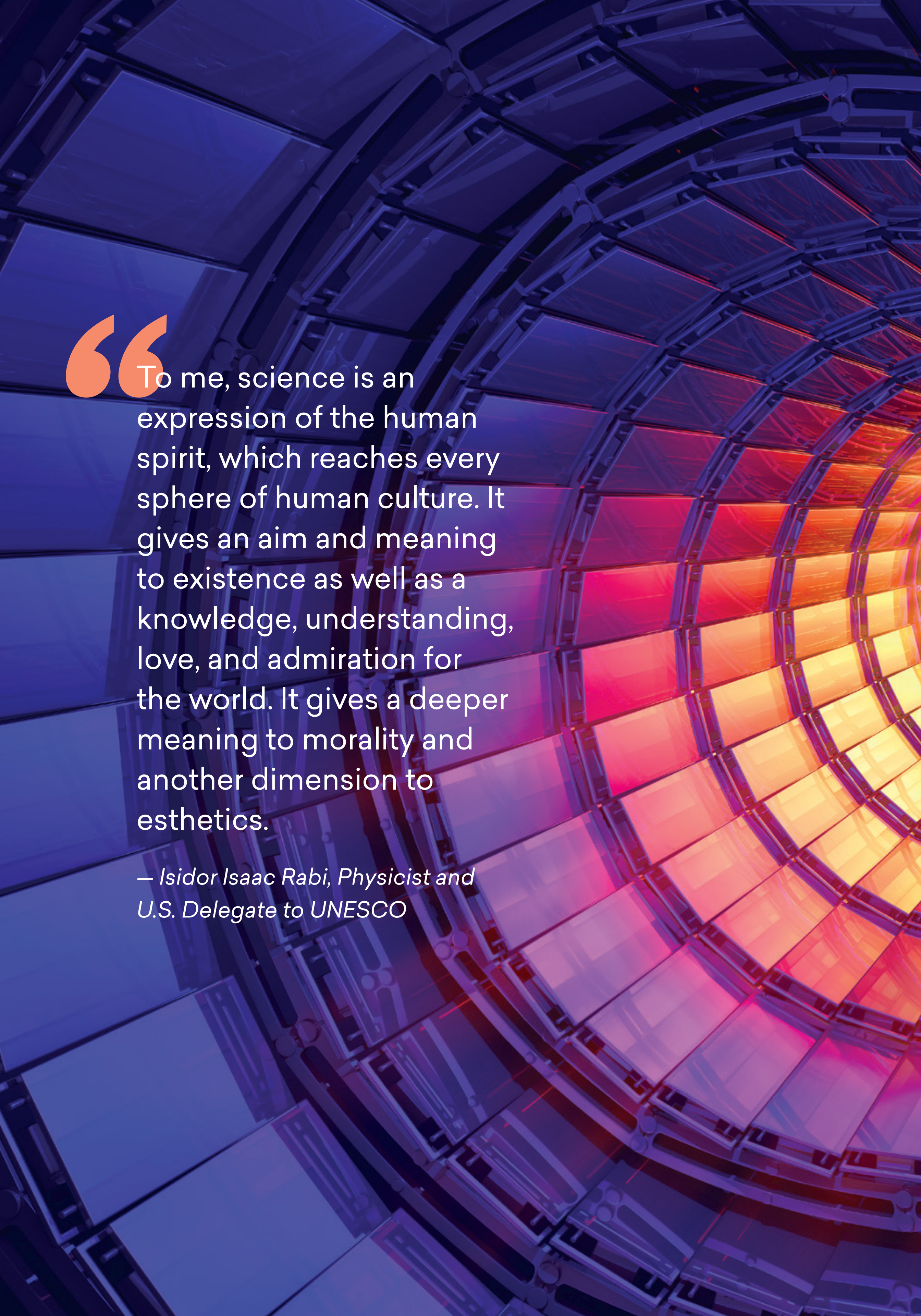
AMERICAN ACADEMY
OF ARTS & SCIENCES

Bold Ambition

International Large-Scale Science

A REPORT FROM THE **CHALLENGES FOR INTERNATIONAL SCIENTIFIC PARTNERSHIPS INITIATIVE**



> “To me, science is an expression of the human spirit, which reaches every sphere of human culture. It gives an aim and meaning to existence as well as a knowledge, understanding, love, and admiration for the world. It gives a deeper meaning to morality and another dimension to esthetics.
>
> *— Isidor Isaac Rabi, Physicist and U.S. Delegate to UNESCO*

A REPORT FROM THE
CHALLENGES FOR INTERNATIONAL SCIENTIFIC PARTNERSHIPS INITIATIVE

Bold Ambition
International Large-Scale Science

AMERICAN ACADEMY OF ARTS & SCIENCES
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Comments on the data and conclusions presented herein may be directed to the following project staff: Amanda Vernon, avernon@amacad.org; Rebecca Tiernan, rtiernan@amacad.org.

Please direct inquiries to:
American Academy of Arts and Sciences
136 Irving Street
Cambridge, Massachusetts 02138-1996
Telephone: (617) 576-5000
Facsimile: (617) 576-5050
Email: aaas@amacad.org
Visit our website at www.amacad.org

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From the President of the American Academy

Some research questions are simply too large to be addressed by one nation's scientists or facilities alone. How can we rapidly identify and mitigate the spread of emerging infectious diseases, which can arise in all regions of the world? Can we harness fusion to produce a carbon-free source of energy at a large scale as climate change threatens the health and well-being of the planet, including its people? What are the physical principles that underlie matter itself?

Science powers economies, discovers cures and therapies, unlocks the mysteries of the universe, and, at its best, has the potential to build a more prosperous and peaceful future for the planet and generations to come. As the United States reengages with the global community under a new presidential administration, a commitment to large-scale scientific ventures is necessary, timely, and an imperative for a United States that wishes to perform cutting-edge experiments with world-class collaborators. Beyond the research opportunities, sustained commitment to international scientific partners, allies and adversaries alike, is essential for the promotion of openness, trust, and diplomacy.

The United States must establish long-term funding and management mechanisms for engagement and support of large-scale initiatives with international partners. These projects require years, and in some cases decades, of project planning and implementation. Without long-term vision and support, the United States will be ill-equipped both to drive and to capitalize on global scientific advancements and, potentially, could be isolated from the next generation of advanced facilities. *Bold Ambition: International Large-Scale Science,* the second report of the American Academy's Challenges for International Scientific Partnerships (CISP) initiative, lays out the importance of international large-scale science, across disciplines, and identifies best practices to mitigate challenges that commonly arise in them. I hope that its findings will be carefully considered by the American policy-making community and implemented in the years to come.

This report joins *America and the International Future of Science*, a report from the CISP initiative published in 2020, in analysis of the challenges and benefits of American participation in international scientific partnerships. It will be followed by a third and final report, *Global Connections: Emerging Science Partners*, which will examine mechanisms for strengthening and making more equitable collaborations with countries working to build their R&D enterprises. The project, established in 2017 under the initiative of then-Academy President Jonathan F. Fanton, is identifying mechanisms by which the United States could become a better partner in such collaborations. It has been a pleasure to continue this important work during my tenure as Academy President.

In this effort, the Academy would like to extend its sincere gratitude to CISP Cochairs Arthur Bienenstock, Professor Emeritus of Photon Science, Special Assistant to the President for Federal Research Policy, and Associate Director of the Wallenberg Research Link at Stanford University, and Peter Michelson, Luke Blossom Professor in the School of Humanities and Sciences, Professor of Physics, and Senior Associate Dean for the Natural Sciences at Stanford University. In addition to their service as CISP Cochairs, Professors Bienenstock and Michelson have provided essential wisdom as Cochairs of the project working group on Large-Scale Science.

The leadership and guidance from the CISP Steering Committee and working group on Large-Scale Science were invaluable for the development of this report, especially identifying the principles for large-scale science and the value of international large-scale science across scientific disciplines (see Appendix B). I am grateful to the Academy's Board of Directors, Council, and Trust for their support of the development of this initiative, along with the contributions of many Academy Fellows. I thank representatives of the large-scale science community, including scientists, agency leaders, policy-makers, facility managers, and others, who provided insight for the development of the principles proposed in this report. The Alfred P. Sloan, William and Flora Hewlett, and Gordon and Betty Moore Foundations provided key financial support of this initiative, for which we are sincerely appreciative.

I would also like to thank the Academy staff who helped to prepare this report: Amanda Vernon, Rebecca Tiernan, Islam Qasem, Tania Munz, John Randell, Gregory Savageau, Phyllis Bendell, Heather Struntz, Peter Walton, and Scott Raymond.

I join with all of those who worked to identify and prepare the findings in this report to call for its uptake by America's scientific and policy leaders. The future of international large-scale science is bright indeed, and our country must fully participate in its endeavors.

Sincerely,
David W. Oxtoby
President, American Academy of Arts and Sciences

Project **Takeaways**

Challenges for International Scientific Partnerships (CISP) is an American Academy initiative to identify the benefits of international collaboration and recommend actions to be taken to address the most pressing challenges facing these partnerships. This project has concluded that:

1. The United States should support and expand international scientific collaborations, including with nations with which the United States has strained relations, such as China. Any restrictions on international collaborations involving federally supported research should be well-justified and carefully and narrowly defined.[1]

- Participation in international scientific collaborations is beneficial not only for U.S. science, but for the United States overall.
    - International scientific collaborations complement and contribute to a strong domestic R&D enterprise and strengthen U.S. economic competitiveness and national security.
    - To perform state-of-the-art science and address global challenges effectively, U.S. scientists must continue to engage with the global scientific community.

2. International large-scale scientific endeavors are an important component of our nation's overall science and technology enterprise. The United States must be prepared to participate in international large-scale science partnerships and work to ensure their success, including contributing support for operations outside the United States.

- Some future large-scale science endeavors will be on a global scale and will necessarily involve international cooperation, with some international efforts and facilities sited outside of the United States but requiring U.S. support.
- Large-scale research instrumentation and facilities are essential for scientific advancement across a variety of disciplines and will become increasingly difficult for the United States to fund unilaterally.

3. Emerging science partners around the world are and will continue to be important scientific collaborators. The United States should support and partner with them in scientific research.[2]

- Scientific talent arises across the globe at an increasing rate as many countries invest in building a more robust S&T enterprise.
- Many of the most pressing scientific questions are not defined by national boundaries and require global collaboration for advancement.

Prologue

Challenges for International Scientific Partnerships (CISP) is an American Academy initiative to articulate the benefits of international collaboration and recommend solutions to the most pressing challenges associated with the design and operation of international partnerships. This initiative, funded by the Alfred P. Sloan, William and Flora Hewlett, and Gordon and Betty Moore Foundations, identifies policy recommendations and best practices to mitigate challenges for international science collaborations, including physical facilities, distributed networks, and peer-to-peer partnerships. The project is cochaired by **Arthur Bienenstock** (Stanford University) and **Peter Michelson** (Stanford University).

The Large-Scale Science (LSS) working group approaches international collaborations through the lens of issues particular to large-scale science, not peer-to-peer or small-scale international work. This group has been tasked with exploring how the United States can enhance its role in these partnerships, both in physical facilities (such as the European Organization for Nuclear Research) and distributed networks (such as the Human Cell Atlas). This group is focusing on recommendations that will bolster U.S. ability to partake in large-scale collaboration efforts as meaningful and engaged partners. The LSS working group is led by CISP Cochairs **Arthur Bienenstock** and **Peter Michelson**.

The Emerging Science Partners (ESP) working group explores issues particular to U.S. scientific collaborations at all scales with countries seeking to boost their scientific capacity, particularly those with limited resources to do so. This working group frames discussions around how the United States can be a better collaborator in its partnerships with emerging science partner countries and work to increase equity in these collaborations. The ESP working group is cochaired by **Olufunmilayo Olopade** (University of Chicago) and **Shirley Malcom** (American Association for the Advancement of Science).

This report, *Bold Ambition: International Large-Scale Science*, describes the essential role of large-scale science initiatives, also referred to as megascience initiatives, for the U.S. scientific enterprise. It identifies best practices for building large-scale scientific collaborations in the future. *Bold Ambition* joins two other reports from the initiative: *America and the International Future of Science* (December 2020) and *Global Connections: Emerging Science Partners* (forthcoming 2021).

Executive **Summary**

The American Academy of Arts and Sciences undertook the **Challenges for International Scientific Partnerships** (CISP) initiative to assess both the importance and the challenges of international scientific collaborations for the United States. CISP began well before the onset of the COVID-19 pandemic that has swept across the globe and continues to devastate individuals and societies as this report goes to print. The pandemic has reinforced CISP's principal conclusion that the benefits of international scientific collaboration for the United States and the world are substantial and growing, including with nations with which the United States has strained relations, such as China. These benefits eclipse the challenges that international collaborations can present. The findings that led to this conclusion are presented in the CISP report *America and the International Future of Science.*

Bold Ambition: International Large-Scale Science focuses on international large-scale science partnerships hosted at or dependent on a large-scale research facility, investigations coordinated across multiple national research facilities, or investigations dependent on extensive networks of scientists pooling data to conduct a coordinated research effort. CISP has identified three principal benefits of U.S. engagement in international large-scale science: 1) enabling discoveries that are otherwise impossible; 2) improving lives; and 3) promoting international understanding. These benefits would keep U.S. science at the forefront, would lead to technological advances, increased competitiveness, and solutions to national and global problems, and would promote the values, ethics, and norms that can positively influence the conduct of science worldwide. As other countries promote increasingly large international projects, the United States runs the risk that future U.S. scientists may be excluded from some of the world's leading scientific projects and associated technological advances. To avoid this isolation, the United States must participate in these advances and prepare strategically to commit to collaboration on the funding, planning, development, and operation of new large-scale scientific research capabilities at home and abroad.

Initiation of, or participation in, international large-scale science has associated complexities not faced by other research efforts that do not require large-scale instrumentation and facilities, multiple international partners, or vast data collections. At the onset of large-scale collaborations, the government should ensure that participation does not conflict with national security or other national goals. From examination of many examples of successful and not-successful large-scale science partnerships and from several workshops and consultations with government funding agencies, the CISP study identified guiding principles for the formation and organization of international large-scale science partnerships to ensure their value and success.

The principles identified in this report provide mechanisms by which the United States can effectively and beneficially participate in these partnerships. These principles include: prioritizing scientific excellence, properly scoping projects, meeting its commitments, and promoting ethical collaborations with strong values across cultures.

1. Prioritize Scientific Excellence and Impact

The scientific rationale for a proposed large-scale project should be compelling and well-supported by the relevant U.S. and international scientific communities. Participation in large-scale science by the United States must be driven by the potential for significant scientific benefit.

2. Develop Well-Defined Project Scope and Effective Project Management

For candidate projects that are scientifically compelling, it is important to provide sufficient resources during a *project formulation phase* of sufficient length that partner relationships can be established and a detailed implementation plan—including scope, budget, schedule, assessment of risks, and management plan—can be developed. The formulation of the project implementation plan should involve all major international partners, provide clear understanding of the goals and parameters of the project and the responsibilities of each partner, and establish mechanisms for dealing with the major challenges that inevitably arise in implementing a complex project. Project partners should share understanding about project decommissioning responsibilities at its conclusion.

Most important, trust among partners and transparency should be established early in a project's lifecycle. Openness and trust among international partners are critical for developing a successful project and are best established during project formulation. Scientific partners should recognize their mutual interdependence, and they should agree on how risks will be managed, how project reviews are to be conducted, and how technical problems and disputes will be addressed. The project must have a strong and diverse scientific leadership team. *All problems, along with all successes, should belong to all partners.*

Before a project proceeds past the formulation phase, the sponsors must independently assess the project implementation plan. Project management and capability to carry the project out must be part of the assessment. Regular independent management and project reviews must be scheduled and implemented as the project proceeds; such reviews can often identify problems at a sufficiently early stage to remedy them effectively.

3. Meet Commitments

Successful initiation and maintenance of international scientific collaborations require long-term, steady financial and political commitments. Further, once made, it is essential for these commitments to be upheld, both for the realization of the project in question and for generally building and maintaining trust that the United States will remain a reliable scientific partner.

Once the United States, through its agency and interagency review processes, has committed to a project, the Congress, U.S. agencies, and the White House Office of Management and Budget (OMB) should bolster mechanisms to ensure that the United States can meet its financial commitments. While this is sometimes very hard to do, it is important to have a clear, documented decision process to reference, should difficulties arise.

