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Changing the Business of Breakthroughs

A new worldwide network of scientists and engineers is demonstrating how philanthropy can leverage a highly effective innovation model to solve urgent global problems.

History tends to turn scientific breakthroughs into stories of lone heroes in which individual researchers doggedly pursued a new discovery or charismatic leaders pointed to the horizon and made massive investments at scale.

What these accounts miss, however, is the reality that solutions to complex problems—and the resulting breakthroughs—more often require a network of diverse contributors with the capacity to drive the work toward a common goal. It isn't only about applying resources; it's also about creating the structures required to deploy those resources to facilitate such a synchronized effort. What's needed to achieve more breakthroughs faster are new ways of working that systematically stack the odds in favor of success.

A case in point has been the development of mRNA vaccines—arguably one of the most important scientific breakthroughs of recent decades. The trauma and upheaval of the past two years have laid bare how much work has to be done in health, equity, and care for the planet. These years have also revealed the difference a single breakthrough can make. Importantly, the pivotal decisions and investments needed to advance mRNA technology and shrink the vaccine development process from years to months were not made at an expansive federal science agency like the National Institutes of Health, in a global pharmaceutical conglomerate like Pfizer, or even by a swashbuckling venture capital firm.

The technology was seeded at a place purpose-built for breakthroughs: the relatively small government agency called the Defense Advanced Research Projects Agency (DARPA), operating with only 0.5% of the Department of Defense budget and a staff of about 250 people.

Few seem to remember the moment now. But we do, because we were there. At the time, we ran DARPA for President Obama. It was one year after the H1N1 pandemic, and he was determined to make sure another pandemic wouldn't catch America by surprise. Inspired by that, a clinical geneticist and young DARPA program manager named Dan Wattendorf came to us with two important questions:

> *What if a novel pathogen causes a global pandemic that forces the world to stand still, and we can't wait years for a vaccine?*
>
> *And what if mRNA injected directly into the body to elicit vaccine-level antibody production could dramatically shrink the standard timeline for vaccine development?*

It was 2010, a year when the world was still reeling from a deep recession, and most of the public and private sectors were unwilling to invest in such questions, much less make a bet on a once-in-a-century pandemic. Moreover, there were many people in the scientific community who contended there was simply no evidence it would work.

Wattendorf argued there was no evidence that mRNA vaccines *wouldn't* work and that if they did, someday it would matter. That day came ten years later.

These types of anticipatory decisions and investments are encouraged at DARPA, where programs are designed to intersect what is possible—albeit perhaps not yet proven—with what matters. By encouraging such "what if" thinking, DARPA fosters exploration and the subsequent actions required to create breakthroughs that provide new options.

We greenlit the program, and work began that year. At the time, Moderna was in start-up mode with a handful of people, and other performers were brought in to start working on delivery and scaling in parallel. Working all elements necessary to demonstrate a breakthrough is part of what DARPA does, because a demonstration at a sufficiently convincing scale is what changes minds. Such programs must move quickly to generate a sense of momentum, be agile enough to enable collaboration across disciplines and organizations, and work toward a goal that is bigger than any one individual so as to unite all involved in pushing past obstacles.

Although DARPA was designed specifically to serve US strategic interests, we are convinced that its model can be retooled to increase the number and pace of breakthroughs needed to address global challenges. Putting such an entity in place requires new approaches that go beyond national borders, beyond the boundaries of basic vs. applied research, beyond the life sciences vs. the physical sciences, and, perhaps most critically, beyond public vs. private funding.

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A model that stacks the odds

After the 1957 launch of the Soviet satellite Sputnik, President Eisenhower created DARPA to ensure that the United States would never again be caught unprepared by strategic surprise. The agency's model was an expressly new structure devised to facilitate seemingly impossible breakthroughs by providing the conditions that make such revolutionary advances possible. Notably, the enduring attributes of the DARPA model don't guarantee a breakthrough; rather, they are designed to improve the odds of getting one.

First, every program has an ambitious goal that is also testable and measurable, since it must be possible to tell if the program succeeds or fails. Program goals articulate and focus on a specific new capability or a specific problem that needs to be solved.

