Undeterred by the risk of failure

The proposal for an Advanced Research Projects Agency for Health (ARPA-H) being considered by the United States Congress is bold and necessary, yet will require unrelenting focus, independence and a measured risk-taking culture.

A passage from an article recently published[1] in *Science* highlights how the newly proposed Advanced Research Projects Agency for Health (ARPA-H) is being presented to the American public and the United States Congress: "ARPA-H should expect that a sizable 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." It is expected that Congress will support it and that it allocates the US$6.5 billion requested in initial funding.

The initiative is bold. It is also opportune in a world reeling from the acute shake-up brought about by a virus with an evolutionarily tuned balance between contagiousness and lethality. The pandemic caused by coronavirus disease 2019 (COVID-19) has placed before our eyes and minds the necessity of preparing our house for a healthier and more equal future. This urgency should help make ARPA-H a reality.

A sense of urgency focuses minds. And diverse teams of focused minds can move further and faster toward clear, specific and important goals. Yet this is not the typical mindset in basic research, where largely unguided exploration, persistence and patience can eventually be highly rewarding — as exemplified by the mRNA vaccines for COVID-19. But when pursuing ultimately unsuccessful paths or the wrong goals, too much persistence and patience result in unnecessarily wasteful efforts. In the private sector, incentives push for shorter timeframes and narrower goals; yet companies have financial constraints and duties, and ultimately are bound by the interests of their shareholders. Still, a government-funded 'fail fast, fail often' strategy relying on time-bound milestones — most typical of silicon-valley companies and less admired in academia — might be more efficient and rewarding for some well-defined problems.

And that's where the rubber meets the road. What sort of bold science projects are amenable to being sufficiently well defined for such a strategy to work? For the technologies and knowledge that made possible the most successful COVID-19 vaccines, could have they been developed and discovered faster or earlier if supported by fail-fast, high-risk–high-reward schemes? Maybe for next-generation sequencing technology, but it is unlikely that such a strategy would have worked for the chemical, biological and immunological knowledge underpinning the vaccines' lipid nanoparticles and mRNA payload. Figuring out how to 'hide' synthetic mRNA from the body's immune system is a much more open-ended problem than optimizing, formulating and scaling up a pharmaceutical product once the immunology involved is clearer. And the development of assays for measuring antibody levels is amenable to being easily defined and broken up into specific and predictable steps; pursuing such a strategy to work out mechanisms of antibody-dependent enhancement is probably futile.

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Mechanistic knowledge is enabling. However, finding solutions to pressing problems in medicine and health doesn't always need to wait for (or rely on) mechanistic understanding[2] — after all, we don't precisely know the mechanisms of action of many successful drugs; and many high-throughput technologies, such as drug screens and machine learning, increasingly allow for the exploration of a huge space of possibilities to find the 'hits', and to predict outputs from inputs without worrying about causality links. And dominant mechanistic hypotheses — notably, that beta-amyloid plaques cause Alzheimer's disease (rather than the plaques being caused by the disease, or the plaques and the disease having a shared unknown cause) — can exacerbate steady reams of scientific and clinical failures.

What practically definable biomedical problems may ARPA-H focus on? Eric

Lander, Francis Collins and co-authors, from the White House Office of Science and Technology Policy and The National Institutes of Health (NIH), briefly outline in their article[1] a few projects in chronic diseases, infectious diseases and healthcare equity. They refer to technology development for mRNA-based cancer vaccines, for affordable manufacturing processes of adoptive cell therapies, for targeted drug delivery, for wearables for health monitoring, for the discovery of better biomarkers for neurodegenerative diseases, for more easily administered plug-and-play vaccines, and for digital-health solutions that increase healthcare accessibility and equity. Early disease detection, the management of chronic diseases, the more precise delivery of drugs, biomarker development, and cheaper and faster platform technologies for manufacturing pharmaceuticals are all technology-driven areas that *Nature Biomedical Engineering* is also keen to help advance — incidentally, the content of this issue features assay-based technologies and wearable or portable devices for the diagnosis of cancers, infectious diseases and ophthalmic conditions. The journal routinely portrays how biomedical technology can be broadly enabling, across diseases and healthcare needs.

Technology development is a focus in the proposed mission for ARPA-H: "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."[1] ARPA-H is explicitly modelled on the Defense Advanced Research Projects Agency (DARPA), which focuses on technologies for national security. Judging by its undeniable success — it can claim credit for contributing to technologies powering the personal computer, the Internet, global positioning systems, drones, and even mRNA vaccines — it is reasonable to assume that the future fruits of ARPA-H may end up paying the investment in it many times over. But it is easier to fail fast and learn from the failures if early prototype technology can be tried in the real world: DARPA's rockets and machines can be sped up and tuned up, but we have less leverage with biological processes; and drugs, implants, assays, and medical software and hardware cannot be quickly tried out in patients or in real clinical environments.

Biomedical research and development needs to be more aggressive in addressing the health issues and health inequities of our time; but the NIH seems to be funding high-risk proposals less frequently[3]. For ARPA-H to take off strongly, it is sensible that it draws on knowledge and resources from the NIH, and that it is allowed, undeterred, to adapt DARPA's "flexible and nimble strategy", flat organization and risk-taking culture[1]. It will indeed need to build a culture that works for the possibly higher failure rates and the regulatorily constrained longer-term challenges that it will have to face. ❐

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