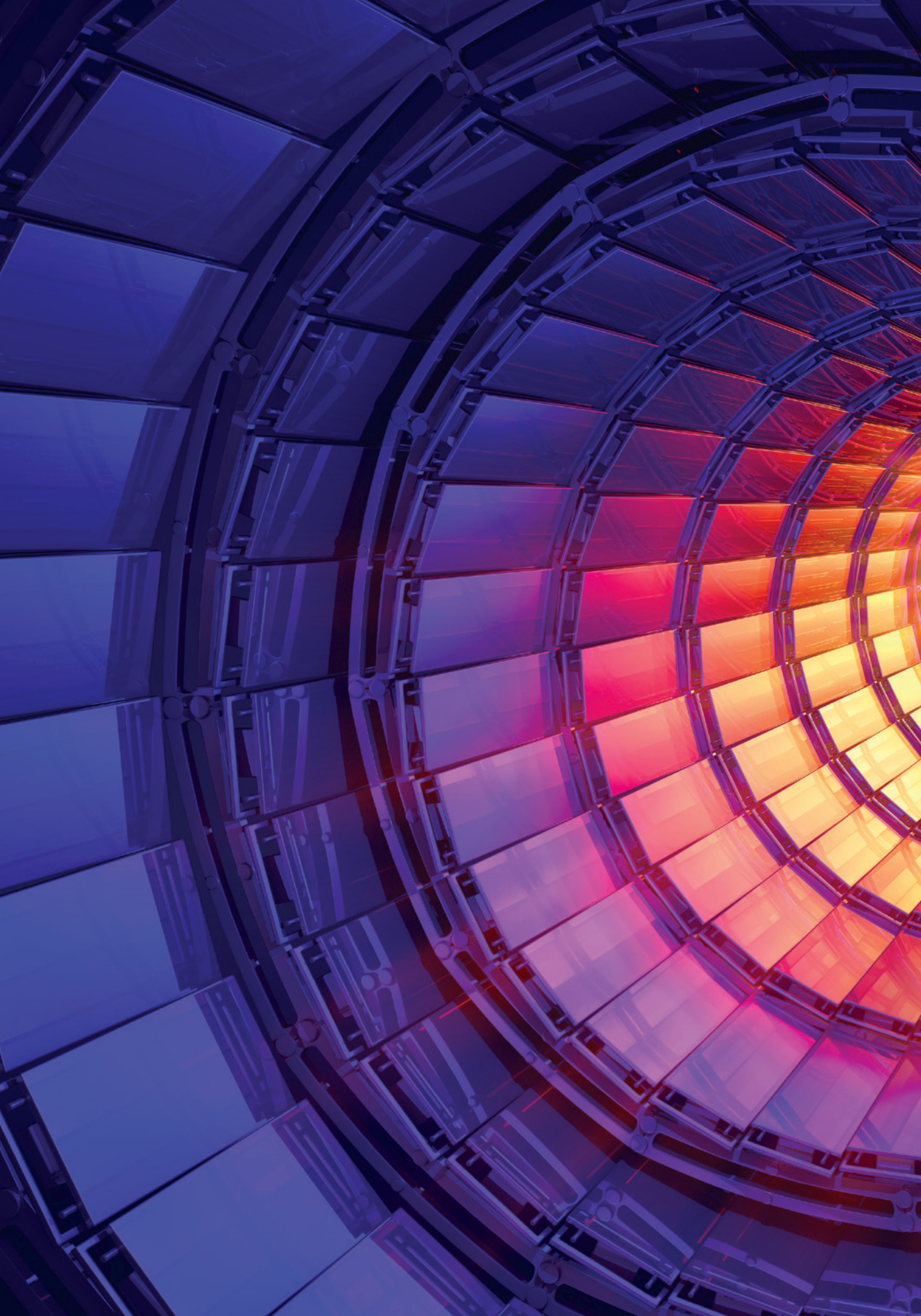
4. Establish Ethical Standards for the Conduct of Research

Building a large, international team of researchers links all partners to each other, and scientific success depends on generating and adhering to ethical codes of conduct that reinforce values of fairness and strengthen inclusive engagement. Codes of conduct, ideally summarized in a written document, are essential and need to be developed jointly by partners, not prescribed, during project formulation. They should anticipate the implementation phase of a project as well as operations in the case of a facility. To be successful, ethical codes need shared buy-in and collaborative development by the scientists and scientific institutions involved, including partners from all nations involved. This is especially true when there are issues of trust, such as strained geopolitical relations or between developed and developing nations. Project leadership must take an active role in cultivating ethical norms and standards, and coming to terms with differing stances through transparent and open dialogue. Relevant stakeholders need to be engaged in this development as well; these groups may include the interested public, local and regional governments, and others.

U.S. government organizations act as major leaders in many international large-scale science endeavors, including those with explicit scientific responsibilities, such as the National Science Foundation (NSF), as well as mission-driven agencies for which science is critical to their overarching goals and operations, such as the Department of Energy (DOE), National Aeronautics and Space Administration (NASA), and the National Institutes of Health (NIH).

> “When engaging in international large-scale science, it is imperative for the United States to prioritize scientific excellence, properly scope projects, meet its commitments, and promote ethical collaborations with strong values across cultures.

From workshops and examination of many examples of successful and not-successful large-scale science partnerships involving U.S. government agencies, CISP has concluded that these federal agencies are successful in most cases in managing large-scale science projects and partnerships on behalf of the nation and have demonstrated that they can manage the inevitable challenges and crises that arise in a complex project. The foundation for success in the face of challenges is a clear understanding of the scientific priorities that are supported by the scientific community, a carefully conceived governance structure, and a robust oversight and management review process that is cognizant of these priorities and identifies risks and mitigation strategies as early as possible.



Introduction

Large-scale international scientific collaborations enable scientific discovery, drive technological innovations, and contribute to economic development. Successful collaborations leverage international talent and lead to discoveries that are simply not possible at smaller scales.[3] As current work progresses on these so-called megascience projects and new initiatives emerge, these large and complex undertakings continue to demonstrate their value to our understanding of the world around us and our ability to expand our technical capabilities.

International large-scale science takes shape in varied ways, depending on scientific objectives. They may involve investigations hosted at, or dependent on, a large-scale research facility, investigations coordinated across multiple national research facilities, or investigations dependent on extensive networks of scientists pooling data to conduct a coordinated research effort. They may also involve the development and support of centralized services, such as computational facilities, data banks, and bio banks (see Structures of International Large-Scale Science Partnerships on page 11). Large-scale science efforts may require very large investments to develop the necessary research facilities and instrumentation or smaller investments to ensure connectivity among research networks. Large-scale science endeavors frequently require substantial multidisciplinary collaborations in both their development and their effective functioning.

At the same time, large-scale international projects can encounter significant developmental or operational setbacks if the partnership agreements for a project do not establish an environment conducive to scientific success and a clear understanding among the partners of the project's goals and the partners' responsibilities.[4] The modern context for large-scale international collaboration includes several challenges that require ongoing communication with partners, diligence, and careful planning to overcome. These issues include the increased complexity of scientific problems, the challenges related to the planning and management of large international teams, financial challenges from both the start-up costs and ongoing operating costs, and visa obstacles for international scientists. There are also the cultural, national, political, and geopolitical issues that can arise in complex international partnerships (see Principles for International Large-Scale Science on page 26).[5] However, there is a decades-long series of megascience efforts that have seen great success. These projects can instruct and inform future collaborations and serve as templates as additional international scientific partnerships are developed.

Imperatives for International Large-Scale Science

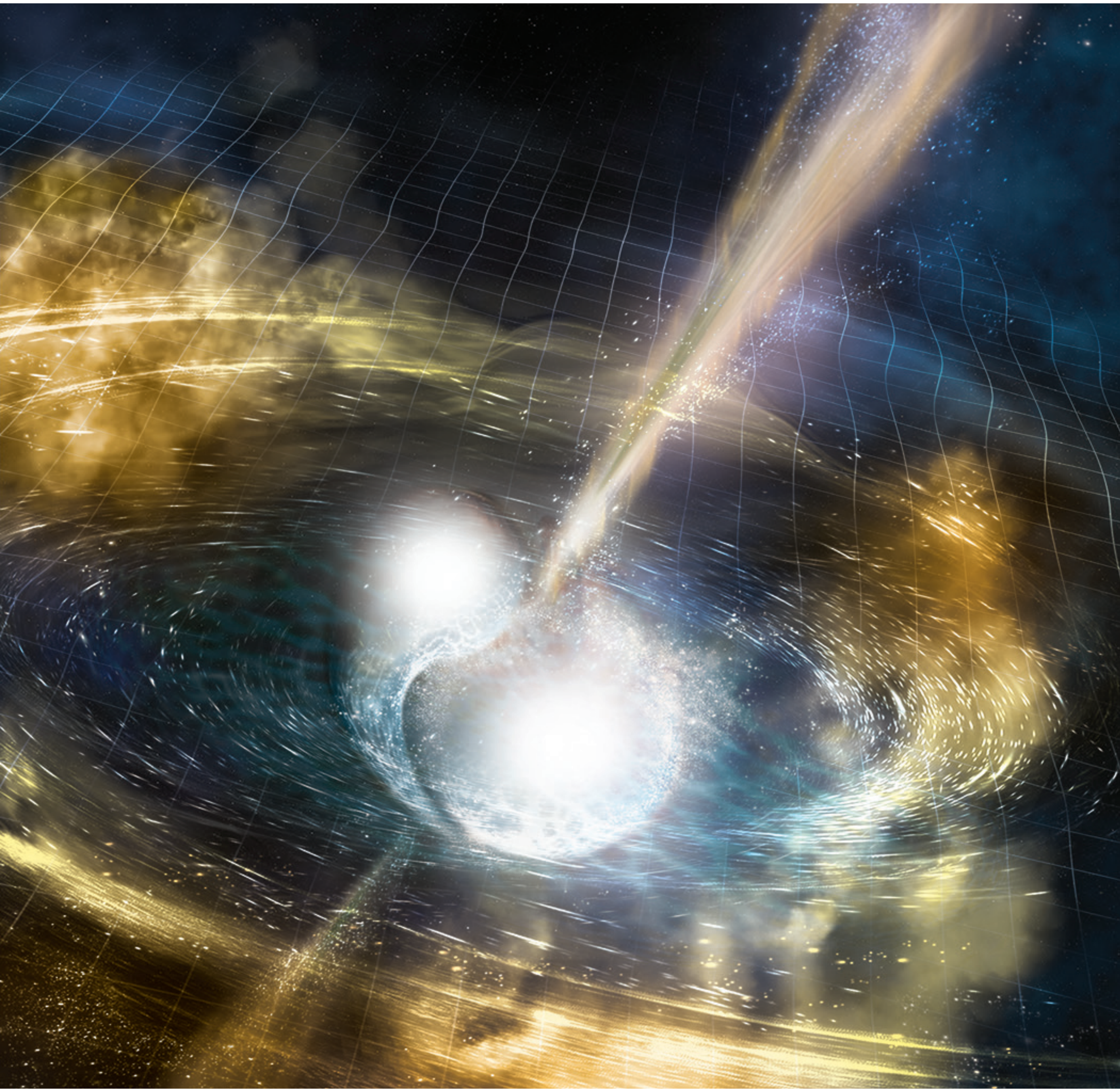
The benefits of international scientific collaboration for the United States and the world are substantial and eclipse the challenges they can present. This conclusion extends to engagement in large-scale science, when such engagement does not conflict with national security or other national goals. The CISP Large-Scale Science working group identified three principal reasons for the United States to engage in international large-scale science: 1) to enable inspiring discoveries that are otherwise impossible; 2) to improve lives; and 3) to promote international understanding. The following sections address each of these imperatives in turn.

Large-Scale Science Enables Inspiring Discoveries that Are Otherwise Impossible

On April 10, 2019, scientists working around the world made history when they captured the first image of a black hole and its shadow. Their achievement seized headlines and inspired wonder in the minds of people seeking to understand the universe around them.

The image was obtained following decades of worldwide investment in astronomy facilities and the use of eight radio telescopes in Chile, Spain, Mexico, Arizona, Hawaii, and Antarctica for a week-long observation in April 2017.[6] Without this concerted, international effort, this scientific achievement would have been impossible.

On August 17, 2017, the Laser Interferometer Gravitational-Wave Observatory (LIGO) Scientific Collaboration (LSC) detected gravitational radiation from a coalescing pair of neutron stars and, combined with observations by its European counterpart, Virgo, as well as detection of a short gamma-ray burst by NASA's Fermi Gamma-ray Space Telescope, localized this source in a distant galaxy.[7] The two NSF-funded LIGO detectors are based in the United States, but an international collaboration of more than one thousand scientists from eighteen countries made key contributions to the U.S. LIGO interferometers. U.S. LIGO scientists collaborate with scientists operating other detectors located around the world and funded by other nations.[8] The international detector locations allow scientists to take advantage of detection delays across facilities to pinpoint gravitational wave source locations, as well as reduce noise from local sources close to individual detectors.[9] Observations by optical observatories around the world of the electromagnetic radiation produced by the merger event directly showed that these mergers are important producers of heavy elements, including gold, thus addressing the long-standing scientific question of the origin of these elements.



Artist's illustration of two merging neutron stars. The rippling space-time grid represents gravitational waves that travel out from the collision, while the narrow beams show the bursts of gamma rays that are shot out just seconds after the gravitational waves. Swirling clouds of material ejected from the merging stars are also depicted. The clouds glow with visible and other wavelengths of light. Illustration by Aurore Simonnet. Image courtesy of National Science Foundation, Laser Interferometer Gravitational-Wave Observatory, and Sonoma State University.

Achievements such as these, which represent just a few of the major milestones reached across scientific disciplines by international megascience, capture the imaginations of people around the globe. They are crowning examples of what humanity can accomplish through imagination, cooperation, and long-term investment in large-scale international endeavors.

Large-Scale Science Improves Lives

Beyond satisfying a human desire to unlock the world's mysteries, large-scale scientific endeavors often require pushing beyond the limits of existing technology and yield major advances that become important for society as a whole (see Using Synchrotron X-Rays to Accelerate Discovery of New Therapeutics on page 7).

Genomic Research

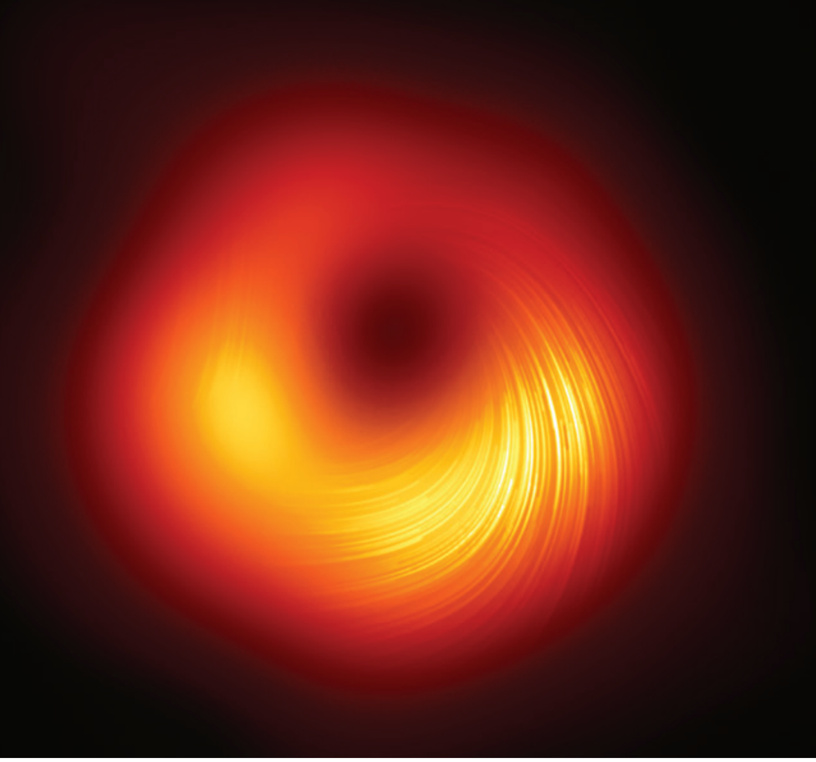
In 1990, the NIH and DOE submitted their initial five-year plan for what was, at that time, an enormous undertaking: sequencing the human genome. The two agencies had formalized their relationship in this endeavor in a memorandum of agreement and articulated the benefit of international collaboration to the United States:

> The Human Genome Initiative is not limited to the United States. Many countries are interested in participating in the project and all are interested in the outcome. . . . There are many opportunities where international collaboration could enhance progress on the Human Genome Initiative. Currently, the United States is in a leadership position with respect to scientific accomplishment and organization of the genome program. However, as other nations organize and initiate their programs, the United States will stand to gain by international collaboration as much as the other countries involved.[10]

In the years that followed, the Human Genome Project (HGP) was undertaken by the International Human Genome Sequencing Consortium, which comprises sequencing centers in the United States, United Kingdom, Japan, France, Germany, and China.[11] The effort was predicted to take fifteen years and cost $3 billion in 1991 ($5.7 billion today), but was accomplished two years early and under budget.[12] All of the sequence data were made public and freely available without restriction on use; they represented 99 percent of the gene-containing sequence of human DNA.

The impact of this project has been monumental. The HGP revealed approximately 20,500 human genes and enabled the characterization of genomes from other organisms, such as mice and fruit flies, that are commonly used in biological research.[13] It revolutionized the biomedical community, accelerating the discovery of genes associated with disease and, in turn, providing improved diagnoses and treatments. The HGP is also estimated to have brought significant economic benefits to the United States, although the magnitude of this benefit varies in analyses conducted thus far.[14]

The technology and the reference genome have become the cornerstone of many ongoing international collaborative efforts. One, the International Nucleotide Sequence Database Collaboration, links three databases from the United States, United Kingdom, and Japan that collect DNA and RNA sequences and synchronize them for use by researchers.[15] Most recently, this collaboration supported global research on the SARS-CoV-2 virus by providing a streamlined, global bioinformatics system



The Event Horizon Telescope utilized radio telescopes positioned across continents to capture the first image of a black hole, a supermassive black hole at the center of Galaxy M87, shown here with a view in polarized light. Image courtesy of the Event Horizon Telescope Collaboration.

that worked to promote rapid, maximally impactful sharing of viral sequences.[16] Another, the Human Cell Atlas, includes scientists and institutes in more than seventy countries. This collaboration is using single-cell DNA and RNA sequencing, among other techniques, to identify new cell types and create a reference map of all human cells, potentially identifying novel targets for disease treatment.[17]

Particle Accelerators

Particle accelerators and their associated detectors and computing facilities, such as those at the European Organization for Nuclear Research (CERN), provide a clear example of large-scale science focused on probing nature on subatomic scales, leading to advances in technology and expertise that contribute to applications in fields beyond high-energy physics and address global challenges in areas such as health and environment.[18] These facilities produce beams of charged particles using electric fields to accelerate the particles to high speeds and energies and are essential for many particle and nuclear physics experiments, including those that led to the observation of a new particle identified as the Higgs boson.[19] The advancements made in particle accelerators, detectors, and associated computing have transformed everyday life. First, they have improved critical technologies used across society, including the manufacturing of computer chips, the inspection of nuclear fuels, X-ray diagnostics, and radiation therapy for cancer patients.[20] Second, they have provided the collaborating nations with economic growth through the development of industrial capabilities related to those nations' contributions to the CERN experiment.

Synchrotron Radiation

Following directly from the development of particle accelerators, synchrotron light source facilities, producing X-rays that are ten million times more intense than those from an X-ray tube, are increasingly constructed by international partnerships. There are now over seventy synchrotron facilities around the world carrying out a range of experiments. The heart of a synchrotron light source is a ring of magnets into which a beam of high-energy electrons, produced by an accelerator, is injected and stored. The circulating electrons emit synchrotron radiation that is used to probe the structure of matter from subnanometer to millimeter scales. The extreme intensities and other characteristics of these facilities make possible transformational investigations in many fields, including materials science, physics, chemistry, structural biology, and medicine. Several Nobel Prizes have been awarded for research that depended on synchrotron light. An example of current research facilitated by synchrotron light sources is the study of the SARS-CoV-2 virus (see Using Synchrotron X-Rays to Accelerate Discovery of New Therapeutics on page 7). These facilities play an increasingly important role in the international science effort needed to address challenges such as pandemics.