This clarity in the goal enables the second attribute: a coordinated network of diverse, multidisciplinary teams from multiple organizations, all working together to solve a problem they cannot solve alone. Importantly, it is rarely, if ever, true that all the expertise or all the advances needed to achieve a breakthrough are resident in one laboratory or organization. This network, crucially, is not static, but is agile and dynamic. Tasks change as progress is made or setbacks are encountered, and the team that set out to reach the goal may not be the team that achieves it. This attention to network effects contrasts with more conventional approaches that tend to fund individuals or small teams working in isolation.

Unifying these temporary project teams is a key responsibility for the program manager, who is central to the whole process. Just as an agile, dynamic orchestra of performers needs a conductor, the program manager pushes, encourages, clears obstacles, and synchronizes the entire effort both scientifically and programmatically. Inputs from the team are important, and collaboration is necessary, but decisions are made by the program manager to avoid groupthink, conventional wisdom, and conservatism that could stymie progress.

Finally, breakthroughs demand a sense of urgency, and a deadline provides it. DARPA projects are given three to five years to solve a problem or create a new capability. Such a timeline sparks a shared and celebrated impatience that forces the team to focus on the big advance and edit away paths that might make modest progress but fail to achieve the goal. In a three-year program, if two weeks go by without progress, you've already lost 1% of your time. That exigency tends to make people intolerant of unnecessary delays or process creep.

Over the past six decades, DARPA's model has proved itself again and again by delivering advanced technological breakthroughs, including miniaturized GPS, microelectromechanical systems technology, stealth technology, the internet, lasers, night vision, and autonomous vehicles.

Catalyzing global problem-solving

It's abundantly clear that the looming threats of today, such as pandemics and climate change, don't recognize national borders. Much as Sputnik highlighted that business as usual wasn't sufficient to meet the needs of national security, business as usual is not sufficient to solve these big, global challenges.

Instead, it will be necessary to bridge gaps not only between disciplines and organizations, but also among national, governmental, academic, and commercial innovation systems. Such an effort in the global commons requires investment capital and independent leaders who can operate without the constraints imposed by existing national systems—a task for which philanthropy is well suited.

While it is difficult for governments to act globally and the private sector cannot bankroll health investments that lack clear financial returns, independent philanthropy can step into this void. And at a time when humanity is in urgent need of action, philanthropy can act quickly, without concern for election cycles or the lengthy process of realigning political will and global economic incentive structures. Independent philanthropy has the ability—even the duty—to actively hunt for the dramatic advances that current and future generations need.

