Advanced Research Project Agency for Health (ARPA-H): Concept Paper[1]

Introduction

America has the most successful biomedical ecosystem in the world, which has delivered advances that not long ago would have been inconceivable, from drugs that unleash the immune system to eliminate certain cancers to highly effective COVID-19 vaccines developed and approved in a mere eleven months. Such advances demonstrate that we stand at a moment of unprecedented scientific promise. They also challenge us to ask: What more can we do to fully realize the promise by accelerating the pace of breakthroughs in medicine and health? How can we transform prevention, treatment, or cure of cancer, infectious diseases, Alzheimer's disease, and other diseases? How can we transform healthcare access, equity, quality, and reduce health disparities?

To seize the opportunity and the responsibility, President Biden recently proposed to create a new entity, the Advanced Research Projects Agency for Health (ARPA-H), within the National Institutes of Health (NIH) "to develop breakthroughs to pre-vent, detect, and treat diseases like Alzheimer's, diabetes, and cancer", requesting $6.5 billion in the fiscal year 2022 budget. The idea is inspired by the Defense Advanced Research Projects Agency (DARPA), which follows a flexible and nimble strategy, undeterred by the possibility of failure, and has driven breakthrough advances for the Department of Defense (DoD) for more than 60 years. To design ARPA-H, it is critical to understand what is working well within the biomedical ecosystem, where there are crucial gaps, and the key principles of DARPA's success.

Current Ecosystem

Progress in medicine and health in recent decades has been driven by two powerful forces: pathbreaking fundamental research and a vibrant commercial biotechnology sector.

Fundamental research is typically performed in university, nonprofit, and government labs, and is mostly funded by the federal government, largely through the National Institutes of Health (NIH). By steadily pursuing important fundamental questions in biology and medicine, scientists have made breathtaking progress in discovering the molecular and cellular mechanisms underlying health and disease — often suggesting new ideas for clinical treatment. Genetic studies, for example, have discovered the genes responsible for more than six thousand rare genetic diseases, opening prospects for gene transfer or gene editing therapies, and pointed to new potential targets for therapy in common diseases, such as cancer and Alzheimer's disease. Such fundamental research is what economists term a public good, in that it produces knowledge available to everyone and thus requires public investment. Some have estimated that every dollar of federal investment yields at least eight dollars in economic growth, and every new therapeutic approved by the U.S. Food and Drug Administration (FDA) can be traced, in part, to

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fundamental discoveries supported by NIH[2,3]. Given its outsized impact, robust federal investment in fundamental research remains crucial to both the health of the Nation and the American economy.

The commercial sector is largely focused on research, development, and marketing of specific products, to bring sophisticated therapies and devices to patients. Biotechnology companies have access to abundant capital to develop products — provided they can protect their intellectual property and recoup the costs by generating sufficient profit in a short enough period of time. Currently, more than 8000 medicines are in development, including 1300 for cancer[4,5].

In many cases, these two components are all that's needed to drive progress towards clinical benefit – though subsequent regulatory approvals, reimbursement, and adoption in healthcare systems can also be optimized.

It's becoming clear, though, that some of the most innovative project ideas, which could yield bold breakthroughs, don't always fit existing support mechanisms: NIH support for science traditionally favors incremental, hypothesis-driven research, while business plans require an expected return on investment in a reasonable time frame that is sufficient to attract investors. As a result, some of the most significant ideas may never mature, representing substantial lost opportunity.

Bold ideas may not fit existing mechanisms because: (i) the risk is too high; (ii) the cost is too large; (iii) the time frame is too long; (iv) the focus is too applied for academia; (v) there is a need for complex coordination among multiple parties; (vi) the near-term market opportunity is too small to justify commercial investment, given the expected market size or challenges in adoption by the healthcare system; or (vii) the scope is so broad that no company can realize the full economic benefit, resulting in underinvestment relative to the potential impact. Evaluations by companies also may not consider the impact of projects on inequities that persist in our health ecosystem. In short, projects with a potentially transformative impact on the ecosystem may not yet be economically compelling or sufficiently feasible for a company to move forward. At the same time, we lack public mechanisms to propel these public goods at rapid speed.