Indirect Benefits of Large-Scale Science

Large-scale facilities commonly produce major technological advances seemingly unrelated to their primary scientific goals: for instance, the World Wide Web was developed at CERN in 1989 when Tim Berners-Lee worked to enable the sharing of data and scientific information among a globally dispersed group of collaborators.[21] Pushing the frontier of knowledge itself has meant that the scientific advancements, such as those made in the development of LIGO, have accelerated or invented numerous technologies, including in the fields of quantum measurement science, materials science and optics, and cryogenics.[22]

The European Synchrotron Radiation Facility (ESRF), located in Grenoble, France, is a partnership of twenty-two nations, of which thirteen are members and nine are scientific associates. The ESRF hosts more than six thousand researchers that use forty-two beamlines at the facility. © by gui00878/Getty Images.

Rapidly Responding to the Challenges of COVID-19: Using Synchrotron X-Rays to Accelerate Discovery of New Therapeutics

As this report goes to print, the COVID-19 pandemic continues to damage the health, well-being, and economy of every nation. There are more than 159 million confirmed cases worldwide, accompanied by more than three million deaths. Both near- and longer-term strategies for controlling the pandemic and mitigating its impacts on human health depend in part on the discovery of new therapeutics to defeat it and vaccines to prevent its spread. Being able to look at the intimate workings of the virus in molecular detail is an essential element of the strategy to rapidly develop and deploy such new pharmaceuticals. Because of the very small size of the virus particles (~0.12 microns), optical light is not effective in imaging their even smaller molecular components, so scientists use other imaging techniques based on X-rays or electrons. X-rays in particular have proven over decades to provide invaluable structural information for guiding the development of new therapeutic approaches, from curing cancers to controlling viral infections such as HIV, SARS, and Ebola.

Such molecular imaging studies depend substantially upon access to brilliant sources of X-rays that are produced in synchrotron light sources. The scale and cost of these machines dictate that they are operated as national or international scientific user facilities. Most of the approximately seventy synchrotron facilities, located in over twenty countries, have active research programs enabling the study of viruses and their components.[23] There are five large-scale synchrotron laboratories in the United States supported primarily by the Department of Energy and one by a consortium of private and public sources.[24] International cooperation among synchrotron light sources is a well-established and important means of providing the most advanced capabilities for the international user community, which is estimated to be in excess of fifty thousand.

The synchrotron X-ray sources enable very rapid, precise studies of molecular details in complex biomolecules. Biologists have determined more than 120,000 3D protein structures from synchrotron X-ray source measurements.[25] These high-resolution structural insights into viruses and other macromolecules help guide the identification of potential drugs and antibodies and, through understanding of how they work, guide their further development.[26]

Each synchrotron X-ray facility is an ecosystem in which techniques for scientific investigation are developed and maintained at the state of the art to serve a large community of academic, research laboratory, and industrial users. Such facilities are well positioned to respond to rapidly emerging threats and national needs, as exemplified in the current COVID-19 pandemic. As seen at many of the synchrotron laboratories worldwide, within weeks of widespread "shelter in place" orders to control the spread of the virus, priority was given to reopening and operating these facilities because of their essential role in COVID-19–related research. Safe laboratory operations procedures were developed and implemented quickly, and light

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source research has led to significant progress against the challenges of COVID-19.[27]

Gaining a molecular level understanding of every aspect of the SARS-CoV-2 virus, the virus responsible for the COVID-19 pandemic, is essential. Studying its life cycle, including how it infects cells, replicates, and multiplies, offers the potential for evolving existing proven therapeutic strategies developed for other viruses and developing new ones for stopping the infection of SARS-CoV-2 in humans. Experimental studies, coupled with advanced computational tools, are already accelerating discoveries of new therapeutics for defeating the SARS-CoV-2 virus and providing the strategies and key infrastructure to rapidly address future drug resistance challenges that will emerge.

Two recent studies, both enabled by X-ray synchrotron radiation crystallography, illustrate complementary approaches to rapidly developing effective therapies for COVID-19. One of the studies, by biologist Ian A. Wilson and colleagues at Scripps Research, has provided remarkable molecular insights into the process of how antibodies recognize the spike proteins on the SARS-CoV-2 virus surface, leading to the design of an experimental vaccine.[28]

The second study, by researchers at the University of Alberta, also facilitated by synchrotron X-rays, investigated a complementary strategy for defeating the SARS-CoV-2 viral infection process by blocking viral replication once it has entered the human cell.[29] The researchers used X-ray crystallography to learn how a candidate drug (and variants of it) interacts with one of the protease enzymes involved in viral replication within the infected cell, much as a key fits into a lock and disables it, preventing the virus from making copies of itself.

While these examples illustrate the quick deployment of synchrotron X-ray techniques to enable rapid development of new therapeutics to help treat and prevent COVID-19, there are other areas of research in which synchrotron radiation is playing a role. These include using X-rays to understand how mask materials, such as those used in N95 respirators, function at the molecular level, how they can be effectively decontaminated, and how improved materials can be designed. An example of a national network focused on all of these approaches is the National Virtual Biotechnology Laboratory (NVBL), which is a consortium of DOE national laboratories coordinating a response to COVID-19.[30] The NVBL coordinates COVID-19–related research that takes advantage of the DOE laboratories' capabilities, including their synchrotron light sources.

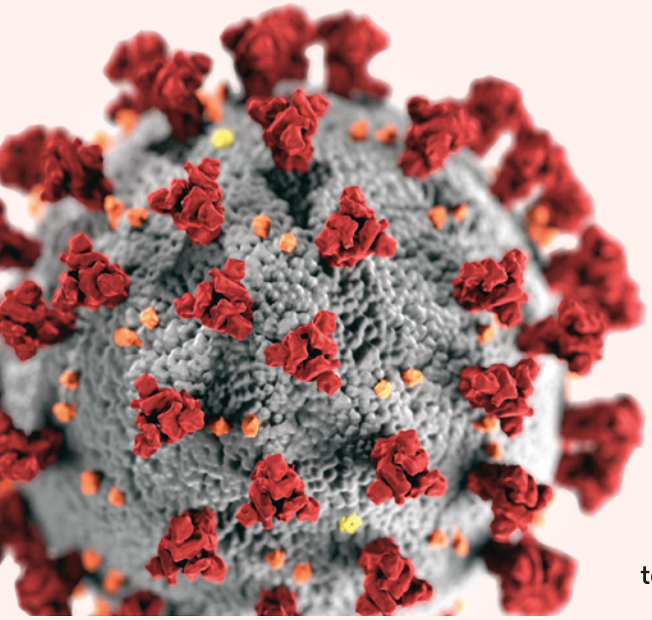


Illustration of the structure of the SARS-CoV-2 coronavirus. Colored in red are the spike proteins that are key in recognizing and infecting the human host cells. Image by Centers for Disease Control and Prevention.

Large-Scale Science Promotes International Understanding

International large-scale scientific facilities and networks provide opportunities to promote understanding between different nationalities and nations, including nations that have strained diplomatic relations. CERN is an important example.

In the post–World War II Cold War era, CERN was one of the few places in the world where Soviet, European, and U.S. scientists worked side-by-side. From its founding in 1954 by twelve European nations, part of CERN's mission has been to "unite people from all over the world to push the frontiers of science and technology, for the benefit of all." CERN's charter states: "The Organization shall have no concern with work for military requirements and the results of its experimental and theoretical work shall be published or otherwise made generally available."[31] From its start, CERN adopted a policy of open access. Since 1954, the number of member states has grown to twenty-three nations, with an additional eight associate member states. Japan, Russia, and the United States formally have observer status at CERN, while an additional thirty-five nations, including China, Egypt, Iran, Jordan, and Saudi Arabia, have signed cooperation agreements with the organization. CERN is run by the CERN Council, comprising two representatives, one a scientist and one a government delegate, from each of the twenty-three member states. The financial viability and stability of CERN derive from its founding structure, which is based on intergovernmental treaties.

"People from all over the world come here, bringing with them different cultures and different ways of working. This diversity is part of our strength, and it's something that we need to nurture constantly." —Fabiola Gianotti, CERN Director-General.[32] © by the European Organization for Nuclear Research (top row) and AP Photo/Denis Balibouse (bottom).

CERN's on-site staff of 2,500 people from around the world are responsible for the design, construction, and operation of CERN's research infrastructure. They also support the preparation and operation of the experiments as well as the data analysis infrastructure for a user community of more than 12,200 scientists of 110 nationalities from institutions in more than 70 countries.

U.S. participation in CERN experiments has been governed in recent years by the 2015 DOE-NSF-CERN International Cooperation Agreement and subsequent protocols.[33] Since 1997, DOE and NSF support for the massive ATLAS and CMS detectors has been implemented via NSF and DOE funding to U.S. universities and national laboratories to develop, operate, and maintain specific components of these detectors. Further, the 2015 agreement paved the way for additional U.S. contributions toward an upgrade to the Large Hadron Collider (LHC) that will enable the instruments to function at much higher collision rates.[34] This mode of participation allows U.S. researchers to be active members of the LHC experiments, even though the United States does not take on all the obligations of full CERN membership.

CERN became a model for the formation of other successful scientific partnerships among European nations, including the European Southern Observatory (ESO) in 1962, the European Molecular Biology Laboratory (EMBL) in 1974, and the European Synchrotron Radiation Facility (ESRF) in 1988. Most recently, the Synchrotron-light for Experimental Science and Applications in the Middle East (SESAME) was built in Jordan in 2002 under the auspices of UNESCO, following the CERN model, and lists its current members as Cyprus, Egypt, Iran, Israel, Jordan, Pakistan, Palestine, and Turkey.[35]

The European Southern Observatory's La Silla facility in La Higuera, Coquimbo Region, Chile. Photo by Martin Bernetti/AFP via Getty Images.

Structures of International Large-Scale Science Partnerships

Megascience projects take place at the regional, national, and international levels and are implemented with a variety of structures, depending on project goals. Table 1 (see page 12) summarizes these structures for large-scale science projects; some build research facilities that serve user communities exploring diverse scientific questions, others work toward answering a specific set of scientific questions, and still others organize a distributed, highly coordinated network of partners that provide measurements and data and build data infrastructures to address an agreed upon set of scientific questions. In general, international collaborations need to be supported when scientific challenges and opportunities are beyond what countries can realize on their own, and when the benefits to the partners are mutually reinforcing.[36]

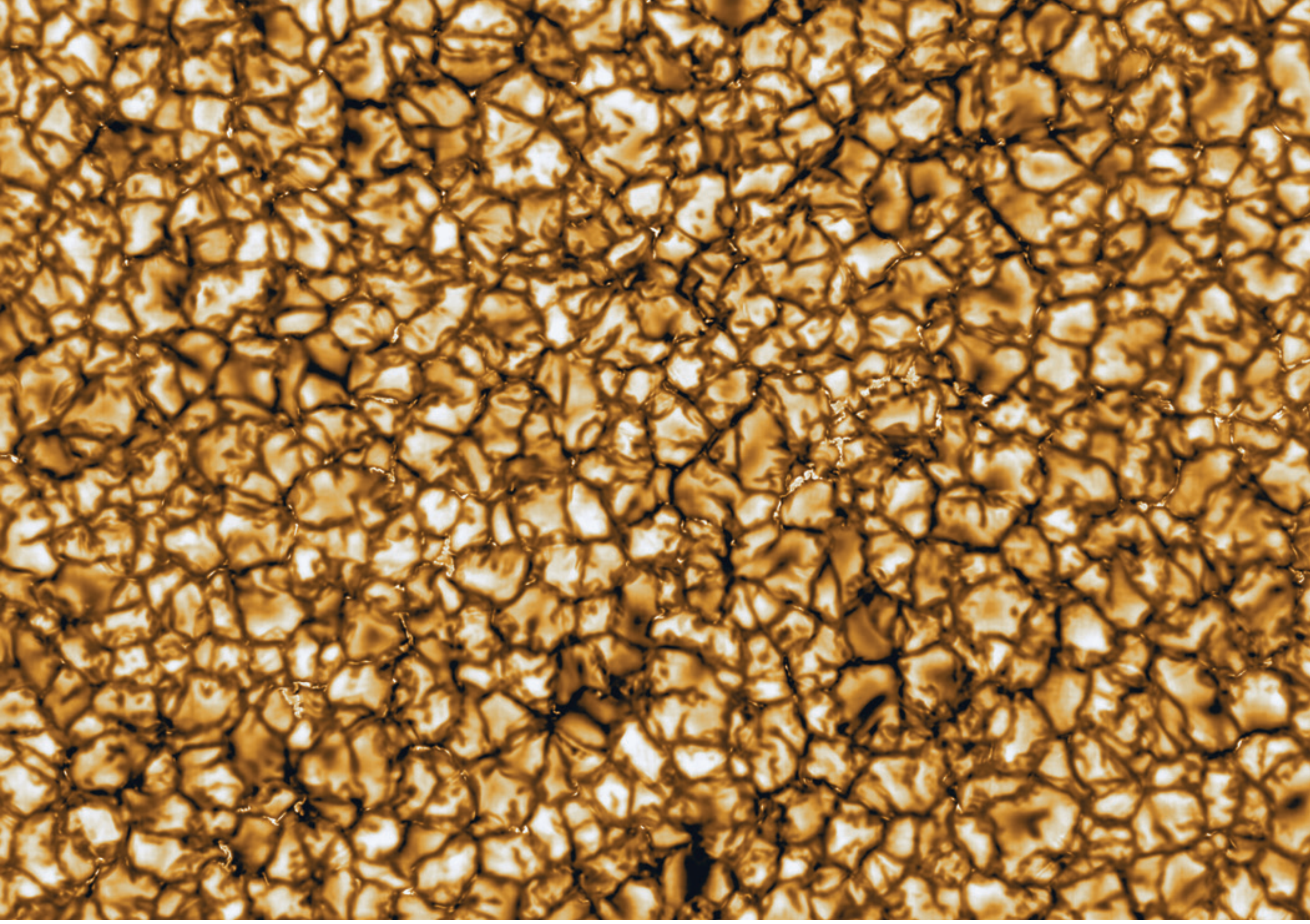
There are some large-scale science initiatives, like the National Ignition Facility, that are pursued by the United States alone, rather than in collaboration with international scientists, due to concerns related to national security. These projects may be related to weapons research and other classified scientific research ventures. National laboratories and facilities are appropriate settings for these initiatives.

For open scientific research, the United States has successfully played a variety of roles within international scientific large-scale collaborations. The United States has acted as primary funder and provided siting as well for a national large-scale research facility that involves international collaborators and collaboration with similar research facilities in other countries (see the Daniel K. Inouye Solar Telescope on page 13). The United States has also played an important leadership role within a multinational partnership that constructed and operates a large-scale facility sited in another country (see the Atacama Large Millimeter/submillimeter Array on page 14). In cases of distributed networks of scientists without centralized facilities, or the establishment of centralized accessible data facilities, the United States may participate as a primary coordinating body and funder (see the Global Alliance for Genomics and Health and the International Mouse Phenotyping Consortium on page 15), or as a participating country member rather than serving in a leadership role (see Global Earth Observation System of Systems Platform on page 16). The specific role that the United States can or should assume in an international large-scale scientific collaboration must be discussed early in the development of the project. Consultation should be sought with the U.S. scientific community and the U.S. funding agencies and, in some cases, with the State Department. This careful consultation is one of the major factors to be considered as such projects develop (see Principles for International Large-Scale Science on page 26).

Table 1

Structures of International Large-Scale Scientific Partnerships

Category	Subcategory	Examples
A. Scientific investigations hosted at large-scale facility	A1. Investigations by many independent investigators using time-shared national or regional instruments and capabilities	Synchrotron light source (such as ESRF); optical telescope, ground or space-based
	A2. Investigations requiring construction and operation of large-scale facility-instruments by an international science collaboration	European Organization for Nuclear Research, including LHC, ATLAS, CMS; Atacama Large Millimeter/submillimeter Array; ITER; Belle II at the SuperKEKB
B. Scientific investigations using multiple facilities	B1. Investigations requiring highly coordinated operations and data acquisition across multiple regional or national research facilities	Laser Interferometer Gravitational-Wave Observatory; Virgo; Event Horizon Telescope; European VLBI Network
	B2. Investigations requiring access to near real-time or archival data	Laser Interferometer Gravitational-Wave Observatory; Virgo; Fermi Large Area Telescope
C. Scientific investigations with network of investigators and distributed measurements with centralized data	C1. Highly coordinated network of investigators	International Mouse Phenotyping Consortium; Human Cell Atlas
	C2. Network of independent investigators that builds a central data facility and shares access to data	Global Biodiversity Information Facility; International NeuroInformatics Coordinating Facility; Global Earth Observation System of Systems; Worldwide Protein Data Bank



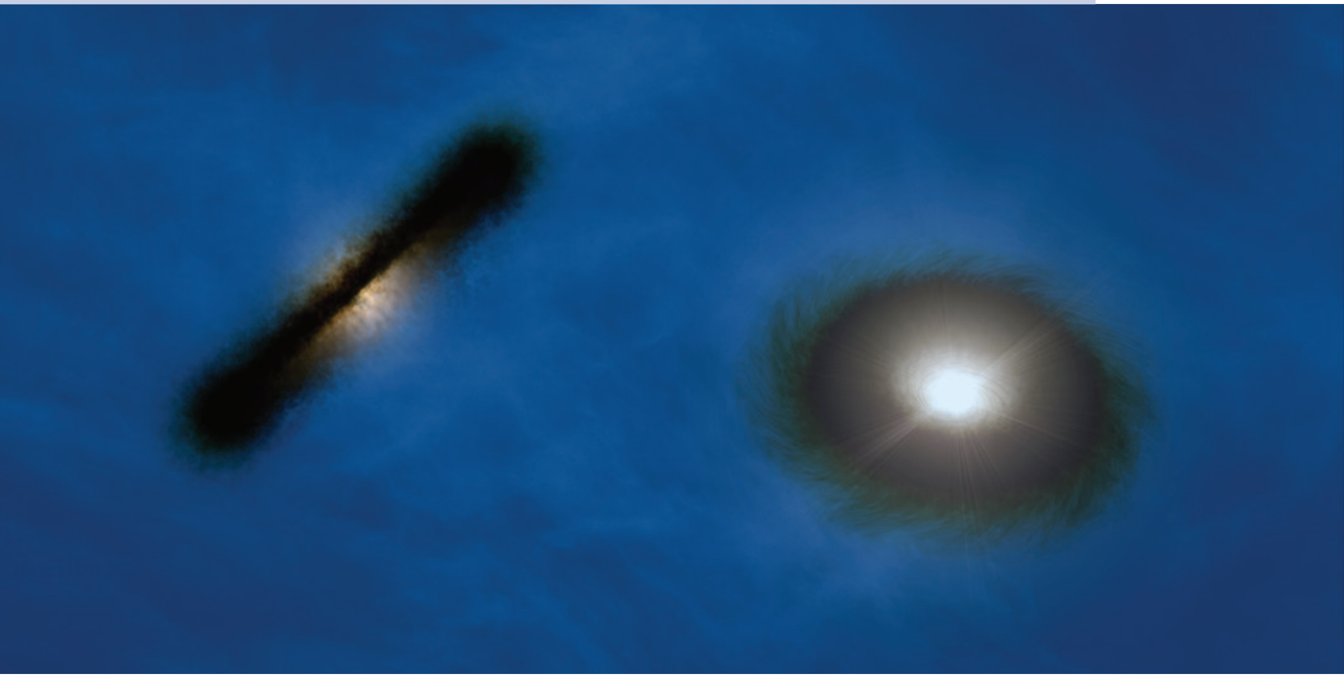
DKIST high-resolution image of the Sun's surface, taken at 789 nanometers, displaying features as small as 30 kilometers in size for the first time. The image shows a pattern of turbulent gas that covers the entire Sun and is the signature of violent motions that transport heat from the inside of the Sun to its surface. Image by National Solar Observatory/Association of Universities for Research in Astronomy/National Science Foundation.