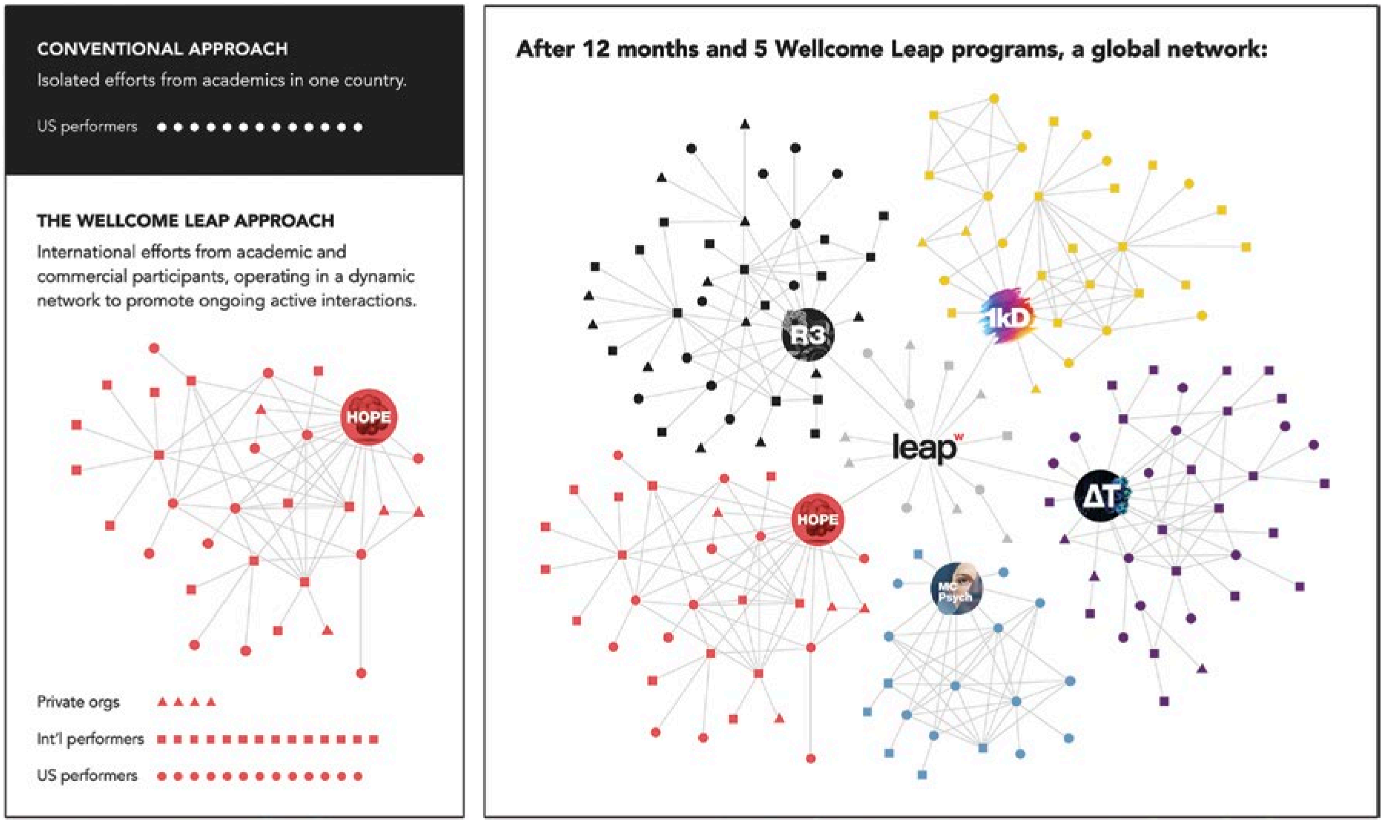
In 2018, Wellcome, a storied global philanthropy focused on health, saw a need emerging for a new entity that could tackle huge global challenges in health. The leadership of Wellcome funded the effort, called Wellcome Leap, and launched it in 2020. Importantly, they hired an experienced leadership team and then gave us and our fellow team members the freedom to operate differently. We were given the mandate to create an agile, ambitious new organization with program goals, funding structures, risk tolerance, and timelines more like the DARPA model and less like conventional research activities. Such a system isn't always comfortable, and that was the point. If you want to build an organization that challenges conventional wisdom, you cannot be surprised when it challenges conventional wisdoms.

Building dynamic networks

Like DARPA, Wellcome Leap stacks the odds in favor of breakthroughs. But to operate globally, we had to reimagine how some of the DARPA attributes—goals, networks, program managers, and deadlines—work in a global context.

The ability to build dynamic networks, not in one country, but across the entire global commons, started with what we

Figure 1: WELLCOME LEAP'S GLOBAL NETWORK



The first Wellcome Leap program that was launched, the Human Organs, Physiology, and Engineering—or HOPE—program, selected 31 principal investigators (PIs) and co-PIs. The typical approach would have been to give awards only to academic investigators in a single country (only 13 were from the United States), working in isolated efforts. In contrast, the program director selected from an international pool of academic and commercial performers. The program director then synchronized these efforts, adding or subtracting participants in the network, and facilitated cross-team activities—all in service to the goals of the program. The bottom left image shows the result of this approach for HOPE, reflecting actual interactions happening between teams in the HOPE program as the networks change over time. The global networks for each of the other five current Wellcome Leap programs is depicted at right.

understand in retrospect was a door-to-door grassroots effort. We spoke directly to university chancellors, chief executive officers, and nonprofit organization leaders around the world to give them the context of the network we wanted to build. We explained our hypothesis—that breakthroughs require a sense of urgency and momentum in a team—so we needed to get teams working.

