

ARPA-H: The Next Frontier of Biomedical Research

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Good morning, Chairwoman Eshoo, Ranking Member Guthrie and Members of the Subcommittee. Thank you for the honor of your invitation to present a statement before you today.

I am Keith R. Yamamoto PhD, Vice Chancellor for Science Policy and Strategy, Director of Precision Medicine and Professor of Cellular and Molecular Pharmacology at the University of California, San Francisco. I received a Bachelor of Science from Iowa State University and a PhD from Princeton University before migrating to San Francisco, where I have been on the faculty for 45 years. My molecular biology lab, which I recently closed, studied the detailed mechanisms by which small molecules made in our bodies, hormones, control important physiological processes such as metabolism, stress responses and immunity; that research has been recognized by my election to the National Academy of Sciences, the National Academy of Medicine and the American Academy of Arts and Sciences, and Fellowship in the American Association for the Advancement of Science, among other honors. In the course of that work, I had the privilege, pleasure and primary responsibility for mentoring approximately 100 PhD students and postdoctoral scholars. Our research was funded throughout by grants from NIH and NSF, as well as grants and fellowships from private foundations.

For my entire career, I have also been active in matters of science and public policy, leading or serving on dozens of committees focused on a broad range of issues, challenges and opportunities, including chairing or participating in 28 NIH advisory

councils, working groups, special initiatives, task forces and review panels focused on the operating principles and practices of that agency, and the investigator-focused culture that grounds every element of its function. I enjoyed the opportunity to interact with, and consult informally, with Dr. Geoffrey Ling, while he developed and directed the DARPA Biotechnology Office under an operating model very different from that at NIH. I also chaired the Board on Life Sciences for the National Academy of Sciences, which produced during that time two relevant reports, "A New Biology for the 21st Century" and "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease"; co-chaired a study committee for the American Academy of Arts and Sciences that authored a report, "Unleashing America's Research and Innovation Enterprise"; and currently co-chair the Science & Technology Action Committee, which is advocating for specific ways that federally supported science and technology can contribute bold solutions to existential societal challenges, including those in public health and healthcare.

These and other activities have provided me with a perspective on two related questions that I'll address today: [1] why, at this moment of spectacular fundamental discoveries about biological mechanisms and disease, most of them sponsored by NIH, should Congress establish yet another agency, ARPA-H; and [2] why should Congress act assertively to ensure that ARPA-H is fully independent, with authority to establish a culture, operating principles and practices that at first glance appear almost polar opposite to NIH's successful model? The answers to these two questions, in my view,

justify the title of this hearing, ARPA-H, the Next Frontier of Biomedical Research.

US science policy: fund university-based knowledge discovery and training

“Without scientific progress the national health would deteriorate; without scientific progress we could not hope for improvement in our standard of living or for an increased number of jobs for our citizens; and without scientific progress we could not have maintained our liberties against tyranny.” So wrote Vannevar Bush, President Roosevelt’s science advisor in 1945, in a pivotal report that set the framework for federal support of US science and technology. That policy directed government funding into *basic* research, the discovery of new knowledge that “provides scientific capital”, as well as training future generations of scientists. Industry, the report asserted, would then take over, innovating and developing the newly discovered knowledge into products from which they, and the American people, would profit. The companies would make money, and the people would enjoy a healthier, happier, more secure, quality of life.

In order to prevent, treat and cure diseases, for example, we needed first to understand more about biological processes – how molecules collaborate to make cells work, how cells specialize to form tissues, organs, organ systems, and how those systems interact to produce a healthy human being. And, what goes wrong in disease

Because we knew so little in 1945, *basic* research would be untargeted – we didn't know what we didn't know. And still today, there's vastly more unknown than known. So, the NIH strategy was to create a competitive funding program for university-based scientists and their trainees, giving scientists complete freedom to choose which biological process they wished to study, and to use their expertise and ingenuity to define their experimental approach, biological system, etc.