United States as Lead Funder and Host Country: The Daniel K. Inouye Solar Telescope

The Daniel K. Inouye Solar Telescope (DKIST), in Maui, Hawaii, with a 4.24-meter diameter, is the world's largest and most powerful solar telescope. Its data center is in Boulder, Colorado.

DKIST captured its first solar images in 2019 and is projected to continue to operate through the 2060s.[37] In January 2020, the telescope produced the highest-resolution image of the Sun ever taken, enabling a more detailed study of solar energy channeling.[38]

In addition to being located within the United States, construction of DKIST was U.S.-funded through the National Science Foundation, with an estimated total project cost of $344 million.[39] Most collaborators on the telescope are American, with the exception of the Leibniz Institute for Solar Physics of Germany and international researchers affiliated with American institutions.[40] The DKIST Science Policy Advisory Committee has developed guidelines for access to DKIST, observing time, and applicable data rights that follow guidelines published in 2014 by the Astronomy and Astrophysics Advisory Committee.[41]



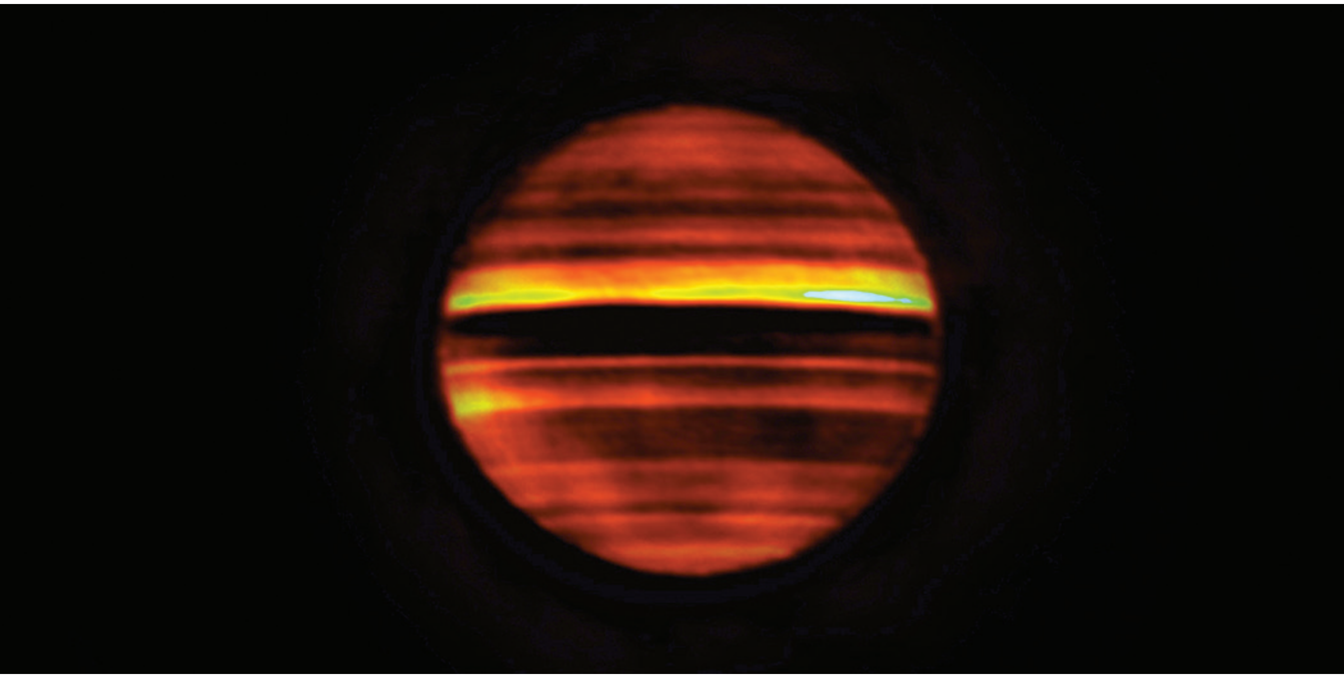
Artist rendering of highly misaligned gaseous planet-forming disks around two young stars in a binary system. This ALMA observation helps explain why so many exoplanets, unlike planets in our solar system, have highly inclined or eccentric orbits. Illustration by Robert Hurt (NASA/JPL-Caltech/IPAC).

United States in a Leadership Role with Another Country Hosting: Atacama Large Millimeter/submillimeter Array

The Atacama Large Millimeter/submillimeter Array (ALMA) is a radio telescope array on the Chajnator Plateau in northern Chile.[42] With fifty-four twelve-meter-diameter dishes available on a high, dry site, as well as much larger bandwidth and improved electronics, ALMA currently provides two orders of magnitude improved performance when compared with previous millimeter-wave arrays. This powerful telescope receives an average of 1,800 scientific proposals annually as scientists carry out observations using the array.[43] In one of these studies, scientists were able to visualize a binary pair of stars in orbit around each other at a higher resolution than was previously possible, enabling them to conclude that the stars' protoplanetary disks were misaligned, which would likely lead to planetary orbits unlike those in our own solar system.[44]

In another study, radio wave images allowed scientists to peer a full fifty kilometers below the clouds of Jupiter to observe the distribution of ammonia gases following an eruption.[45] These observations demonstrated, for the first time, that energetic eruptions on Jupiter bring up high concentrations of ammonia gas and help to explain what causes the planet's surface storms.

The United States, through the NSF, plays a major leadership role in this international collaboration that built and operates the ALMA instrument, along with the European Southern Observatory and the Japanese National Institutes of Natural Sciences.[46]



Radio image of Jupiter made using ALMA data. Bright bands indicate high temperatures and dark bands low temperatures. The dark bands correspond with the zones on Jupiter that often appear white at visible wavelengths. The bright bands correspond with the brown belts on the planet. This image contains more than ten hours of data, so fine details are smeared by the planet's rotation, like a long exposure photograph of a moving object on Earth. Image by ALMA (ESO/NAOJ/NRAO), I. de Pater et al.; NRAO/AUI NSF, S. Dagnello.

The collaboration was developed at a time when the United States, Europe, and Japan were each independently planning to enhance their millimeter-wave astronomy facilities. It quickly became clear that international collaboration and pooled resources would extend the opportunity for scientific discovery further than any region could achieve on its own. With the selection of the Chajnantor Plateau in the Chilean Andes as the optimal site, a Chilean representative was added to the board.

Construction of the observatory started in 2004 and initial observations began in 2011, with a total shared building cost of $1.4 billion and an average annual operating cost of $100 million.[47] Ongoing operations are funded by several European countries through the European Southern Observatory; by the United States, Canada, and Taiwan through the U.S. National Radio Astronomy Observatory; and by Japan, Taiwan, and South Korea through the National Astronomical Observatory of Japan.[48] Each partner has established and maintains a national data center (or multiple centers) that disseminates data and supports its respective ALMA observers.

The United States as a Major Coordinating Body and Funder for Distributed Networks: GA4GH and the IMPC

Example 1 The Global Alliance for Genomics and Health (GA4GH) was founded in 2013 to establish norms for internationally sharing genomic and clinical data. It works to enable all people to benefit from scientific advancements and to preserve "human rights of privacy, non-discrimination, and procedural fairness."[49] The GA4GH has identified core elements of a framework for responsible data sharing: transparency; accountability; data quality and security; privacy, data protection, and confidentiality; risk-benefit analysis; recognition and attribution; sustainability; education and training; and accessibility and dissemination.[50]

The GA4GH maintains multiple workstreams on these topics, moving toward establishing policies and guidance that will shape the fields of genomics and clinical research around the world. Meeting minutes and data toolkits are made freely available for use by the broader research community.

The United States participates in the GA4GH both as a host institution, through the Broad Institute of MIT and Harvard, and as a core funder, through the NIH. Host institutions, which also include the Wellcome Sanger Institute and the Ontario Institute for Cancer Research, provide administrative support and services, while core funders, which also include the Wellcome Trust, the Canadian International Data Sharing Initiative, and the Medical Research Council of UK Research & Innovation, provide financial support.

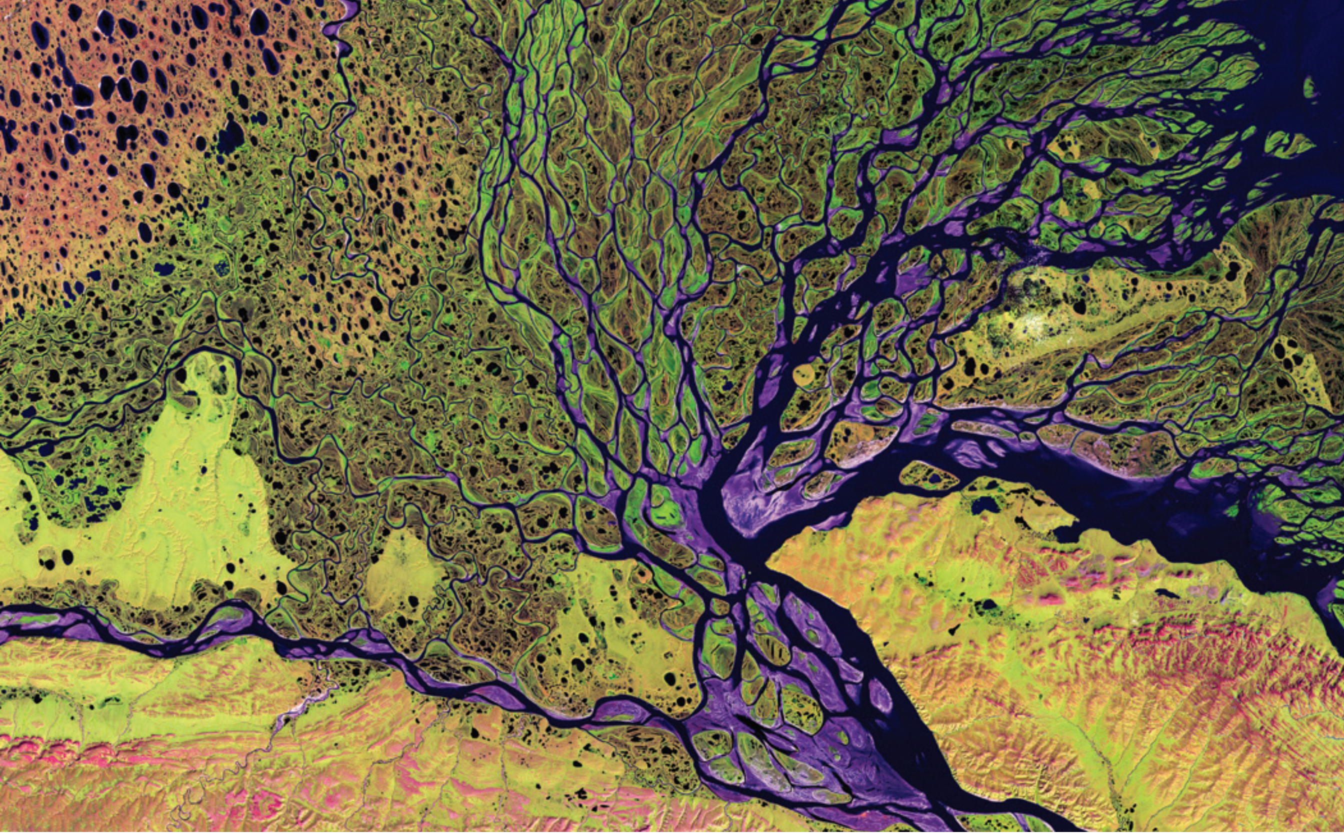
Example 2 The International Mouse Phenotyping Consortium (IMPC) is a coordinated international effort across nineteen research institutions in eleven countries. While the entire genomes of many species are known and published, the function of the majority of genes remains unknown. The IMPC's mission is to identify and catalog protein-coding gene functions for all twenty thousand protein-coding mouse genes and make this information freely available to researchers.[51]

The IMPC coordinates coalitions working on specific subgoals, such as the Knockout Mouse Project (KOMP), which has worked to produce and phenotype five thousand knockout mice to establish resources and databases for researchers studying diseases including cancer, diabetes, and heart disease.[52] Gene function is determined by systematically switching off each gene and subsequently performing physiological tests.

Many U.S. research institutions participate in the collaboration as voting members, and the NIH acts as the U.S. funder. International funding sources include the European Union's Intrafrontier program, the Wellcome Trust, Canadian genetic research programs, and several French national bodies and university programs.[53] The NIH contributed $110 million for a Phase I initiative recognizing the importance of this effort to overall disease modeling research, especially as members of the IMPC receive free access to mouse resources of lasting biological and medical value, including influencing gene selection and how they are tested, among other benefits.[54]

U.S. Participation in a Global Distributed Network: Global Earth Observation System of Systems Platform

On February 16, 2005, fifty-five countries, including the United States, endorsed a ten-year plan to develop and implement the Global Earth Observation System of Systems (GEOSS) for the purpose of achieving comprehensive, coordinated, and sustained observations of the Earth system.[55] GEOSS now integrates data sets of Earth observations from participating organizations in 111 countries with information and processing systems for users from both the public and private sectors.[56]



Landsat-7 satellite image of Lena river delta, part of a wildlife reserve in northern Russia. The United States participates in GEOSS primarily through the USDA, but the United States also contributes data collected from NASA, including from the Goddard Space Flight Center. See GEOSS Portal, https://www.geoportal.org/. Image courtesy of the NASA Goddard Space Flight Center.

GEOSS facilitates access to Earth data in service of the United Nations Sustainable Development Goals (SDGs) and Office for Disaster Risk Reduction (DRR).[57] It does so through an Internet portal as well as through a network of satellites for access in contexts with limited or no Internet.[58] In addition to incorporating data, GEOSS continues to improve its interface to increase accessibility and generate productive results for researchers and policy-makers.[59]

One way that the United States draws upon GEOSS data is through the U.S. Department of Agriculture Foreign Agricultural Service International Productions Assessment Branch, which monitors agricultural production worldwide in order to provide early crop yield warnings, such as in cases of drought abroad, for U.S. domestic interests.[60] Doing so allows the United States to monitor food supply concerns and prepare in advance of shortages.

GEOSS is administered through the Group on Earth Observations (GEO) and has over one hundred member organizations and participating international organizations.[61] The United States participates in GEOSS through the Integrated Earth Observation System (IEOS) and contributes data from all levels of government, industry, academia, and the nonprofit sector.[62] Since 2016, GEO has received funding from twenty nations around the globe, including the United States, plus the European Commission, the Institute of Electrical and Electronics Engineers (IEEE), and the University Corporation for Atmospheric Research.[63]

The Future of Large-Scale Science

Opportunities for major new scientific discoveries are on the horizon. To name just a few: gravitational wave observation technologies that will drive innovation; particle physics facilities that will enable breakthroughs in studies of the building blocks of matter itself; and advancements in brain science that will unlock treatments for some of the most devastating diseases and disorders on the planet.

The Future of Gravitational Wave Observations

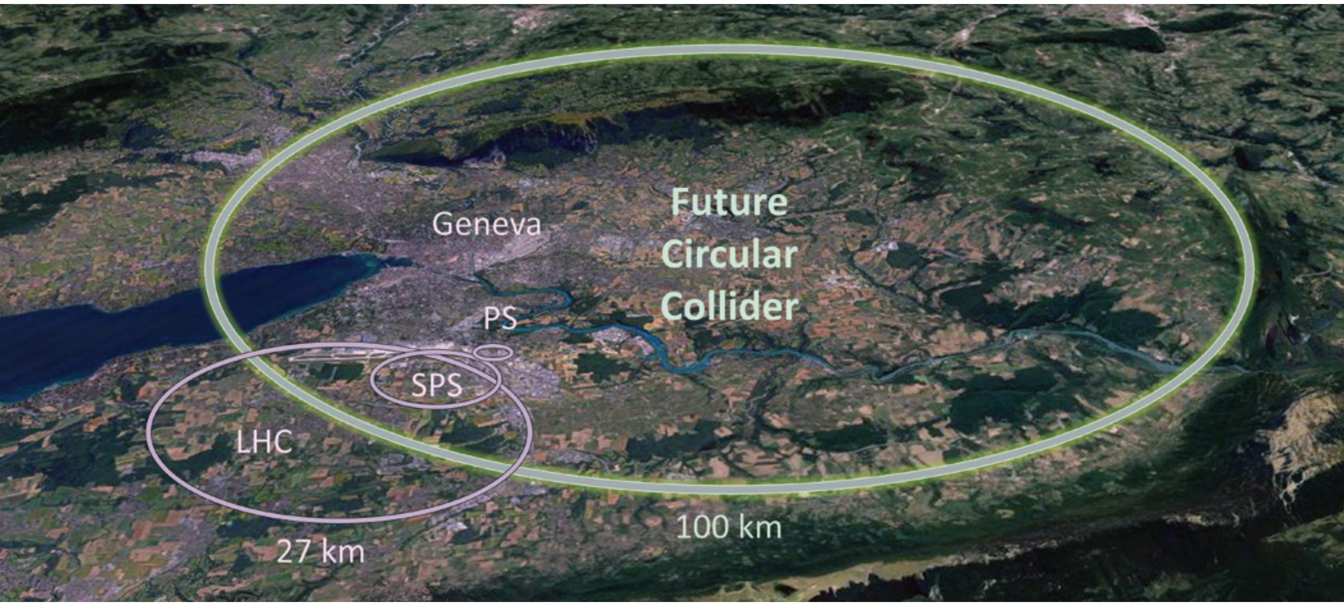
Advanced long-baseline interferometer construction around the world will provide new capabilities to observe gravitational waves. With the three interferometers (two based at LIGO in the United States and one at Virgo in Italy), localization is provided for about half of all possible locations on the sky; a fourth detector operating simultaneously with these three will allow directional determination of sources for all possible sky locations, thereby facilitating follow-up observations by astronomical telescopes. The United States and India are currently working together to build a detector in India, a collaboration between LIGO and three Indian institutes.[64] The United States is providing hardware, data, training, and assistance, while India is providing the site, infrastructure, labor, and materials. The lead agency for India is the Indian Department of Atomic Energy, which is cofunding the construction with the Indian Department of Science and Technology.[65] Japan completed construction of its interferometer, KAGRA, in October 2019 and began initial observations in February 2020. With five interferometers located around the world, it becomes much more likely that there will be four operating observatories at any one time.[66]

The international scientific community is also developing capabilities for considerably more advanced next-generation gravitational wave observatories that could observe gravitational waves from sources all the way back to the Big Bang itself.[67] For example, Europe is considering building the Einstein Telescope, for completion in the late 2020s at a cost of between $1 billion and $2 billion; the NSF is providing early design study funding for a third-generation observatory study based in the United States.[68] The European Space Agency is also leading development of LISA (Laser Interferometer Space Antenna), a space-based gravitational wave observatory, in partnership with NASA and an international consortium of scientists.[69] LISA will operate at low frequencies that cannot be accessed from the ground, thus providing a new capability for discovery. The technical demands of this instrumentation will drive the development of innovating technologies, such as microNewton thrusters to provide precise control of spacecraft position and pointing.