We knew the biggest obstacle to speed and momentum was contracting. Therefore, we asked leaders of this new network to pre-sign a master funding agreement—not to secure an edge in selection or guarantee any funding, but to enable the rapid formation of networks of researchers. The pre-signed contract does offer a key advantage to institutions that are selected because it means that anyone in their organization could be funded and working in days or weeks instead of the usual months or even a year it can take to complete contract paperwork in other organizations. And if an organization is not a signatory when selected for funding, we ask them to sign as the first step in contracting. To date, all have done so.

We didn't know if such an approach would work, but within the first year, 21 organizations on six continents had signed. Today, the number of organizations has quadrupled to more than 80. The resulting Wellcome Leap Health Breakthrough Network is arguably the largest, most readily "activatable" network in the world, encompassing more than 650,000 scientists and engineers globally. This type of grassroots effort doesn't work unless the appetite to work in this dynamic way on a global level is already there: we simply found a way to facilitate it.

The excitement quickly bore fruit. When we made our first program announcement (about eight months after standing up Wellcome Leap), we received 164 proposal abstracts from 21 countries. For all subsequent programs since, we've seen similar and growing international interest and participation in proposals and, ultimately, in selections.

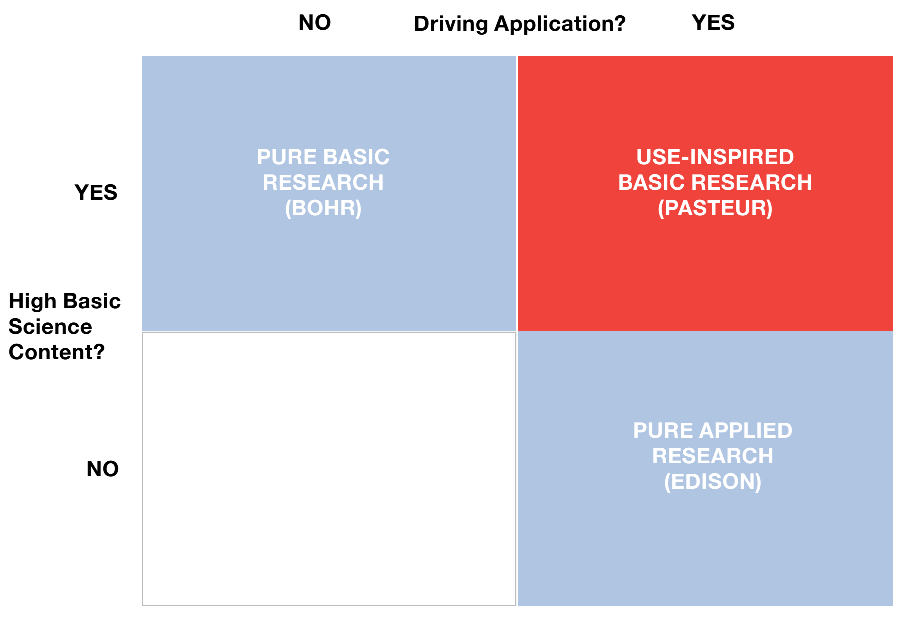
Wellcome Leap's commitment to clearing obstacles has allowed it to move at extraordinary speed. A mere 30 days after making the first announcement, we received abstracts. Within two weeks, we provided feedback and recommendations for submission of full proposals. Proposers then had 30 days after receiving feedback to submit a full proposal, and we made funding decisions 30 days after that. What this means is that while other models might take more than a year for a project to actually begin, we're off and running in under 100 days from the program announcement.

Another important attribute that Wellcome Leap shares with the DARPA approach is that we do not use a consensus-based peer review process that requires rank ordering. Instead, we evaluate every proposal's ability to contribute to the specific goals outlined in the program announcement. That is the benefit of having a specific goal in mind: it provides a point of view for decisionmaking. Each program director chooses specific program goals and activities using an analytic framework. Because the program managers put in the work to form this point of view, they have the conviction required to make confident selections and adjustments along the way.