Many such bold ideas involve creating platforms, capabilities, and resources that could be applicable across many diseases. Whereas most NIH proposals are 'curiosity-driven', these ideas are largely 'use-driven' research — that is, research directed at solving a practical problem.

DARPA as an Inspiration

DARPA was launched in the wake of Sputnik with a singular mission: to make pivotal investments in breakthrough technologies for national security. By any measure, it has been successful in generating bold advances that have shaped our world. DARPA has played a key

[2] https://www.nih.gov/sites/default/files/about-nih/impact/impact-our-nation.pdf
[3] https://pubmed.ncbi.nlm.nih.gov/29440428/
[4] https://www.phrma.org/Science/In-The-Pipeline
[5] https://www.phrma.org/Report/Medicines-in-Development-for-Cancer-2020-Report

role in legendary projects, such as the Internet, Global Positioning Systems (GPS), self-driving cars, and has contributed to the development of many others, including messenger RNA vaccines. However, failure, especially failing early, and learning from that failure are also hallmarks of DARPA.

DARPA has a distinctive organization and culture that contrasts with traditional approaches in biomedical research. It is a flat and nimble organization whose work is driven by approximately 100 program managers (PMs) and office directors. The PMs are often recruited from industry or top research universities, and they come for limited terms of 3-5 years. They typically bring bold, risky ideas, and they are encouraged to pursue them, mitigating risk through metric-driven accountability and by pursuing multiple approaches to achieve a quantifiable goal.

It can support research at three stages (basic research, applied research, and advanced technology development); can fund efforts in multiple sectors (industry, university, national labs, and consortia across these sectors); can provide the critical mass of funding needed to tackle bold goals; and is empowered to promote collaboration and integration across performers. DARPA does not perform its own internal research. While proposals are reviewed on a competitive basis, PMs have authority to select a portfolio of projects intended to achieve a particular program goal.

DARPA has long encouraged a culture that values a relentless drive for transformative technical results and a willingness to take risks. Notably, it does not focus on merely accelerating ordinary products to the market or making incremental progress, but on creating true breakthroughs. To act in this way, DARPA makes broad use of flexible hiring, procurement, and contracting authorities, provided by law.

Although DARPA is an excellent inspiration for ARPA-H, it is not a perfect model for biomedical and health research. It serves the needs of a single customer, the DoD, and its mission is focused on national security. Its projects typically involve engineered systems. By contrast, health breakthroughs (i) interact with biological systems that are much more complex and more poorly understood than engineered systems, requiring close coupling to a vast body of biomedical knowledge and experience; (ii) interact with a complex world of many customers and users — including patients, hospitals, physicians, biopharma companies and payers; (iii) interact in complex ways with human behavior and social factors; and (iv) require navigating a complex regulatory landscape. ARPA-H can learn from DARPA, but will need to pioneer new approaches.

DARPA-like Approaches at NIH

NIH has some experience with running large, complex programs using DARPA-like approaches to drive highly managed, use-inspired breakthrough research. A classic example was the Human Genome Project, aimed at reading out the complete three-billion-nucleotide human genetic code. When the project began in 1990, the technology to accomplish the goal hadn’t been invented. By driving innovation, it was completed ahead of schedule and ultimately decreased the cost of

sequencing a human genome from $3 billion at the outset to $500 today[6]. While the exact estimates vary, it is clear that the overall economic return on investment has been enormous, with notable analyses estimating a nearly 180-fold return[7,8].

A very recent example is the NIH's response to the COVID-19 pandemic. Within weeks, NIH created two highly effective programs. The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) program is an unprecedented partnership with government, industry, non-profits, and academia to drive preclinical and clinical therapeutics, developing master protocols for testing prioritized compounds in rigorous randomized clinical trials. These efforts accelerated the development and testing of several of the vaccines that are now being widely used to help return the world to normalcy. The Rapid Acceleration of Diagnostics (RADx) program used an 'innovation funnel' approach to identify promising ideas for COVID-19 tests and support 32 new technology platforms that collectively are contributing 2 million tests per day, mostly at point-of-care[9].

Although these programs have been successful, they required bespoke solutions and herculean efforts to get them off the ground. Because NIH lacks a regular framework for such projects, many bold ideas are hard to realize. That's where ARPA-H can help.