The Future of Particle Accelerators

Advances in particle physics facilities are taking place around the world. The CERN Council, in collaboration with the United States, Canada, and Japan, is working to complete the High-Luminosity LHC within the next ten years. This instrument will achieve luminosity that is ten times greater than that of the current LHC.[70] In 2019, the Council also authorized development of the design of a next-generation Future Circular Collider, intended to be the most powerful particle collider in the world.[71] Japan is considering hosting the International Linear Collider, which would allow for more in-depth exploration of the Higgs boson, and is discussing collaborative options with the United States and European countries for cost-sharing. China has unveiled planning for a future electron-positron collider that would have a circumference over three times that of the LHC. After ten years of operation, China plans to upgrade the facility to a proton-proton collider with more than seven times the energy of the LHC at its peak energy, similar in concept and scientific reach to the CERN Future Circular Collider.[72] The cost estimate for the initial collider is ¥30 billion, or $4.3 billion. Given the significant cost of future high-energy colliders, these facilities will likely require significant international partnership on a scale that exceeds CERN. In this regard, CERN provides a successful model of openness and cooperation among nations.

Fourth-generation facilities have been built in Brazil, France, and Sweden, with additional synchrotrons planned for China, Japan, and



The Future Circular Collider, currently under study by CERN, would use the existing Large Hadron Collider as an injector accelerator. © by Panagiotis Charitos and the European Organization for Nuclear Research.

the United States.[73] These facilities are investments that can enable diverse and international user communities to advance the frontiers of science over the course of decades. These circular sources are augmented by X-ray free electron lasers, driven by linear accelerators, that produce nine-to-ten orders of magnitude greater peak power in extremely short pulses, enabling structural studies of atomic motion. There are also plans for a multinational African Light Source, which would be the first synchrotron light source on the African continent.[74]

The Future of Brain Science

Treatments for neurological diseases and disorders are sorely needed. Stroke and neurodegenerative diseases represent leading causes of death, with 270,000 deaths reported from stroke and Alzheimer's disease in the United States in 2017.[75] However, pharmaceutical companies, initially drawn to neurological research in the 1990s by profitable discoveries of antidepressants and antipsychotics, have been shuttering their neuroscience divisions due to ongoing failures to identify novel therapeutics.[76] Federal and philanthropic funding in the United States and international funding for open basic and applied research have generated enthusiasm and promise for a greater understanding of the human brain, as well as the potential for future development of cures and therapeutics for brain-based diseases and disorders.[77]

As a field more broadly, brain science is undergoing a revolution that will have major implications for networks of international collaborators. The development of groundbreaking technologies is allowing researchers to peer into the workings of the brain like never before. This includes neuroimaging technologies such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and positron emission tomagraphy (PET).[78] Guided by theoretical insights in behavioral and cognitive science, the increasing accessibility and accuracy of such technologies is increasing our understanding of the complex neural circuitry supporting reading, learning, action, and emotion.[79] Brain-computer interfaces permit people with paralysis to operate machines with just a thought.[80] Genome editing, through technologies including CRISPR, allows for precise alterations of cellular function at different developmental times and in distinct cell populations.[81] Optogenetic approaches give researchers the ability to control neuronal signaling with the flash of a light, and ongoing clinical trials are attempting to use this technology to restore field of vision.[82] Single-cell sequencing has revealed new neuronal cell types never before known to exist.[83] Neuronal organoids, which approximate mini-brains in a petri dish, can now be easily grown from human skin cells and used for personalized therapeutics and mechanistic studies.[84]

However, each of these technologies and developments requires a common acceptance of protocols and approaches if researchers are to understand and build upon their colleagues' discoveries. Further, the use of these technologies remains labor-intensive enough that no one scientist or laboratory can develop a full data set for the entire brain using them; researchers must be able to directly compare their results and pool analyses in order to move forward in a holistic manner.

International networks of brain scientists will need to develop innovative ways of establishing these standards and openly pooling data to advance the field's understanding. The Brain Cell Data Center (BCDC) at the NIH brings multiple research centers, laboratories, and data repositories together to provide a reference of diverse brain cell types from multiple animal models and humans.[85] Although its mission extends beyond the brain to all cell types, the Human Cell Atlas provides an example of an international network of scientists using single-cell sequencing to build another repository.[86] Brain scientists have long worked in consortia to advance their studies; this approach will only become more critical in the years to come.

Beyond the challenge of collaborating to leverage a single novel technology, many scientists within the brain science community are simultaneously attempting a second shift: moving toward interdisciplinary research that will bring disparate fields together to understand the brain as a system of systems. For experimentalists, a true understanding of how neurons communicate with each other and give rise to the mind requires contributions from molecular biologists, anatomists, immunologists, bioengineers, psychologists, and experts in brain vasculature, among others. Some research questions require the combined approaches of theorists and experimentalists to find success.

To this end, the United States, through the NIH, NSF, DOE, Defense Advanced Research Projects Agency, Intelligence Advanced Research Projects Activity, and Food and Drug Administration, has crafted a vision for unlocking the mysteries of the brain by means of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative.[87] It coordinates awards across ten institutes of the NIH alone.[88] The initiative encourages international communication and collaboration at all stages, particularly on areas of shared interests like compatible data sharing approaches.[89] In the first five years of the initiative, the NIH invested over $559 million and funded more than five hundred scientists.[90] The NSF's investments have also expanded considerably through their Understanding the Brain activities.[91] These investments have led to major breakthroughs, including the development of advanced imaging tools that allow direct measurement of neuronal activity, smarter deep brain stimulation to treat diseases such as Parkinson's disease, and brain-machine interfaces that allow paralyzed people to operate computers.[92]

In addition to working through the U.S. government, the BRAIN initiative has partnered with NGOs such as the Allen Institute, the Howard Hughes Medical Institute, the IEEE, and the Kavli and Simons Foundations and with firms including Google and General Electric (GE) to advance its goals.[93] The initiative currently has several international partners in Australia, Canada, and Denmark. International scientists are eligible to apply for funding, which has so far totaled $1.8 billion through 2020.[94] Long term, the initiative has identified the establishment of international collaborative networks as a key goal, including partnerships with other brain science coalitions such as the Human Brain Project, an EU Flagship program, the China Brain Project, the International Brain Initiative, and the International Neuroethics Society.[95]

Working across silos can enable scientists to unlock the mysteries of the brain and the mind more rapidly and fully and thus enable new discoveries. Such an approach requires careful collaboration and organization that brings scientists of multiple disciplines together to solve common problems, valuing diverse perspectives. Although interdisciplinary brain science will certainly take place at the level of individual domestic institutions and U.S. initiatives, it will also occur among international endeavors, and the United States should work to partner with these efforts as they develop.

SPECIAL SECTION

COVID-19 and International Large-Scale Science

In the time this report was drafted, the COVID-19 pandemic spread around the globe, disrupting or shifting nearly all government, economic, and social systems. International large-scale scientific projects are not immune to these disruptions, and scientists around the world have scrambled to maintain operations and continue construction of new facilities as well as they can during the crisis. In addition, there is a growing realization that large-scale science initiatives will be important post-pandemic for addressing the threat of newly emerging infectious diseases that could result in future pandemics and threaten global and national security, economic prosperity, public health, and societal resilience. The important research on the SARS-CoV-2 virus at synchrotron X-ray facilities was highlighted earlier in this report. The importance of such facilities and the international network of scientists who rely on these facilities cannot be overstated in the post-pandemic world.

Immediate Challenges

As one example of the immediate COVID-19 related challenges faced by many scientific projects, CERN was temporarily closed, with most personnel working remotely and only about six hundred people, or 24 percent of the usual staff, on-site to ensure necessary safety. Teleworking was rapidly deployed, with an estimated peak of 13,900 connections to CERN's remote conferencing tool in one day.[96] Even once activities were able to resume, there were constraints on multiple experiments that were intended to occur in the same location, which significantly delayed project goals.[97]

Progress toward constructing ITER components was jeopardized in 2020 because China and Italy, two early epicenters of the pandemic, were responsible for substantial manufacturing roles. However, critical operations, including the arrival of ITER components from India, Italy, Japan, and China, have been maintained thanks to teleworking and digital communication infrastructure alongside essential on-site staff.[98]

Across the board, the pandemic has disrupted major components of development and management of international large-scale science projects. These disruptions include a lack of ability to travel for in-person meetings and site visits; an acceleration of the biomedical research community's trend toward publishing preprints, which moves research more quickly but also increases the risk of amplifying poorly conducted or incomplete studies; supply-chain crises; and everyday loss of access to scientific facilities.

The COVID-19 crisis has taught us many lessons, with more to appear as the effects of the pandemic continue to unfold, including:

- **Technological infrastructure that allows for remote operations can promote more effective initiatives.** Disruptions to travel and regulations against in-person gatherings have forced collaborators to engage with each other on virtual platforms and to operate systems from their homes. In some cases, these distributed approaches may actually prove more efficient than pre-pandemic norms.

- **The COVID-19 pandemic underscores the need for adaptability and resilience in large-scale science initiatives.** Although disruptions such as pandemics and other "acts of God" are not considered foreseeable risks, when they do occur, flexibility from appropriators, funders, and managers is important to ensure scientific goals will still be met; it should be understood and accepted that projects will be delayed and costs will increase. Extensions alone are not sufficient and must be accompanied by additional funding that addresses costs incurred during the pandemic.

- **National concerns could threaten investments in international large-scale science initiatives.** Many countries are suffering devastating economic circumstances because of the pandemic. Investments in domestic research and development (R&D) projects are often, rightly, looked to as opportunities to generate jobs and stimulate innovation. At the same time, participation in international collaborations is an essential component in sustaining a strong American science and technology enterprise and should not be ignored.

Preparing for the Future: Post-Pandemic Large-Scale Science

COVID-19 will not be the last pandemic we face, with prominent scientists suggesting we may be entering a pandemic era.[99] Some predictions estimate that as many as 1.6 million viral species have yet to be discovered in mammals and birds, with between 650,000 and 840,000 of those capable of spreading to humans.[100] The risk of these diseases reaching humans is compounded by climate change and the fragmentation of environments due to human encroachment, such as agriculture, deforestation, and urban development.

As COVID-19 has shown, pandemics have the potential to devastate economies, livelihoods, and communities; viruses also have no regard for national borders and politics. Being able to study and respond quickly to unfamiliar pathogens—for instance, by developing public health interventions, drug and treatment therapies, and vaccines—in addition to preventing the emergence of diseases in the first place, requires international scientific collaboration and science-driven policy-making. Collaborations to develop infrastructure for global coordination with established and emerging science partners alike are critical for ensuring that all regions have the research capacity and infrastructure available to respond when the next pandemic hits.[101]

Many international groups had been preparing for an outbreak such as COVID-19, and now are already hard at work preparing for the next. The World Health Organization (WHO), a specialized agency of the United Nations, has a long history of supporting vaccine campaigns and coordinating responses to disease outbreaks, including the SARS epidemic in 2003 and outbreaks of Ebola in West Africa and the Democratic Republic of the Congo in 2014 and 2018, respectively. The WHO has, of course, also been at the forefront of the response to COVID-19.[102] Collaborative efforts like the Global Virome Project are working with a variety of sectors, including business, academia, government, and nonprofit, to conduct essential research in this critical space (See the Global Virome Project on page 25).[103]

The United States has historically been a leader in emerging infectious disease research. The PREDICT program, led by the UC Davis One Health Institute, USAID, EcoHealth Alliance, Metabiota, the Wildlife Conservation Society, and the Smithsonian Institution, was launched in 2009 to identify hotspots for the emergence of zoonotic diseases and propose One Health surveillance methodologies in such areas.[104] Since its formation, the program has worked with collaborating scientists and researchers around the world to collect over 140,000 biological samples and detect more than one thousand new viruses, in addition to serving as a capacity-building effort by training scientists and strengthening research laboratories in more than thirty countries in Africa and Asia.[105] The program seeks to bring an organized and coordinated scientific response to emerging biological threats. Although it was discontinued in October 2019, just months before the COVID-19 pandemic began, an extension to the program in April 2020 allowed it to resume its efforts and provide key support to partners around the world in the response to COVID-19.[106]

Researchers continue to advocate for and engage in international collaboration in circumstances of crisis, such as the COVID-19 pandemic.[107] This engagement must continue to include both research on the virus SARS-CoV2 and investigations, such as those led by the WHO, into the circumstances that led to the pandemic.[108] As a leader in life science and health related research, the United States has a key role to play in the international study and prevention of emerging infectious diseases, as well as the international standards for such studies. The United States also has a vested interest in partaking in such vital collaborations to ensure both national and economic security. As the world braces for the next pandemic, the United States should strongly invest in prioritizing research in global health.

> “Large-scale science initiatives will be important post-pandemic for addressing the threat of newly emerging infectious diseases.

The Global **Virome Project**

As recently as 2019, some were questioning the need for dedicating substantial funding to research at the animal-human infectious disease nexus.[109] Since the emergence of the COVID-19 pandemic just a few months later, the importance of research to prepare and respond quickly to large-scale, global threats has become apparent.

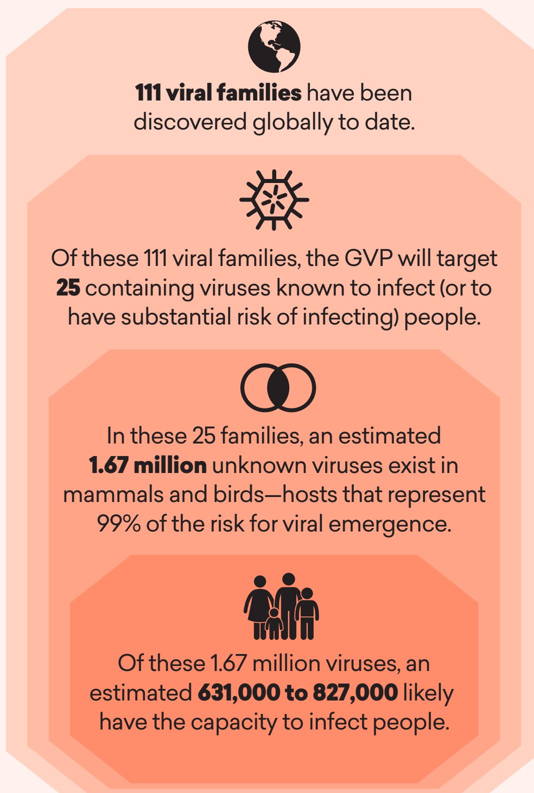
The Global Virome Project (GVP), an international collaboration initially proposed in 2016, seeks to address this need through an ambitious international collaborative effort to build an atlas for infectious diseases.[110] Estimating that there are likely 1.67 million undiscovered viruses existing in birds and mammals, with a significant portion of those potentially able to infect the human population, the GVP has begun work to complement the efforts of USAID's PREDICT program, with its goals to aid in capacity-building and epidemiological analysis, by conducting a large-scale sampling and viral discovery undertaking.[111] While the collaboration is still in its early days, it has gathered significant attention in the past few months as COVID-19 spread across the world, although some scientists are still skeptical about its proposed efficacy given that viral sequencing cannot directly predict pathology.[112]

The collaboration emerged following a gathering of international experts from a variety of sectors at the Bellagio Forum in 2016, where attendees agreed to a set of goals and core principles that would allow the collaboration to build a safe world and quickly respond to and address the threats posed by infectious diseases.[113] The GVP engaged stakeholders across the world in Asia, Africa, the Americas, and Europe, including from academia, industry, intergovernmental agencies, NGOs, and the private sector, to build a framework for the GVP collaboration: the development of financing streams, data and sample sharing protocols, collaborative field and laboratory networks, risk assessments, capacity-building strategies, and more.[114]

Using the 1980s Human Genome Project as its model, the collaboration hopes to catalyze an era of research in the space that will return significantly more than its investment and yield key benefits for the well-being of people around the world.

GVP Targeting Strategy

The project will capitalize on economies of scale in viral testing, systematically sampling mammals and birds to identify currently unknown, potentially zoonotic viruses that they carry.



Original figure by V. Altounian/*Science*.

Principles for International Large-Scale Science

Initiation of, or participation in, international large-scale science has associated complexities not faced by other research efforts that do not require large-scale instrumentation, multiple international partners, or vast data collections. The CISP Large-Scale Science working group examined many examples of successful and not-successful large-scale science partnerships and held several workshops and consultations with government funding agencies to identify guiding principles for the formation and organization of international large-scale science partnerships to ensure their appropriateness and success.

International large-scale science can involve multiple approaches, scores of countries, thousands of scientists, and billions of dollars. Marshaling these forces to make significant scientific gains requires vision, organization, and management. These efforts are more likely to succeed when collaborator relationships are built on mutual trust and respect and significant attention is paid in the earliest phases to planning, governance, operations, and sustainability.