NIH set up a unique-in-the-world funding apparatus driven by peer review, in which working scientists volunteer to serve on committees that judge the merits of research proposals submitted by their colleagues, with those peer evaluations determining which would win funding needed to carry out the work. In this system, success is defined as new knowledge uncovered – and because not every idea is right and not every approach works, NIH funded research projects often deviate from proposed plans. Not infrequently, however, serendipitous observations take scientists down unanticipated paths to new knowledge, perhaps in an entirely different area of biology -- but new knowledge nonetheless. With enough trained scientists, each supported by NIH to pursue whatever biological process intrigues them, the gaps in our knowledge are being filled to create a progressively detailed picture of how biology works, and how it can go wrong.

This untargeted, peer review system is not perfect. First, those reviewers in their day jobs are the very scientists whose work has defined the prevailing paradigms – the

consensus opinions on how things work. So, they tend not to be supportive of bold ideas that challenge the conventional thinking. Second, working scientists tend to review favorably proposed experiments that seem the most likely to succeed, so risky studies, those taking on a big challenge or trying out an untested idea, are deprioritized relative to those that take small incremental steps. Finally, NIH-funded research projects advance slowly, with unexpected findings not infrequently diverting scientists into areas different from those proposed. Dr. Francis Collins, just retired after twelve years as Director of NIH, has acknowledged that the NIH process “is a little slow, maybe a little conservative, and it isn't necessarily going to embrace the really big transformative projects.”

Yet, despite its weaknesses, the NIH culture and operating model -- curiosity-driven, individual scientist-driven – is by any measure, the world's greatest knowledge discovery engine for biomedical research. Take the Nobel prizes, for example: three are awarded each year for fundamental scientific discoveries, considering scientists the world over – of the 230 Nobel prizes in chemistry, physiology or medicine that have been awarded, 99 have gone to 163 NIH-supported scientists. Astonishing dominance. The NIH knowledge discovery model works!

Federal support is needed for breakthrough applications of new knowledge

At first glance, it appears that our federal science policy has got it right – funding knowledge discovery seems sufficient to motivate private sector development of applications that serve society. For example, of the 210 new drugs approved by FDA between 2010 and 2016, pharma-driven development of every single one of them originated from new knowledge uncovered by NIH-funded research. However, the process is painfully, alarmingly slow. Among the 24 most impactful drugs on the market (as judged by a physician survey), the median time between the key bit of knowledge discovery and FDA approval was 32 years!

Moreover, severe underinvestment relative to potential impact leaves many ideas simply unpursued. Among the 9000 known human diseases, there are approved treatments for only about 500. Pharma and biotechs face many barriers: (i) perceived risk in the hypercompetitive global economy is too high; (ii) the near-term market is considered too small; (iii) the scope is so broad that no single company can capitalize on an opportunity and expect to realize economic benefit; (iv) successful development would require coordination across multiple sectors – industry, government, universities – to bring together the needed skills and resources.

Thus, federal science and technology policy must adapt to a new reality: profit motive is *not* sufficient for industry to fully fund the bold innovation and development needed to rapidly create applications of new knowledge that serve the public. Moreover, industry alone cannot and should not “go it alone” with these challenges. Government

support is required to de-risk industry participation, and government coordination and management is required to create multisector partnerships and teams capable of setting and meeting audacious milestone driven goals. Clearly, NIH's curiosity-driven, individual scientist-dependent, serendipity-redirectioned, peer review-governed culture and process, remarkably powerful as a knowledge discovery engine, won't suffice.

ARPA-H: Transformative Application of New Knowledge to Counter Disease

ARPA-H promises a culture and operating model very different from NIH. Its goals, strategies and outputs would not overlap or duplicate NIH efforts, but rather exploit NIH-discovered knowledge as a foundation for innovative development of breakthrough platform technologies, devices, therapeutics, diagnostics and preventatives. ARPA-H will deliver transformative advancements in health by building program-specific, transdisciplinary, multi-sector partnerships and teams -- de-risking industry participation in particular.