Mission of ARPA-H: Breakthroughs from the molecular to the societal

ARPA-H should have a clear mission. Building on DARPA's mission statement, an initial mission could be: "*To make pivotal investments in breakthrough technologies and broadly applicable platforms, capabilities, resources, and solutions that have the potential to transform important areas of medicine and health for the benefit of all patients and that cannot readily be accomplished through traditional research or commercial activity*."

Notably, ARPA-H's focus should be broad—ranging from molecular to societal—because breakthrough technologies are needed and are possible at many levels (see Box 1).

[6] www.genome.gov/about-genomics/fact-sheets/DNASequencing-Costs-Data
[7] https://www.nih.gov/about-nih/what-we-do/impact-nih-research/our-society
[8] https://www.ashg.org/wp-content/uploads/2021/05/ASHG-TEConomy-Impact-Report-Final.pdf
[9] https://www.nibib.nih.gov/news-events/newsroom/radx-diversifies-covid-19-test-portfolio-four-new-contracts-including-one-detect-variants

Box 1. Examples of potential transformative projects that ARPA-H could drive:

Cancer and Other Chronic Diseases

- **Vaccines that can *prevent* most cancers**. Use mRNA vaccines to teach the immune system to recognize 50 common genetic mutations that drive cancers, so that the body will wipe out cancer cells when they first arise.
- **New manufacturing processes to create patient-specific T-cells to search and destroy malignant cells,** decreasing costs from $100,000s to $1000s to make these therapies widely available.
- **Molecular 'zip codes' that target a drug or gene therapy vector to any specific tissue and cell type**, to make treatments much more effective by treating diseases at their source and eliminating side effects due to effects in other tissues or cells.
- **Small, highly accurate, inexpensive, non-intrusive, wearable 24/7 monitors (e.g., smart watches) for blood pressure and blood sugar**.
- **New approaches to accelerate discovery of brain imaging and blood biomarkers** capable of measuring synaptic loss, neuronal death, and glial inflammatory pathways, as a means of tracking responses to potential Alzheimer's disease therapies.

Infectious Diseases

- **Ability to design, test, and approve a vaccine against any newly emerging human virus in 100 days**.
- **Ability to administer vaccines through a skin patch or oral spray, to allow rapid, massive vaccination campaigns**.

Healthcare Access, Equity, and Quality

- **Platforms to reduce health disparities in maternal morbidity and mortality**, which are among the highest in the world, by identifying those at highest risk for pregnancy complications and providing ethically-integrated, regular virtual house calls by nurses and midwives, from early in pregnancy through at least 6 months postpartum.
- **Platforms to promote better health outcomes through substantially improving how medication is taken**, as recommended, on a regular basis or over a standard course (e.g., for hypertension, diabetes, infections), by engaging community health workers aided by privacy-preserving smart devices and telehealth.

When President Biden challenges the nation to "end cancer as we know it", basic scientists naturally think about solutions at the laboratory bench: powerful ways to enlist DNA and RNA readouts, genetic regulation, novel chemistry, and the immune system to prevent, detect, and treat cancers. Technologists think about new sensors and AI-assisted medical decision making.

As importantly, though, there are also opportunities for highly impactful breakthroughs at the macro level to ensure equity in healthcare access and health outcomes for all patients. Equity considerations (including race, ethnicity, gender/gender identity, sexual orientation disability, and income level) must be woven throughout the ARPA-H mission — with some projects

focused directly at addressing equity and all projects considering equity in their design. Breakthroughs aimed at the least-served and most vulnerable groups are not only just and necessary, they will likely improve care for all patients.
ARPA-H's mission will clearly be different from the mission of the existing NIH Institute and Centers (ICs). For example, the name and mission of the National Center for Advancing Translational Sciences (NCATS), an NIH institute created in 2011, might suggest some overlap. However, NCATS' primary focus is to support a national network of clinical research centers and a drug screening hub. These two programs account for nearly 90% of its resources. A modestly sized component within NCATS, the Cures Acceleration Network, is aligned with the general directions of ARPA-H.

Similarly, the NIH Common Fund, a program created by law in 2007, is aimed at a different goal than ARPA-H's use-driven objective: It supports programs to explore new areas of foundational research that cut across multiple ICs—for example, the human microbiome effort. ARPA-H would also be distinct from other existing agencies, such as the Biomedical Advanced Research and Development Authority (BARDA), which focuses on medical countermeasures for public health security threats.