The following principles are recommendations for U.S. participation in successful large-scale international collaborations, across scientific disciplines and project goals.

Prioritize Scientific Excellence and Impact

Principle 1.1 *Participation in large-scale science by the United States must be driven by the quality of the science and the potential for significant scientific benefit, as determined by the relevant U.S. and international scientific communities. Projects may also have diplomatic or economic justifications, but without sound scientific basis, they are more likely to fail.*

Support of the scientific community may manifest in different ways depending on the project and field. For large networks of scientists working toward shared goals, grassroots engagement may provide evidence of enthusiasm. For projects that require upfront and long-term substantial investments from the U.S. government, as is frequently the case for large-scale facilities, decadal surveys or specially constituted advisory committees composed of scientists in the relevant field can serve as an indication of support for a given venture.

The U.S. research funding agencies have well-established procedures for determining the scientific justification and community support for large-scale domestic projects. Often, but not necessarily, these include assessments by the National Academies of Sciences, Engineering, and Medicine. It is equally important that similar procedures be adapted and employed for consideration of large-scale

international projects, especially projects aimed at capacity-building in emerging scientific regions. When research objectives or funding involve multiple U.S. research funding agencies, a clear, transparent interagency decision-making process is needed.

Some international large-scale scientific projects have political and/or economic drivers in addition to scientific benefits at the outset. These may include strengthening international relations, as in the case of the International Space Station and ITER; bringing economic benefit, as in the case of EU Flagship programs; or increasing the research capacity for the development of emerging science partners.[115] If these goals rise to the level of becoming primary drivers of the collaboration, project management and sustainability are likely to become more challenging and complex. Even if these factors are present and emphasized, the United States must still anticipate meaningful scientific benefit as a prerequisite of the project.

Finally, the project must have a strong and diverse scientific leadership team (see Principle 2.1).

Develop Well-Defined Project Scope and Effective Management

Principle 2.1 *Strong scientific leadership is required, both in executive offices and in oversight, such as on government councils, boards, and review committees.*

Principle 2.2 *A project's formulation phase should receive sufficient resources and be of sufficient length for partner relationships to be established and for partners to develop a detailed implementation plan that includes project scope, budget and schedule, an assessment of risks, a management plan including risk management, and, as appropriate, an understanding among the partners about decommissioning at the conclusion of a project.*

Openness among international partners is recognized as the best approach to developing a successful project and is best established during project formulation. There should be a recognition that problems are inevitable and should not be hidden. Problems and their resolution are a normal part of a project. All partners should own the problems, and all partners should share the successes.

Diversity, broadly, is a key component of strong scientific leadership (see Principle 1.1). Specific considerations in international large-scale science collaborations include nationality, scientific discipline, academic or private sector background, relative seniority, gender, and race.

Principle 2.3 *The scientific objectives, technical readiness, and managerial competence of the project must be formally and thoroughly assessed. The partners and their national sponsors should agree on the project goals. Project budgets and schedules should be systematically developed and reviewed. There should be agreement on the way each nation is to support the project. Project management and capability to carry the project out must be included in this assessment. Regular independent management and project reviews must be scheduled and implemented as the project proceeds.*

Agreement by all international participants on the goals and parameters of a project is crucial for the project to succeed. Mechanisms for reaching decisions, if it is appropriate to modify these goals and/or parameters with new information, should be agreed upon beforehand. Such mechanisms are particularly important when major challenges arise in projects, as they almost inevitably do.

For large-scale physical facilities, it is vital that the entire project, as well as U.S. major in-kind component developments, are subject to careful reviews, such as those carried out by the DOE Office of Science, on a regular basis. Such reviews can often identify problems at a sufficiently early stage to remedy them effectively.[116]

When projects require sequential phases of construction and operation, as in the case of facilities, success in each of these phases may in turn require distinct approaches, including a different management structure, new personnel, and evolving budget and task responsibilities.

Project partners should agree in advance on whether intellectual property (IP) protection will be necessary. Collaborators should build a framework under which inventions will be disclosed and patents will be filed, including a clear framework of how IP will be owned and how disputes will be resolved.

Principle 2.4 *Collaborators must identify appropriate governance and project management models for achieving their scientific goals. A transparent approach, discussed and ratified at the earliest stages of the collaboration, is essential.*

There are many models for addressing leadership and governance in international scientific partnerships and for dealing with crises or major problems, should they occur. Addressing these considerations early, ideally during project formulation, can help minimize later project risks and avoid confusion.

ITER is one project example in which inadequate management and organizational structure, along with prioritizing diplomatic justifications above scientific rationale, led to significant cost increases, delays, and risk of cancellation (see page 29). It also serves as an example of how improvements in management restored public trust in the project and renewed scientific progress.

As collaborative governance structures frequently lack clear organization and hierarchies and work across time zones and physical locations, consistent operations and efficiency can be challenging. There is no one-size-fits-all solution, as there is variation in the objectives and governance structures across international collaborations. As with other challenges that confront international science partnerships, organization and general operating principles should be discussed early on and reviewed regularly to ensure that the entire team is well-informed. Procedures for approval of scope changes should be included in the basic agreements.

Modifications in governance need to be transparent and communication procedures clearly established.

Meet Commitments

Principle 3.1 *Once the United States, through its agency and interagency review processes, has committed to a project, the Congress, U.S. agencies, and the White House Office of Management and Budget should bolster mechanisms to ensure that the United States can meet its financial commitments.*

While this is sometimes very hard to do, it is important to have a clear, documented decision process to refer back to, should difficulties arise.

ITER and the **Challenging Road to Fusion Power**

ITER is a project to build the largest tokamak, or magnetic fusion device, in the world.[117] It is a collaboration of thirty-five countries, including the United States, sited in southern France. Its goal is to advance fusion science, to contribute to the development of fusion power plants, and to act as the first fusion device to produce net-positive energy.[118] Cost of the construction of the instrumentation is estimated to be as high as $65 billion, according to the DOE, though the ITER organization estimates the cost to be closer to $22 billion.[119] Costs are shared across the members of the ITER organization, with the European Union covering 45 percent of the construction costs and the remaining members—China, India, Japan, South Korea, Russia, and the United States—contributing 9 percent of the costs each.[120] Originally scheduled for completion in 2016, the most recent estimate for its full deuterium-tritium operation is 2034–2038.[121]

In the summer of 2013, ITER requested its regular internal audit, which is required every two years.[122] This audit found deep structural issues within ITER, including the inability of the ITER organization to successfully manage each member's domestic agency, units created within the ITER structure with their own budgets and staff. Decision-making capabilities were constrained under this format due to the underlying governance structure pitting political interests of domestic agencies against the overarching ITER council.[123] This review was quite critical of the ITER project and led to immediate reform discussions within the collaboration.[124]

In late 2014, ITER nominated a new director-general, Bernard Bigot, who committed to reforming management and governance structures and developed a more realistic, science-based schedule, reducing political influence. This shift has delivered on its promises, leading to restored support from the European Union and other nations, including cash contributions from the United States.[125] In July 2019, ITER installed its cryostat base and lower cylinder, a major construction milestone that brought the project to 65 percent completion.[126]

The International Thermonuclear Experimental Reactor construction site for its experimental tokamak, a magnetic plasma confinement device intended to produce controlled thermonuclear fusion power, in Saint-Paul-les-Durance, France. Photo by Christophe Simon/AFP via Getty Images.

Principle 3.2 *The United States should be open to participating in international large-scale science projects based outside of the United States and ensure that funding commitments for the U.S. contribution to the project are honored. Given the realities of annual appropriations, U.S. agencies considering participation in large-scale international projects should weigh at least two options:*

A. *Full membership participation, similar to U.S. participation in ITER.*

B. *A substantial but limited and well-defined commitment that is highly likely to be met even under budget uncertainties. Examples are the DOE's and the NSF's commitments to CERN (see Appendix A).*

Option A provides the agency with a direct role in the governance of the project, but with the danger that the United States may not meet its commitments. Option B may only assure an indirect governance role.

Principle 3.3 *Procedures should be in place to ensure continuity of project leadership, stakeholder engagement, and risk management. Further, scientific and political leadership teams need to work in tandem to ensure goal alignment.*

Successful initiation and maintenance of international scientific collaborations require long-term, steady financial commitments. Further, once made, it is essential for these commitments to be upheld, both for the realization of the individual collaboration in question and for building and maintaining trust that the United States will remain a reliable partner.

Both new and long-standing international collaborations, depending on scale, can be challenging for the United States to fund, although projects that are a high priority for the scientific community and its related funding agency partners are more likely to continue to be built into federal budgets. The U.S. budget is developed and approved by the president and Congress on an annual basis, but for decades, this process has not been completed in a timely fashion, and Congress has maintained funding through continuing resolutions that may or may not be consistent with previous commitments. Further, leadership changes on congressional committees and at scientific agencies and offices such as the Office of Science and Technology Policy (OSTP) and the OMB, both across and within presidential administrations, can reverse funding directions if the project does not have strong political support and is not prioritized by the scientific community.

While the United States can join a long-term international collaboration and discuss long-term funding, it is usually unable to guarantee that funding beyond one year. The budgets for science funding agencies fluctuate with each annual appropriations cycle, affecting the resources available for international programs and complicating participation in international large-scale science. One exception, likely related to geopolitical considerations, is the Israel-U.S. Binational Industrial Research and Development Foundation, which is endowed. Several nations use multiyear funding plans, including the European Union and China, but even then, aligning various national funding schedules with a project budget can be very challenging.

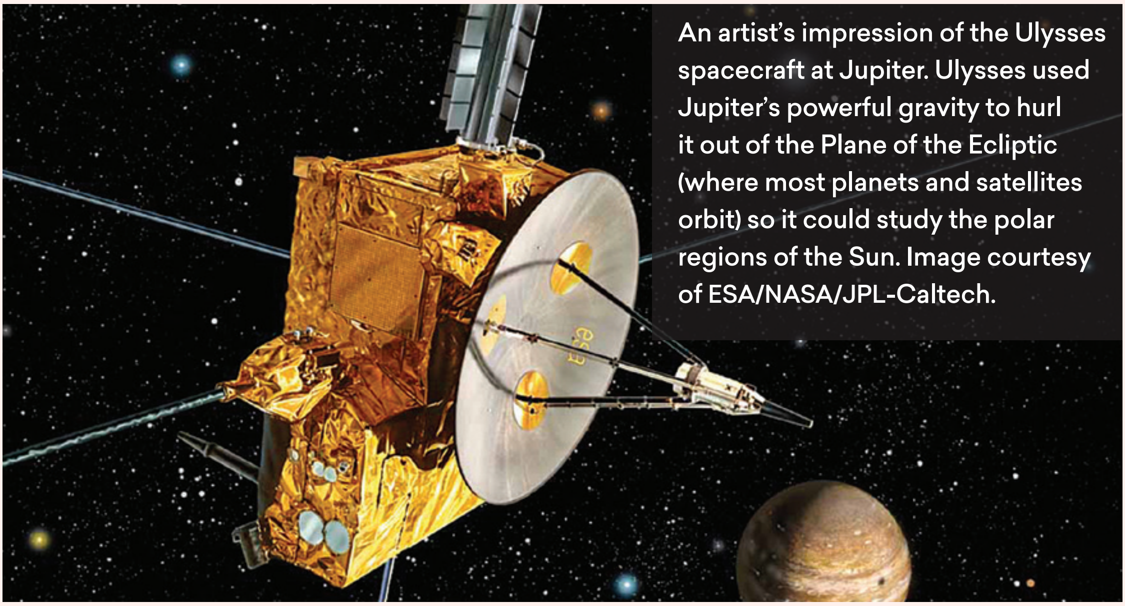
The International Solar Polar Mission (ISPM) is a prime example of the potential pitfalls of annual appropriations: uncertainty in U.S. funding led to a project breakdown between NASA and European partners that required a descope of the mission for the collaboration to continue (see page 31).

Challenges to Meeting Financial Commitments: The International Solar Polar Mission

The International Solar Polar Mission (ISPM), a collaboration between the U.S. National Aeronautics and Space Administration (NASA) and the European Space Agency (ESA), was a two-satellite mission designed between 1974 and 1979 to study the Sun's poles. NASA and the ESA each committed to providing a satellite and instruments and signed a memorandum of understanding (MOU) in 1979 for a planned launch in 1983.[127]

In contrast to the ESA funding, NASA's ISPM budgetary requests, a total of $250 million, encountered significant obstacles. In 1980, the planned ISPM launch was pushed back from 1983 to 1985 due to budget cuts to NASA, which not only delayed the launch but also decreased the payload capability of the launch by 40 kilograms.[128] In 1982, the overall NASA science budget was cut from $757.7 million to $584.2 million, a gap that forced NASA to choose between funding ISPM or the Galileo mission to Jupiter and the Hubble Space Telescope. In response, NASA canceled its ISPM spacecraft, which further delayed the launch of the ESA satellite.[129]

The ESA argued that the United States had breached its MOU and generally expressed frustration, which then pressured U.S. offices including the Office of Management and Budget and Office of Science and Technology Policy to recommend making funding available for a reduced mission.[130] This did not occur, and the project proceeded with the ESA providing instruments and a single spacecraft it renamed Ulysses in 1982.[131] NASA provided a radioisotope thermoelectric power generator for the spacecraft and tracking after launch with the Deep Space Network. The spacecraft was launched by NASA from the Space Shuttle Discovery cargo bay and carried out a successful eighteen-year mission as the first exploration of space above and below the Sun's poles.[132]



An artist's impression of the Ulysses spacecraft at Jupiter. Ulysses used Jupiter's powerful gravity to hurl it out of the Plane of the Ecliptic (where most planets and satellites orbit) so it could study the polar regions of the Sun. Image courtesy of ESA/NASA/JPL-Caltech.

When political support for international scientific partnerships decreases, particularly in the context of strained bilateral international relationships, they can be difficult to sustain. A lack or change of political support may manifest in a variety of ways, such as decreasing or cutting off funding, maintaining a funding rate below that of peer nations, and restricting collaborations between U.S. researchers and researchers in other countries.[133]

Other politically charged obstacles to international cooperation include increased difficulty obtaining visas, export/import issues, sanctions, and onerous regulations. In addition, domestic politics can affect international research efforts, as partisan politics may target activities supported by political opponents for ideological reasons. Although many scientists consider their research endeavors to be distinct from political interests, international scientific collaborations are not conducted in a political vacuum, and while they can be used to strengthen international relations, they can also become victims of political priorities. The International Institute for Applied Systems Analysis (IIASA) has served as one institution that allows collaboration to continue even in cases where political support wanes (see page 33).

As geopolitical circumstances evolve, political support for certain forms of international collaboration can ebb and flow. This fluctuation presents a challenge for sustaining long-term scientific partnerships that require national data, funding contributions, and strong peer-to-peer relationships. It is important for scientific partnerships to persevere in the face of these political challenges, especially when international relationships are strained.

Technical and project management strain can pose severe threats to large-scale scientific undertakings, and difficulties can arise at any point in the collaboration, from project design through construction and ongoing management. Any of these challenges can result in questions about ongoing funding. Risk assessment, a risk management plan, and, in some cases, project descoping plans are essential for addressing and mitigating project challenges.[134] Trust among partners and transparency should be established early in a project's lifecycle. Interdependence of all scientific partners is key for successful project continuance, and it is important to have agreement among partners on how risks will be managed, how project reviews are to be conducted, and how technical problems will be addressed. All problems, alongside all successes, belong to all partners.

Ethics, Culture, and Values: Establish Ethical Standards for the Conduct of Research

Principle 4.1 *Codes of conduct are essential and need to be developed jointly by partners, not prescribed. To be successful, ethical codes need shared buy-in and collaborative development by the scientists and scientific institutions involved, including scientists and scientific institutions representative of partners from all nations involved. This is especially true when there are issues of trust, such as strained geopolitical relations or between developed and developing nations.[135] Project leadership must take an active role in cultivating ethical norms and standards through transparent and open dialogue.*

Principle 4.2 *Social scientists and ethicists should be included in the earliest stages of developing an ethical code for collaboration. Relevant stakeholders need to be engaged in this development as well; these groups may include the interested public, local and regional governments, and related organizations.*

Institutional Independence and IIASA

The International Institute for Applied Systems Analysis (IIASA), housed near Vienna, Austria, conducts multidisciplinary, systems-analysis research on policy-relevant topics such as climate change, aging, development, and energy. The United States and the Soviet Union, along with ten other states, including East and West Germany, founded IIASA in 1972 to promote nongovernmental, independent research that would build diplomatic bridges during the Cold War.[136] Today, IIASA has twenty-three national member organizations that sponsor research activities.[137] The United States participates in IIASA through the National Academies of Sciences, Engineering, and Medicine (NASEM), and its membership is funded by the NSF.[138]

IIASA's institutional independence allows scientists from states that do not formally recognize each other or are locked in adversarial relationships to work together, as seen perhaps most dramatically between the United States and the Soviet Union during the Cold War. Although the United States formally cut off funding to IIASA for several years in the 1980s, the American Academy of Arts and Sciences acted as the U.S. member and, along with the American Association for the Advancement of Science, worked to provide funds from private sources until the U.S. Congress allocated funds once more.[139] The American Academy remained the U.S. committee sponsor for IIASA until 2003, when NASEM retook the role.[140]

During the 1980s, an IIASA research team conducted a study on water pollution that is still used by water policy-makers today in the United States, the former USSR, and Japan.[141] IIASA's impact has spread to other research endeavors, serving as an example in the formation of the Intergovernmental Panel on Climate Change as well as the International Geosphere-Biosphere Programme.[142]

The 30th Scientific Committee Meeting of the International Geosphere-Biosphere, titled "Integrated Science for Sustainable Transitions," in Laxenburg, Austria, April 2015. Photo © by Matthias Silveri/IIASA.

Principle 4.3 *A written code of conduct, with sign-off from all collaborating parties, should be developed by the project to ensure adherence to the agreed-upon norms.*

Building a large, international team of researchers links all partners to each other, and scientific success depends on generating and adhering to ethical codes of conduct. Building and maintaining trust in a "culture of conscience rather than a culture of compliance" is important.[143]

Misconduct

Early and respectful discussion of project approaches and shared expectations is essential for establishing a framework accepted by all partners that works to prevent and address issues of misconduct. Such a framework should consider issues of potential bias, exploitation, representation on management teams, career advancement, and equal compensation, among others. It should promote fairness, equity, and trust and establish a process for resolving disagreements. It is important to build these policies from the grassroots of the collaboration so that it is embraced by all participants, regardless of institution, but it is the responsibility of project leadership and senior scientists to ensure that this process is appropriately conducted and structured.