Interestingly, we have also found that not requiring a consensus process creates more diverse teams, linking early-career researchers, established researchers, and researchers across the academic, nonprofit, and commercial spectra. Our method tends to elevate young investigators with new ideas that challenge the conventional wisdom in ways that consensus peer review does not—in part because it isn't necessary to have proof that new ideas will work before they try.

This kind of risk tolerance is, counterintuitively, facilitated by our use of contracts rather than grants. We can agree, together, to take a shot at something in year one. If it works, we can make the decision to fund years two and three. If it doesn't, we can shake hands and part ways with the knowledge that it was worth the attempt. Our firm belief is that this process also allows us to spend less time trying to make perfect decisions at the proposal phase. The proposal, after all, is not the work; the work is the work. This belief has the ultimate effect of suppressing "grantsmanship" and elevating the outcome—the breakthrough itself—as the measure of success.

Figure 2: **STOKES'S THEORY OF BREAKTHROUGHS**



> Philanthropy can act quickly, without concern for election cycles or the lengthy process of realigning political will and global economic incentive structures.

Choosing Pasteur's quadrant

Perhaps the single most common question we are asked about the model is not about the program construct or its execution, but how we choose a program in the first place. Wellcome Leap has an unwavering commitment to work in what political scientist Donald Stokes described as "use-inspired research" in his 1997 book *Pasteur's Quadrant*. Work in Pasteur's quadrant, exemplified by the microbiology research of Louis Pasteur, is mission-driven, designed to create a new capability or solve a specific problem. Unlike pure applied research, work in Pasteur's quadrant requires the simultaneous advancement of science to create a new solution. And unlike pure basic science, which is curiosity-driven but need not have a specific application in mind, work in Pasteur's quadrant needs a bold goal to focus the work and unite a diverse set of performers.

This commitment drives every Wellcome Leap program to the same kind of "what if" thinking of DARPA programs. And although the first six programs we've launched over the past two years differ in program goals and focus, they share the attribute of being grounded in creating new solutions. A few representative examples are the following:

> *What if we could cultivate human tissue so that no one had to wait on an organ donor list?*
>
> *What if we've been approaching the first three years of a child's cognitive development all wrong, and a new way would lead to healthier, more productive lives?*
>
> *What if the treatment of depression didn't have to feel like rolling the dice?*

Although no program has yet completed its full three-year timeline, early and emerging results are showing progress toward meeting goals in several areas. Work on 3D printing of kidney organoids is now sufficient to conduct early studies in animal models. Teams of commercial and academic researchers are collaborating on state-of-the-art data pipelines to feed new models of cognitive development. A project focused on understanding how diseases progress shows promise for dramatically increasing the speed of single-cell imaging from a weeks-long, process-intensive task using expensive equipment into an hours-long task doable on widely available gene sequencers. And a fourth project has demonstrated a 100-fold reduction in the dose—and cost—of mRNA-based monoclonal antibodies that can be used to treat viral infections.

Transforming for the future

In the coming decades, science policy needs to transform and adapt to attend to the big questions facing humanity and with the urgency they demand. Some people will say this is too hard. Or they will argue that the scientific research community should simply do more of what it's been doing because that's safer. This kind of inertia is the enemy of possibility—it makes global challenges such as human health and climate change seem too big. It makes politics seem too small and the public too mired in a fog of distrust, disinformation, and deepening cynicism to believe in the ability of institutions to solve such problems.

To meet these challenges requires seeing beyond borders, disciplines, and barriers to begin actively changing the way science is done, as well as the way it's funded. At this time, independent philanthropy has the ability to do what others cannot: take an unconventional and optimistic view of what's possible in order to act on behalf of future generations.

Our team built Wellcome Leap to harness global collaboration and find solutions to humanity's urgent needs. But also to create something else we need: hope. We see multiple generations disillusioned by institutions that tell them to set their sights lower, temper their expectations, accept the way things have always been done. They deserve somewhere to put their efforts and their faith. That faith must be rewarded, not with promises but with progress—one breakthrough at a time.

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