The teams will be assembled to achieve tightly-focused contract goals set and maintained by ARPA-H program managers, who themselves are in term-limited positions "on loan" from industry, government and academia, bringing urgency to the execution and completion of their stated goals. The teams will establish unique capabilities for developing and leveraging advanced technologies, powerful computational tools, novel

materials, revolutionary imaging methodologies and the like. Importantly, these efforts will be targeted to chronic and infectious diseases that sicken or kill hundreds of millions of people worldwide, and to countless rare diseases, which in aggregate, afflict many millions as well, but have not received needed and deserved attention, due in large measure to concerns over market-size. To be clear, the ARPA-H model will de-risk industry participation in development of treatments and cure of rare diseases.

For ARPA-H to succeed, Congress should provide both authorities and flexibilities that empower an ambitious, visionary director to construct a flat and nimble organization dependent on outstanding program managers, who themselves compete for and win appointment to the agency by defining an important but daunting health challenge, and a distinctive path to a breakthrough solution. Congress should ensure that the director and program managers are granted authorities for hiring diversity, contracting, cross-agency, cross-sector partnering, and ethical and efficient IP and tech transfer, and are appropriated sufficient funding to support their programs. Properly structured, these provisions will attract and resource powerful cross-sector teams willing to embrace bold, risky approaches, and willing to chance failure, in order to achieve transformational breakthroughs in health and disease.

In creating ARPA-H, it is essential that Congress recognize that NIH must continue to thrive for ARPA-H to succeed. Thus, safeguards should be put in place that prevent ARPA-H funding from supplanting NIH investment.

Finally, Congress would be wise to recognize that ARPA-H's success will depend upon its creation of a structure, culture, operating model and practices that differ dramatically from NIH, enabling it to take and overcome risks, to achieve breakthrough *applications*, rather than *discovery*, of knowledge. Program managers will envision problems at a different scope and scale than individual investigators, will propose radical solutions, and will recruit and build multidisciplinary teams that perform on and achieve milestone-driven contracts – all of that foreign to NIH's knowledge discovery approach.

To develop such a distinct culture and approach to problem visioning and solving, ARPA-H should be authorized as a free-standing agency within HHS, rather than as a component of NIH. Dr. Regina Dugan, former director of DARPA and now CEO of Wellcome Leap in the UK, where she is bringing an ARPA-like model and culture to biomedical research and development initiatives, has a clear-eyed perspective on the matter: "An organization like ARPA-H exists to challenge conventional wisdom. You shouldn't put it inside the very organization that holds the conventional wisdom." Dr. Dugan's intent here was not to denigrate "conventional wisdom", but rather to underscore that creating a new culture and operating model is difficult, but that developing a new culture within an existing, very different and highly established one may be impossible.

Thus, the specific actions of Congress in authorizing this agency will strongly

influence, if not actually determine, its success or failure. While this is not a legislative hearing, and it is thus inappropriate to delve into the details of a particular bill, let me say simply that the still-evolving legislation (HR5585) developed by Chairwoman Eshoo and her subcommittee wisely recognizes and takes into account the critical elements of independence, authority, culture, policy and practice that will place ARPA-H on a positive trajectory.

Perspective

ARPA-H is a concept for innovation, development and application of scientific knowledge that seeks to address points of weakness in our federal science and technology policy that have emerged since its establishment three quarters of a century ago. ARPA-H will consolidate new scientific knowledge, and will adopt risky strategies and approaches that, if successful, have the potential to extend and improve lives for all, including those long disadvantaged. Success of ARPA-H will depend on creation of a culture and operating model that attracts, de-risks and empowers innovative teams drawn from industry, private foundations, academia and government.

This concludes my testimony. I would be pleased to answer your questions or address your comments. Thank you again for the opportunity to consider this important matter with you.