Race- and gender-based misconduct and inequities, including bias, harassment, and violence or the threat of violence, can severely obstruct research goals and can make it so scientists are unable to perform or are hindered in their work.[144]

Scientists and engineers should consider possible ethical ramifications of their technology developments, including social change, economic change, cultural disruption, systemic bias, and environmental impacts. A primary ethical concern for international collaboration is exploitation, especially in paternalistic relations between countries.[145] Careful attention to ethical issues is particularly important for researchers unaccustomed to linking their developments to broader societal implications.

Heightened challenges arise in research contexts involving countries with limited scientific resources, where some U.S. scientists' activities have been widely recognized as unethical, insensitive, or inappropriate, and have undermined trust in collaborations with U.S. researchers. Taking account of historical forms of colonialism or the presence of xenophobia can also be important when building ethical scientific collaborations. Human Heredity and Health in Africa (H3Africa), a genomic research consortium, is one organization working to address such issues as international genomic collaborations evolve (see page 35).

Integrity of Results and Data Sharing

Ethical codes of conduct should consider how to ensure integrity of results, including on issues of plagiarism, alignment of scientific goals, and publication and authorship expectations. This is especially important for early-career researchers who frequently depend on these metrics for career advancement.[146] Too often, agreements between U.S. scientists and foreign collaborators have few constraints and are established with broad MOUs.[147] This may in part be because forming these agreements is viewed as being a burden, inconvenient, and legalistic.[148] However, these agreements become increasingly important as projects proceed and results, large data, and potential inventions are generated, especially when ensuring privacy and equity is essential. In developing MOUs, efforts should be made to anticipate and

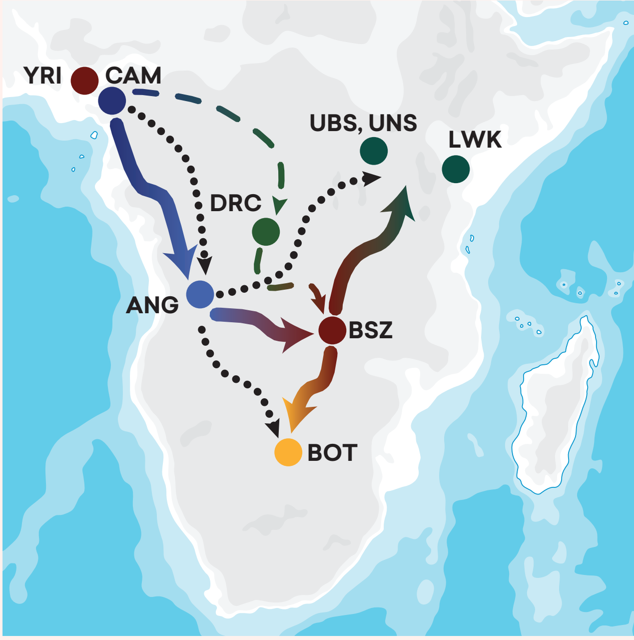
H3Africa: Generating Research—and Ethical Principles for Research

Human Heredity and Health in Africa (H3Africa) is a research consortium that applies genomic technologies to better understand health and disease.[149] It consists of more than 500 consortium members and has directly led to 219 publications on studies of samples of over 70,000 participants across the continent.[150] The collaboration is funded by the Wellcome Trust, the NIH through its Director's Common Fund and Global Health Program, and the African Academy of Sciences.[151]

In addition to funding 51 African-led research projects, the consortium develops ethical guidelines, conducts trainings, and builds scientific infrastructure. H3Africa has been notably invested in generating ethical principles for research from its inception through the creation of a working group on ethics that established governance frameworks.[152] At a conference hosted in Abuja, Nigeria, in 2011, a group of bioethicists, scientists, and policy-makers from Africa, the United States, and the United Kingdom convened to develop the first plan for ethical genomic research conduct in Africa.[153]

More recently, in 2018, the H3Africa ethics working group released a set of voluntary guidelines for ethical genomics research based upon conversations with African researchers and ethics review boards.[154] Its recommendations are specifically geared toward prevention of so-called helicopter or parachute research, in which foreign scientists take African samples to their home institutions to study and often fail to include African scientists in data analysis and publications. The recommendations encourage inclusion of "meaningful and substantive" African intellectual contributions, minimal removal of samples from the African continent, and the prioritization of research that will benefit African citizens.[155] The acceptance and implementation of these recommendations is an ongoing process, however, as capacity-building for African computational facilities continues and some commercialization efforts in the United Kingdom have led to accusations of improper use of samples collected on the African continent.[156]

New models for population migration patterns were inferred by genetic distance estimates from the H3Africa collaboration. The figure below is a re-creation of an illustration printed in Ananyo Choudhury, Shaun Aron, Laura R. Botigué, et al., "High-Depth African Genomes Inform Human Migration and Health," *Nature* 586 (7831) (2020).



address potential issues, making such agreements effective when they are needed.

As "big data" increasingly become the norm across numerous scientific disciplines and collaborations of all scales, consideration of data management upfront becomes paramount. Data management challenges are manifold and vary by research topic.[157] In collaborations with researchers in countries with limited data infrastructure, issues of data hosting and processing may be at the forefront. In other cases, personally identifiable information may need to be protected in data collection and analysis. Likewise, there are various international agreements in existence and discussions underway about the handling and ownership of genetic resources and data or research related to military or dual-use technologies.[158] Finally, conversion across data analysis processes may require substantial upfront investment.

Privacy concerns are increasingly salient as large data sets are generated, often from human subjects. The European Union's General Data Protection Regulation (GDPR) is a major driver of constraints on data sharing in international life sciences collaborations. In many collaborations, the GDPR must be addressed in early project stages along with additional country-specific guidelines.

Some countries are hesitant to release or openly share data, while others, including the United States, are host to movements toward open science and increasing public access to publications and their associated data.[159] It is important to discuss data rights, ownership, use, and publication policy in advance of project initiation and data generation, preferably through written agreements and clear publication processes, as well as a management strategy for making changes to agreements (see MOSAiC on page 37).

Cultural Differences

Different cultures, including variations across scientific disciplines, may have divergent views on issues such as authorship rights, definitions of plagiarism, data ownership, and the ethical implications of technological development.[160] They may also have varied perspectives on interpersonal interactions based on gender, race, discipline, or seniority. As one example, the United States has a particularly strong culture of publication that may not be present in all international collaborations.[161] Frequently, these differences are not sufficiently discussed when establishing scientific partnerships, leading to significant disputes as the research matures.[162] Each partner should understand the limitations imposed on others by their respective cultures, budget cycles, and funding sources before attempting to modify them.

Cultural differences can be both fundamental and not obvious, frequently taking place at the level of language and what is considered "common sense."[163] Long-term partnerships tend to be the most challenging to create and maintain, and for academic research, building understanding at the individual level becomes a key factor.[164] U.S. postdoctoral trainees and graduate students native to the collaborating country may be especially well-positioned to provide insight into cultural differences.[165]

It is possible that cultural differences will become apparent over the course of addressing other topics (such as management or publications). Explicitly spelling out details of the collaboration can help to ensure that the cultural differences are understood and addressed as early as possible. For some projects, memoranda of understanding followed by memoranda of agreement can be valuable for clarifying cultural differences.[166]

MOSAiC: Filling the Holes in Climate Data

Climate change models and projections are used by governments and international bodies around the world for the generation of evidence-based climate policies. These models are built upon global observations of climate data, and their utility improves as the data do. Currently, the Artic climate system is relatively less represented in climate models due to challenges in collecting data from the Central Arctic in the year's coldest months. Data from this region are especially important for understanding the effects of climate change on the Arctic system, since the Central Arctic has a significant role in warming rates, as evidenced by its increasingly frequent ice-free summers over the past century.[167] In response to this research need, a massive international collaboration has launched to study the Arctic climate system year-round.

The Multidisciplinary drifting Observatory for the Study of Arctic Climate (MOSAiC) is a floating facility in the form of a German research icebreaker ship and observatory surrounded by distributed monitoring systems. Built to collect consistent data in the Arctic region over the period of a year, the collaboration is working to improve global understanding of the Arctic climate system to strengthen climate change models.[168] The expedition, which launched in 2019 with a total project budget of approximately €140 million, includes hundreds of scientists from seventy research institutes across twenty countries, including Canada, China, Japan, South Korea, Russia, and many EU member countries.[169] The United States participates via federal bodies, including the NSF, DOE, NOAA, NASA, and the Navy, as well as through numerous public and private universities.[170] Led primarily by the Alfred Wegener Institute in Germany, the United States also provides key support through the U.S. Cooperative Institute for Research in Environmental Sciences (CIRES), located at the University of Colorado Boulder, and through the NOAA Earth System Research Laboratories Physical Science Division; the United States is the second-largest funding contributor to the collaboration with support from the NOAA, NSF, DOE, and NASA.[171]

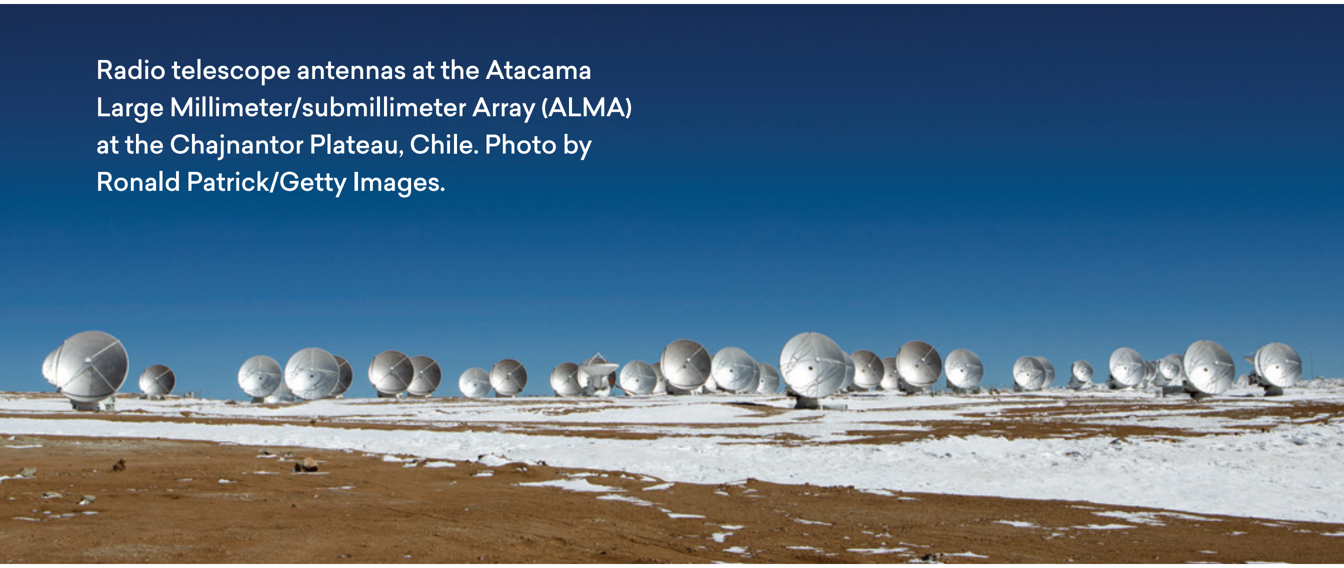
One of the pillars of the MOSAiC collaboration is open data sharing practices.[172] All participants are required to store their data on the central MOSAiC database, which is accessible to all collaborators. These data will remain internally accessible to the collaboration until 2022, and then will become open to all people on January 1, 2023. The project is committed to scientific integrity practices: as one example, any manuscript that uses data obtained from the collaboration must be reviewed and approved by the owners of those data, who also must be cited in publications written by other researchers. This approach is explicitly linked to the scientific mission, which seeks to improve the lives of all people, and not one nation or group alone.

Photo © by Alfred-Wegener-Institut/
Mario Hoppmann.

Conclusion

The United States and its scientists played key roles in all of the major scientific advancements described in this report. This was made possible by continuing substantial U.S. engagement with the international scientific community and financial investment in large-scale science. Although major advancements can be made on a national level, international engagement will be imperative for much of the future of large-scale science. If the United States does not continue to collaborate and fund large-scale science, tomorrow's scientific cutting edge will move forward without American leadership and participation. Not only will our nation no longer be at the forefront of scientific research, but we will also lose the enormous economic and social benefits generated by the innovation and technology based on scientific discoveries that are developed to pursue research questions.

Recognizing both the importance and the complexity of international large-scale science means we must be realistic when considering such partnerships. When engaging in international large-scale science, it is imperative for the United States to prioritize scientific excellence, properly scope projects, do everything it can to meet its commitments, and promote ethical collaborations with strong values across cultures. The principles identified in this report provide mechanisms by which the United States can more effectively and beneficially participate in these partnerships.



Radio telescope antennas at the Atacama Large Millimeter/submillimeter Array (ALMA) at the Chajnantor Plateau, Chile. Photo by Ronald Patrick/Getty Images.

Appendix A

U.S. Government Leadership in International Large-Scale Science

Several U.S. government organizations act as leaders in many international large-scale science endeavors, including the NSF, whose primary responsibility is the support of science, as well as mission agencies for which science is critical to achieving their overarching goals and operations, such as the DOE, NASA, and the NIH. They may provide a workforce, expertise, infrastructure, and/or funding. Each of the examples overviewed below highlights the varied and multidisciplinary roles that these U.S. government agencies play in modern-day megascience. A key conclusion is that in most cases these federal agencies have been successful in managing large-scale science projects and partnerships on behalf of the nation and have demonstrated they can manage the inevitable challenges and crises that arise in a complex project. Having a clear understanding of the scientific priorities supported by the scientific community and a robust oversight and management review process that is cognizant of these priorities and identifies risks and mitigation strategies as early as possible is a strong foundation for success in the face of challenges.

Department of Energy Office of Science

Mission: "To deliver scientific discoveries and major scientific tools to transform our understanding of nature and advance the energy, economic, and national security of the United States."[173]

The Department of Energy was officially established in 1977 to centralize several agencies focused on energy, power, and environment research and administration, with its history tracing back to the Manhattan Project and the creation of the atomic bomb in World War II.[174]

Today, through the DOE Office of Science, it is responsible for a diverse portfolio of programs, including energy and environment related initiatives, high-energy physics, nuclear physics, basic energy science, biological and environmental research, fusion energy sciences, and advanced scientific computing research, as well as the operation of ten of the nation's national laboratories. The Office of Science is the nation's largest supporter of basic research in the physical sciences.[175]

Through the national laboratories, the Office of Science currently supports large-scale science efforts at twenty-eight user facilities across the country with an array of cutting-edge scientific tools, including high-energy particle colliders, powerful X-ray light sources, a neutron scattering source, nanoscale science research centers, a genomics research center, and supercomputers.[176] Research conducted at these facilities is intended to facilitate U.S. leadership in pushing the frontiers of science across all disciplines, discovering and using advanced scientific tools, and investigating and paving the way of science for energy and environmental conservation and use. Scientists from the United States and abroad are eligible to apply to use the facilities at no cost if the results will be openly published, while users doing proprietary work must pay user fees covering the full operating costs. Allocation of access is determined by review of proposal submissions with the goal of identifying exceptional scientific merit and potential.

DOE Office of Science project management practices: The DOE is highly regarded for its robust project development and management cycle, which is designed to ensure successful and sustainable management of facilities and rigorous scientific outcomes. Projects are primarily overseen by the DOE's deputy secretary, who serves as the secretarial acquisition executive (SAE) and is responsible for key decision-making throughout project development, and by the Energy Systems Acquisition Advisory Board (ESAAB), who serve as objective advisors in evaluating project proposals and providing expert recommendations.[177] At the start of a project, performance baselines (PBs) are determined, which provide high-level summaries and goals to aid projects in building detailed plans for defining technical, scheduling, cost, and performance parameters.[178] To meet PBs, a project's development stages are defined by a series of critical decisions (CDs). CDs serve as key transition points in the life of a project that require a certain number of deliverables to be met for the SAE to approve the project to progress to its next phase.[179] Developing projects follow the directive DOE Order 413.3B, Program and Project Management for the Acquisition of Capital Assets, which outlines a series of steps, with relevant guidance, to ensure project success.[180] Once a project reaches CD-2/3 (approve performance baseline/approve start of construction), the DOE's Office of Project Management will conduct an independent scientific review to meet the independent review and peer review requirements outlined in DOE Order 413.3B and to promote successful project outcomes.[181]

DOE partnerships in international large-scale facilities: There are a variety of ways the DOE supports U.S. involvement in international large-scale scientific facilities. Take, for example, how the DOE supports CERN and ITER.

