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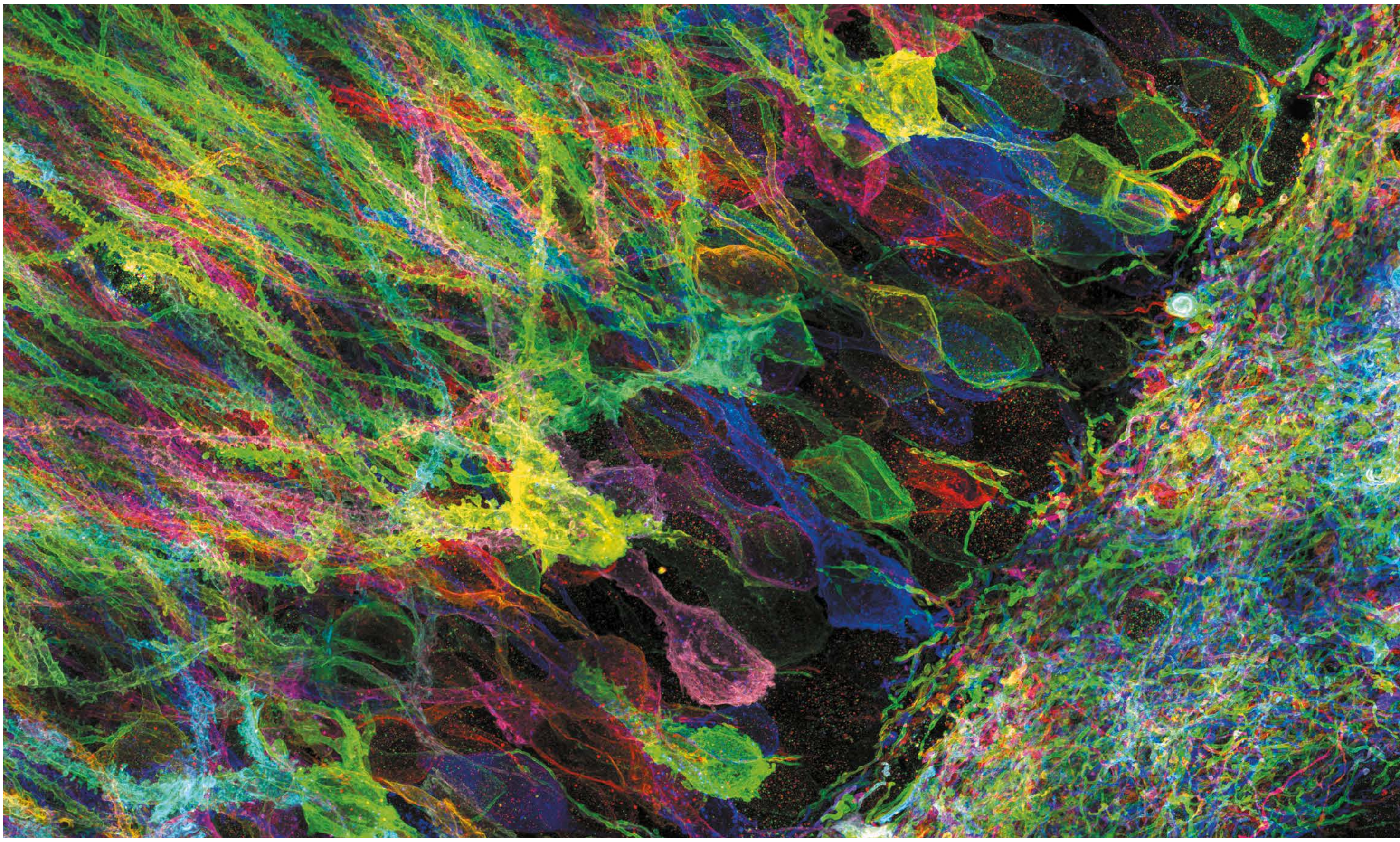


Mouse neurons imaged using a method similar to one being developed as a high-throughput tool by a focused research organization.

