 703-839-7382 or margarita.valdez@astro.org.

Sincerely,

Laura Thevenot

Laura I. Thevenot
Chief Executive Officer