Designing ARPA-H: A Distinct Division, Culture, and Organization at NIH

ARPA-H should be housed as a division within NIH, rather than being a stand-alone entity, for two reasons. First, the goals of ARPA-H fall squarely within NIH's mission[10] ("*to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability*"). Second, ARPA-H will need to draw on the vast range of biomedical and health knowledge, expertise, and activities at NIH. Setting up ARPA-H within NIH will promote scientific collaboration and productivity and avoid unproductive duplication of scientific and administrative effort.

It is important to acknowledge, however, that a DARPA-like approach is radically different from NIH's standard mechanisms of operation and will require a new way of thinking. The creation of ARPA-H will benefit from transparency, accountability, and a healthy skepticism to ensure that the entity does not become a typical NIH institute.

Taking many features from the DARPA model, ARPA-H needs to have a distinctive culture, organization, authorities, leadership, and autonomy[11,12]. . ARPA-H's organization should be flat, lean, and nimble. The culture should value bold goals with big potential impact over incremental progress. The organization should lure a diverse cohort of extraordinary PMs from industry or leading universities, for limited terms, with the chance to make a huge impact. They should be empowered to take risks, assemble portfolios of projects, make connections across organizations,

[10] https://www.nih.gov/news-events/videos/nih-mission-its-about-life#:~:text=NIH's%20mission%20is%20to%20seek,and%20reduce%20illness%20and%20disability
[11] https://hbr.org/2013/10/special-forces-innovation-how-darpa-attacks-problems
[12] https://www.dayoneproject.org/post/how-to-unlock-the-potential-of-the-advanced-research-projects-agency-model

help clear roadblocks, establish aggressive milestones, monitor progress closely, and take responsibility for the project's progress and outcomes.

Projects should be bounded in time, typically a few years with longer periods allowed for efforts that are highly complex. ARPA-H should expect that a significant fraction of its efforts will fail; if not, the organization is being too risk-averse. The best approach is to fail early in the process, by addressing key risks upfront. To determine which risks should be taken and to evaluate proposed programs and projects, ARPA-H should adopt an approach similar to DARPA's "Heilmeier Catechism," a set of principles that assesses the challenge, approach, relevance, risk, duration, and metrics of success[13].

The ARPA-H director should have substantial authority to act. To keep the entity vibrant, the director should typically serve a single term of five years, with the possibility of a single extension in rare cases. For ARPA-H to accomplish its goals, it will need to be provided by Congress with certain authorities parallel to those provided to DARPA, including the authority to recruit, attract with competitive pay, and quickly hire for a set term extraordinary PMs.

Unlike DARPA's focus on a single customer, ARPA-H will need to create breakthrough innovations that serve an entire ecosystem and all populations. ARPA-H should have a senior leader responsible for ensuring issues of equity are considered in all aspects of ARPA-H's work—from scientific program development to staff recruitment and hiring.

Within the Department of Health and Human Services, it will be important for ARPA-H to collaborate with other key agencies—CDC, FDA, CMS, BARDA/ASPR, OMH, ACL, AHRQ, and HRSA—to identify critical needs and opportunities and to partner on complex projects that interact, for example, with public health infrastructure or medical regulation. DARPA should also play a role in advising ARPA-H on its experiences in driving breakthrough innovation and collaborating on specific projects of shared interest. And, it would be valuable to engage science-based agencies and departments, such as NSF, NIST and DOE.

It will be critical for ARPA-H to engage with the broader biomedical community, including patients and their care-givers, researchers, industry, community groups, and others, to understand the full range of problems and the practical considerations that need to be addressed for all groups and populations.

Conclusion

The potential opportunity before us is extraordinary. Through bold, ambitious ideas and approaches, ARPA-H can help shape the future of health and medicine in the U.S. by transforming the seemingly impossible into reality. Ultimately, ARPA-H will strive to propel us towards one goal: to directly improve the health of all Americans faster than was ever imagined to be achievable. The time to do this is now—we cannot afford to wait.

[13] www.darpa.mil/work-with-us/heilmeier-catechism