Unblock research bottlenecks with non-profit start-ups

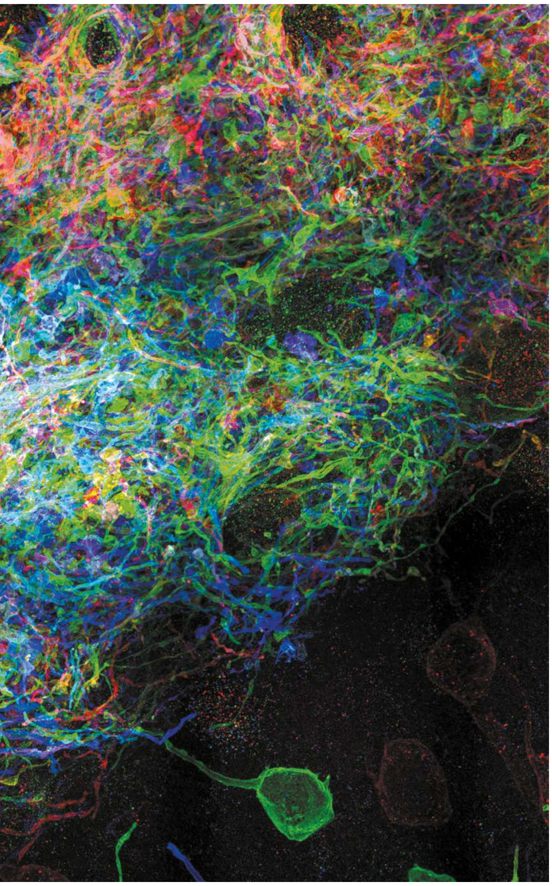
Adam Marblestone, Anastasia Gamick, Tom Kalil, Cheryl Martin, Milan Cvitkovic & Samuel G. Rodriques

'Focused research organizations' can take on mid-scale projects that don't get tackled by academia, venture capitalists or government labs.

It takes more than a great idea to accomplish a great project. Our research and experience have convinced us that many worthy projects wither or are never launched because neither academic laboratories, start-up firms nor government facilities can support them.

This applies particularly to projects that would produce public goods, such as data sets or tools, that could make research faster and easier. Few research-enabling projects will be commercially viable enough to attract venture capital. Nor is academia a suitable incubator. Academics can rarely muster the time, focus and workforce coordination needed to turn a proof-of-principle technology into a robust, scalable technique or to transform a research project into a platform. These engineering improvements do not fulfil teaching requirements or provide the papers or pizzazz that both senior academics and their trainees need to propel their careers.

A type of non-profit start-up could be a better way to support projects that enable research. These would have full-time scientists, engineers and executives, and total funding



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of about US$20 million to $100 million that would last around 5 years — longer than most grants or venture-capital funding rounds allow. And they would be set up to pursue predefined milestones, such as improving the resolution of a measurement system by tenfold, or gathering a pre-specified amount of data. We call them focused research organizations (FROs).

Fledgling FROs

FROs are conceptually similar to grand projects established to support ambitious and charismatic initiatives. The Human Genome Project, the Large Hadron Collider at CERN (Europe's particle-physics laboratory near Geneva, Switzerland) and the Hubble Space Telescope come to mind. Other examples include large data-collection projects such as the Human Cell Atlas, ENCODE (the Encyclopedia of DNA Elements) and the BRAIN Initiative Cell Census Network. Each of these produced research resources that are now considered essential for routine work.

But such grand projects are one-off, once-a-decade efforts that require feats of coordination and consensus, not least because most work is usually done by academics who are employed not by the project, but by their own research institutions. The Human Genome Project, for instance, cost $5.4 billion in today's dollars and took almost 13 years. The FRO model would support a steady stream of smaller-scale projects that could be launched with much less effort.

How did we arrive at this idea? Starting in 2014, two of us (S.G.R. and A.M.) began working on efforts to establish non-academic projects in brain-mapping technology and realized that no suitable organizations existed. We then interviewed more than 100 people who had developed research-enabling tools (administrators and researchers at university, government, corporate and military labs, as well as entrepreneurs). What hampered their work? What did they think of the FRO idea? In May 2021, a workshop on national networks of research institutes, sponsored by the US National Science Foundation, vetted the concept and explored new models of institutional innovation that could lead to the next generation of science institutes and FROs. (C.M. was a co-organizer of that event.)

In October 2021, after months of ideation, review and design work, three of us (A.M., T.K. and A.G.) launched an incubator to support FROs, called Convergent Research (where M.C. also works) in Arlington, Massachusetts. It is part of the Schmidt Futures Network, which aims to help scale and diversify the funding sources of promising early-stage initiatives supported by Schmidt Futures, a philanthropic organization headquartered in New York City. We also helped to launch two philanthropic FROs with the support of Schmidt Futures, and a third effort supported by the non-profit Astera Institute in Berkeley, California. The proposed 'products' include high-throughput brain-mapping techniques, tools to engineer non-model microorganisms and comprehensive analysis of ageing interventions in mice. The projects have begun to hire core technical staff and recruit advisory boards. Each has secured its own lab space and purchased initial equipment. Experiments will begin early this year.

In a few years, we'll learn whether these FROs can accelerate research in neuroscience, synthetic biology and longevity. We will also test how well FROs support the overall goal of enabling research.

Industry innovation

In the second half of the twentieth century, Bell Labs, Xerox PARC and other large US corporate labs famously merged aspects of fundamental research with large-scale product development and manufacturing (see 'Innovation invented'). They are credited with introducing laser printers, photovoltaic cells in solar panels, the programming language C++, transistors and more. Such innovation continues, as shown by the success of Alphabet's subsidiary Google DeepMind in developing its AlphaFold algorithm for predicting protein folding just last year. Overall, however, most industry labs today lack the freedom to pursue projects that are divorced from nearer-term commercial objectives, and the resulting knowledge is often kept proprietary.

The Defense Advanced Research Projects Agency (DARPA) model is widely, and reasonably, considered an exemplar of institutional innovation. It identifies highly specific technological needs and charges research groups with fulfilling well-defined tasks[1]. The United States has extended this model to other Advanced Research Projects Agencies: ARPA-E for energy and IARPA for intelligence-related projects[2].

Several other DARPA-like agencies have been created in the past year or are under discussion. These include ARPA-C (climate) and ARPA-H (health) in the United States[3]; the Advanced Research and Invention Agency in the United Kingdom; and Wellcome Leap (focusing on global human health). Others are Actuate, a US non-profit organization that will "create breakthroughs" for complex societal problems, led by former DARPA director Arati Prabhakar, and PARPA, a 'private ARPA' effort focused on space and Earth technologies. Launched by the technologist Ben Reinhardt, PARPA will support work that is "too researchy for a start-up and too engineering-heavy for academia" (see go.nature.com/3h6idjy).

ARPA-like programmes do many things that FROs should also do. They focus on technical milestones that are challenging. Programme managers have the power to start up, and shut down, high-risk projects. And DARPA deliberately plans for projects to end in a finite time and for resulting technologies to move to broader applications. But the ARPA model still relies on researchers who are employed elsewhere. This means that, within companies, projects can fail when they are not aligned with the company's main focus. ARPA projects in academia can struggle when they are not aligned with a lab's need to generate publications.

Some organizations are set up to take on tightly specified government- or industry-sponsored applied-engineering projects. Research institutions with this purpose include the non-profit SRI International in Menlo Park, California, the Fraunhofer Society institutes in Germany and the Battelle Memorial Institute in Columbus, Ohio. The European Union has a mechanism called the European Innovation Council Accelerator that makes mid-scale investments in 'deep tech' start-ups. Germany's Helmholtz Association enables large partnerships between a Helmholtz Centre and a university, bringing more-scalable resources to basic science, as do similar institutes elsewhere.

Some permanent institutes, such as the Allen Institute for Brain Science in Seattle, Washington, or the Howard Hughes Medical Institute's Janelia Research Campus in Ashburn, Virginia, are distinct enough from academia to conduct large-scale data collection and to develop broadly used tools. For example, the Allen Brain Atlas established a technique that can be used on an industrial scale to map gene expression across the mouse brain, standardized such that data from many experiments are easily unified. Likewise, a Janelia team developed a systematic, industrialized approach to produce a fluorescent calcium indicator protein that allows neuroscience researchers worldwide to record when neurons fire in the brain. This came from a project called GENIE (Genetically Encoded Neuronal Indicators and Effectors).

Janelia separates its large-scale projects, which are professionally staffed and managed, from its academic research projects. The latter are staffed by students and postdocs in small labs led by principal investigators. But such institutes are few and expensive, and are difficult to create. Furthermore, their nimbleness is hard to sustain. Janelia's first director, Gerald Rubin, wrote in 2019 that "without an opposing force provided by management, there is a slow, steady drift toward a more conventional environment increasingly focused on maintaining successful programs and documenting individual achievement at the expense of risk-taking and collaborative, interdisciplinary work"[4].

Expanded playbook

Our goal is to create a model to support an ecosystem of small- to mid-scale projects that fall between the cracks of what start-ups, academia and other organizations do. Start-up companies have a standard playbook involving business agreements and pitch meetings. Academic funding has standard requirements such as CVs and project proposals. We hope to develop a similar playbook as we monitor our FROs. This will make future launches easier.

Projects that can be achieved through start-ups or in an academic lab should be done in those ways – the existing infrastructure is vast and fit for purpose. The mission of each FRO should be to get technologies or data sets deployed quickly so they can be used effectively across the research community.

That means FROs should move beyond academic proof-of-concept into standardized systems that don't rely on graduate students to fix glitches with tweezers and tape. For example, an FRO might have a milestone both to develop a technology and to demonstrate that independent labs can implement it. It should have time-bound milestones unrelated to academic publishing, and strong project management to help achieve them. Training students or aiming to become a permanent institution must not be part of the mission.

There are known and unknown hurdles to the FRO model. One key question is how to maintain strong relationships and interactions with existing academic efforts that might have planted the seeds for an FRO. Another is how to get logistics in place and a lab running quickly, as well as smoothly establishing partnerships with other organizations, where needed. And finally, crucially, we need to learn how to ensure that resources developed in FROs are applied to meet real needs.

"Although some of the organizations will fail, others will make research more powerful and efficient."

Perhaps semi-permanent teams of project managers and administrators can be matched with scientific staff from the start, essentially serving as hosts for a focused scientific leadership team. Other questions involve career progression, including what will lure talent away from academia or the potential financial returns of a start-up, and how to enable strong, post-FRO career options for all staff.

These are questions we will have in mind as we track the FROs that were launched last October, and as we iterate, launch more FROs and expand the base of philanthropic support. We and others hope to develop the model to a point at which governments could set goals to fund a certain number of FROs each year, confident that, although some will fail, others will make research more powerful and efficient.

The US National Institutes of Health, DARPA, the National Science Foundation, venture capitalists, US National Laboratories, the modern research university, and every other institution that advances science and technology are human inventions that can be refined with experience and experimentation. We believe the same will be true of FROs.

INNOVATION INVENTED

Selected launches of institutions that support research.

1925: Bell Telephone Laboratories set up in the United States for fundamental research in communications.
1933: US Rockefeller Foundation funds molecular-biology initiative.
1942: US government launches Manhattan Project to develop nuclear weapons.
1958: Advanced Research Projects Agency (ARPA) founded by US government to advance military technologies.
1970: US laboratory Xerox PARC emerges from early computer-research communities convened by ARPA.
1972: ARPA renamed Defense Advanced Research Projects Agency (DARPA).
1976: US biotechnology firm Genentech founded with venture capitalists.
1990: Human Genome Project launches. Governments invest billions.
1998: Europe's particle-physics laboratory CERN begins construction of the Large Hadron Collider near Geneva, Switzerland.
2006: HHMI Janelia Research Campus opens in Ashburn, Virginia, to pursue neuroscience in a collaborative way.
2008: Large Hadron Collider starts up.
2009: Advanced Research Projects Agency–Energy (ARPA-E) founded to focus on energy challenges using the DARPA model.
2016: Francis Crick Institute opens in London. It has strong links with universities and provides internal funding.
2018: European Innovation Council pilot launches to support commercialization of high-risk, high-impact technologies.
2021: Institutional experimentation in science, including launch of the first focused research organizations (FROs).

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The authors declare competing interests, see go.nature.com/3jft8da for details.