The United States is an "observer with special rights" to CERN.[182] The United States achieved this status in 1997 following an agreement with CERN to contribute $531 million for the Large Hadron Collider project.[183] The DOE provided physical equipment and materials valued at $200 million for the construction of the LHC, and an additional $250 million, along with $81 million from the NSF, for the construction of the detectors ATLAS and CMS.[184] Since the agreement, the DOE has supported the design and construction of physical elements for ATLAS and CMS to install at CERN, whose construction was coordinated primarily through the Brookhaven National Laboratory and Fermi National Accelerator Laboratory.[185] In 2015, the DOE and the NSF signed an agreement with CERN that will align U.S. and European strategies for particle physics research and will automatically renew every five years.[186] In 2018 and 2019, the DOE provided $100 million and $75 million, respectively, in grants for research proposals to study high-energy physics.[187] Upgrades to the accelerator and to the ATLAS and CMS detectors are estimated to cost approximately $550 million.[188]

In the case of the ITER project (see page 29), the United States is a joint member along with the European Union, Japan, Russia, China, South Korea, and India.[189] In 2006, the members signed an international agreement in the facility's home country, France, that officially established the ITER International Fusion Energy Organization for implementation of the ITER project.[190] The United States participates in ITER through the DOE Office of Science, which manages its contributions mostly through the Oak Ridge National Laboratory in Tennessee, with additional partners at the Princeton Plasma Physics Laboratory and Savannah River National Laboratory. The U.S. commitment to ITER is to provide roughly 9 percent of the overall project costs, regardless of what that may be.[191] The 9 percent commitment was originally estimated to be $1.1 billion, but delays and changes in the project more than quadrupled the estimate of the required U.S. contribution to between $4 billion and $6.5 billion as of 2016.[192] This caused concern in the U.S. Congress and uncertainty regarding congressional approval of DOE budget requests needed to maintain the U.S. commitment to ITER.[193] In response to an internal audit that found significant structural issues with ITER project management, ITER appointed in 2015 a new director-general to implement necessary management changes.[194] Subsequently, calls from the DOE secretary in 2016 and the National Academies of Sciences, Engineering, and Medicine in 2018 encouraged the United States to maintain its commitment to ITER because of the immense scientific potential the facility offers.[195]

National Aeronautics and Space Administration

Mission: To "drive advances in science, technology, aeronautics, and space exploration to enhance knowledge, education, innovation, economic vitality and stewardship of Earth."[196]

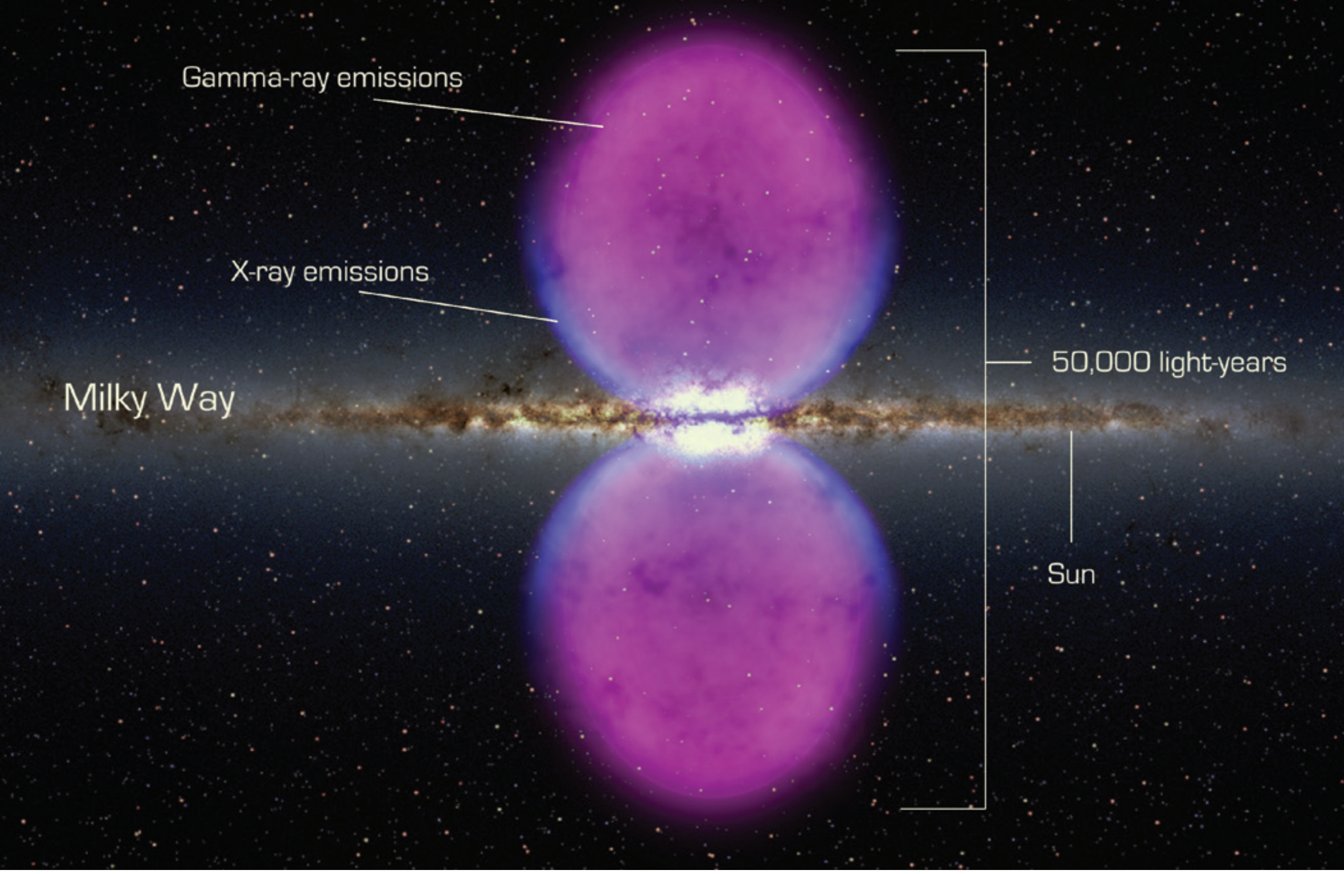
NASA was established in 1958, in response to the Soviet Union's 1957 launch of the world's first artificial satellite, *Sputnik I*, to vigorously promote U.S. leadership in space exploration and aeronautics.[197] Since its start, NASA has contributed significantly to inventions used by people around the world every day, including the development of robotics with applications for surgical operations, space suit technology for deep-sea diving suit materials, new materials like the memory foam commonly used in mattresses, and new camera technology developed to improve panoramic photography on Mars.[198]

NASA's contributions to scientific research are primarily through its development and operation of scientific missions. The agency's Science Mission Directorate (SMD), with its four science divisions (heliophysics, Earth science, planetary science, and astrophysics), is responsible for scientific observations and exploration enabled by access to space.[199] This is accomplished through observatories in Earth's orbit and deep space, spacecraft visiting planetary bodies, and robotic landers, rovers, and sample return missions. These missions address a broad range of compelling scientific questions as practical as hurricane formation and as profound as the origin of the Universe. NASA's science missions are often managed and implemented through one of its centers, in partnership with aerospace industry contractors and the science community. NASA R&D funds are not only allocated to space exploration and the development of appropriate technologies, but also to Earth and planetary sciences, physical and astronomical sciences, and aeronautics, as well as to STEM engagement and education.[200] NASA provides funding to support the development of science instruments and spacecraft, such as the James Webb Space Telescope, as well as to large international facilities like the International Space Station (ISS). The ISS is one of the major international collaborations in which NASA takes part, involving the United States, Russia, Europe, Japan, and Canada as the principal space agencies, among many other contributors.[201]

To inform its research priorities, NASA, like other federal agencies including the NSF and DOE, partners with the National Academies of Sciences, Engineering, and Medicine, which conducts decadal surveys to inform the agency's scientific direction.[202] NASEM convenes panels of experts from various fields, including astronomy and astrophysics, solar and space physics/heliophysics, planetary science, and Earth science and applications from space, to set priorities for the decade to come. Its reports in turn transform the scientific community's goals into action through the proposal of facilities and technologies, infrastructure, education, and more. Midterm assessments within the decade allow for evaluation of progress on priorities, and midterm review committees are then able to make recommendations for how to proceed for the remaining years before the next decadal survey.[203]

NASA and international partnerships on space science missions: NASA often partners with international space agencies on both missions it leads and missions led by an international partner agency. The European Space Agency (ESA) has been a major partner with NASA on many missions since the ESA's formation in 1975. These include the Hubble Space Telescope, the Solar and Heliospheric Observatory (SOHO), and Ulysses. NASA contributed to instrumentation for the ESA-led Planck and XMM-Newton missions. The ESA is a major partner on the development of the NASA-led James Webb Space Telescope. NASA has also partnered with the Japan Aerospace Exploration Agency (JAXA) on several JAXA-led science missions.[204] The NASA Office of International and Interagency Relations (OIIR) provides coordination for all NASA international and interagency activities and partnerships, and for policy interactions between NASA and other U.S. executive branch offices and agencies.[205]

The Fermi Gamma-ray Space Telescope, both an international and multi–U.S. agency space mission, enables the study of cosmic sources of high-energy radiation, including their formation and evolution starting from times near the Big Bang.[206] The mission is an international astrophysics and physics partnership that NASA codeveloped with the DOE and academic institutions and partners in France, Germany, Italy, Japan, Sweden, and the United States.[207] The international partnerships were part of the instrument proposals that NASA selected through a competitive review process. Projected costs of the project were initially $690 million, with the United States contributing $600 million and the international community contributing, in-kind, $90 million.[208] However, project delays and some challenges with partner commitments ultimately led to a $45 million increase to the cost.[209] Originally called the Gamma-ray Large Area Space Telescope (GLAST), the concept for the primary instrument was developed in the 1990s by a group from Stanford University and the DOE's SLAC National Accelerator Laboratory.[210] In 2000,



Using data from Fermi's Large Area Telescope, scientists have discovered a gigantic, mysterious structure in our galaxy. This never-before-seen feature looks like a pair of bubbles extending above and below our galaxy's center, as shown in false color in this figure. Image courtesy of the NASA Goddard Space Flight Center.

the Astronomy and Astrophysics Decadal Survey conducted by the National Academies of Sciences, Engineering, and Medicine ranked GLAST as the top-priority mid-sized project.[211] NASA subsequently issued a call for instrument and science investigation proposals for the GLAST mission and ultimately selected the DOE-sponsored Stanford/SLAC proposal for the Large Area Telescope, GLAST's primary instrument.[212] Eight years later, on June 11, 2008, GLAST successfully launched into space, at which time it was renamed Fermi in honor of Enrico Fermi, a renowned pioneer in the field of high-energy physics.[213] Since launch, data from observations by Fermi's instruments have been made openly available to the entire global scientific community and have been used by scientists and students from more than twenty countries. The Fermi LAT Science Collaboration includes participation from members from more than forty universities and labs in twelve countries.[214] Fermi's two instruments, the Large Area Telescope and the Gamma-ray Burst Monitor (GBM), are aiding scientists in discovering new information about the most extreme environments in the universe.[215] A key contributor to the success of Fermi was the partnership established between NASA and the DOE, which was most critical at the working level of the two agencies' national labs, NASA Goddard Space Flight Center and the SLAC National Accelerator Laboratory. Each agency had clear management responsibilities, including well-defined agreements with all international partners.

National Science Foundation

Mission: To "promote the progress of science; to advance the national health, prosperity, and welfare; to secure the national defense; and for other purposes."[216]

The National Science Foundation was established under the National Science Foundation Act of 1950 and continues to support basic research and the furthering of knowledge, contributing approximately 25 percent of all federal funding for basic research. It is the only federal agency that currently funds basic nonbiomedical research and education across all science and engineering fields, and at all levels of education.

The NSF, as opposed to other U.S. agencies, is overseen by both an agency director and by the National Science Board (NSB), which acts similarly to a corporate board and has similar power of final and resolute decision-making regarding the NSF's scientific priorities and funding allocations. The NSB consists of twenty-five scientists appointed by the president of the United States and has two overarching responsibilities: 1) establishing the policies of the NSF to operate within the priorities established by the president and Congress; and 2) serving as an independent body of advisors on science policy matters. Within this, the NSB has full power to approve NSF funding contributions for large-scale scientific facilities located in the United States and abroad.

The NSB's report to Congress and the president, *Science and Engineering Indicators*, provides quantitative data on the science and engineering enterprise in the United States and, importantly, on science R&D and scientific output internationally. These data, released every other year, allow the United States to have a better understanding of the science research ecosystem, nationally and globally, to inform strategic priorities and directions and to identify new potential avenues for collaboration with global partners.[217]

It is the role of the NSF to invest in high-risk, high-reward scientific endeavors to identify new frontiers, and push past existing frontiers, for the advancement of U.S. scientific excellence (see the Atacama Large Millimeter/submillimeter Array on page 14).[218] To accomplish this, the NSF advances science at many scales through a variety of funding schemes. It specifically contributes to large-scale science efforts through its support of facilities and equipment, like LIGO, through cooperative research agreements with institutions and agencies in the United States and abroad. The NSF Office of International Science and Engineering is a focal point for international activities both inside and outside the NSF.[219]

LIGO, the largest project ever funded by the NSF: Just over forty years ago, the NSF began funding the science and technological developments that ultimately led to the detection of gravitational radiation with the Laser Interferometer Gravitational Wave Observatory. LIGO's early development was led by scientists at MIT, the University of Glasgow, and Caltech in the 1960s and 1970s to detect the waves predicted by Albert Einstein's General Theory of Relativity near the start of the twentieth century.[220] The NSF began funding scientists at MIT and Caltech in the mid-1970s and later encouraged them to officially form a collaboration to simplify funding for one project.[221] After further planning and scoping, the National Science Board approved LIGO's construction in 1990, and Congress appropriated funding for joint construction in 1991. In 1994, the LIGO project underwent organizational and management

NIAID Director Dr. Anthony Fauci (right) discusses vaccine development and ongoing infectious disease research with African delegates at the U.S.-African Leaders Summit. Photo by the Fogarty International Center, National Institutes of Health.

changes to address significant issues that had slowed the project and were of concern to the NSF. In 1997, the LIGO organization created a separate entity from the LIGO laboratories based in the United States: the LIGO Scientific Collaboration (LSC), which is responsible for coordinating research and data analysis and for expanding LIGO to include scientists beyond the two main home U.S. institutions. In tandem with initial data collection and searches by the first generation LIGO detectors, which ultimately did not detect any gravitational waves during its nine years of operation, the LSC worked with the European Virgo project, which included scientists from France, Italy, the Netherlands, Poland, and Hungary, to form an international collaborative effort to develop data collection and analysis capabilities and ultimately improve the measurements of gravity wave source locations. In 2008, the NSF approved funding for significant upgrades to LIGO, resulting in a next generation of advanced interferometers ("Advanced LIGO"), which benefited from important contributions from the United Kingdom, Germany, and Australia.[222] This improved interferometer led to the 2015 breakthrough discovery of gravitational waves from the coalescence of two neutron stars.

National Institutes of Health of the Department of Health and Human Services

Mission: 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."[223]

The NIH traces its roots back to 1887 with the Marine Hospital Service, which was charged by Congress to assess incoming passengers for signs of infectious disease.[224] Today, the NIH invests more than $30 billion per year in biomedical research around the world, seeking to improve health, drive economic growth and productivity, and broaden understanding of biomedical fields through cutting-edge research and increased capacity of the biomedical workforce.[225]

The NIH contributes to large-scale scientific efforts through its support of individual experimental stations at facilities funded by other agencies such as the DOE as well as its funding and support of global, clinical studies. The NIH often partners and collaborates with other internationally based funding organizations, like the Wellcome Trust based in the United Kingdom; foundations, like the Bill & Melinda Gates Foundation; and multinational pharmaceutical or medical device companies, like Merck.

The NIH, unlike some other agencies, is able to provide grant funding directly to non-U.S. citizens and internationally based institutions.[226] Many of its global health research grants are administered through the NIH's Fogarty International Center (FIC), which seeks to support and facilitate global health research and build further capacity in global health research around the world.[227] The FIC focuses on inherently global issues that require the engagement and capacity of international talent, such as infectious diseases like Ebola and Zika and noninfectious diseases like Alzheimer's disease. Included in its work is the effort to build a global health research workforce of the future through building research capacities of individuals, institutions, and networks, including by supporting training of early-career scientists in low- and middle-income countries. As of 2014, the FIC has directly supported training for over 4,500 of these scientists in over one hundred countries, many of whom have remained in their home countries and have become national leaders in health fields.[228]

H3Africa, a partnership between the NIH and the Wellcome Trust, is managed through the African Academy of Sciences, which seeks to build a research agenda for studying genetic diversity in health and disease in Africa.[229] NIH leadership in the collaboration proceeds through the NIH Common Fund, the National Human Genome Research Institute, and the FIC, and many NIH institutes and centers partner to support H3Africa research goals. H3Africa has been funded for ten years spanning 2011–2021 with a current commitment of approximately $180 million, which is awarded through the NIH, the Wellcome Trust, and the African Academy of Sciences through the Alliance for Accelerating Excellence in Science in Africa.[230]

Establishing International Standards

The National Institute of Standards and Technology, housed in the U.S. Department of Commerce, is a physical science laboratory that develops measurement tools and provides standards for an array of research needs.[231] NIST works internationally to agree to standards, such as weights and measures, for how international systems of units are defined. Such agreements are essential for scientific advancements, trade, and global commerce, and will continue to have significant impact on society as standards are developed for artificial intelligence, 5G, wireless communications, and quantum communication systems.

Philanthropic Sources of Funding

Along with the U.S. government, American philanthropic institutions sometimes play a major role in international large-scale science. Foundations contribute substantial support, often hundreds of millions of dollars, for large-scale scientific initiatives, including telescopes, marine biology network studies, climate change consortia, neuroscience, and global public health research programs.[232]

Appendix B

Steering Committee and Working Group Members

Steering Committee on Challenges for International Scientific Partnerships

Arthur Bienenstock (*Cochair*), Professor Emeritus of Photon Science, Special Assistant to the President for Federal Research Policy, and Associate Director of the Wallenberg Research Link, Stanford University; Member of the National Science Board

Peter Michelson (*Cochair*), Luke Blossom Professor in the School of Humanities and Sciences, Professor of Physics, and Senior Associate Dean for the Natural Sciences, Stanford University

Claude Canizares, Bruno Rossi Professor of Physics, Massachusetts Institute of Technology

Matthias Hentze, Director, European Molecular Biology Laboratory

John G. Hildebrand, Regents Professor and Professor of Neuroscience, Chemistry & Biochemistry, Ecology & Evolutionary Biology, Entomology, and Molecular & Cellular Biology, University of Arizona

Kerri-Ann Jones, Former Vice President of Research and Science, Pew Charitable Trusts; Former Assistant Secretary of State for Oceans and International Environmental and Scientific Affairs

William Lee, Partner, Wilmer Cutler Pickering Hale and Dorr

Shirley Malcom, Senior Advisor and Director of SEA Change, American Association for the Advancement of Science

Cherry Murray, Deputy Director for Research, Biosphere 2, and Professor of Physics, The University of Arizona; Former Director, Office of Science, U.S. Department of Energy

Venkatesh Narayanamurti, Benjamin Peirce Professor of Technology and Public Policy, Engineering and Applied Sciences, and Physics Emeritus, Harvard University; Former Director, Science, Technology, and Public Policy Program, Belfer Center for Science and International Affairs, Harvard Kennedy School; Former Dean, School of Engineering and Applied Sciences and Dean of Physical Sciences, Harvard University

Olufunmilayo Olopade, Walter L. Palmer Distinguished Service Professor in the Biological Sciences Division, Professor of Medicine & Human Genetics, and Associate Dean for Global Health, The University of Chicago

Vaughan Turekian, Executive Director of the Policy and Global Affairs Division, National Academies of Sciences, Engineering, and Medicine; Former Science and Technology Advisor to the U.S. Secretary of State

Caroline Wagner, Ambassador Milton A. and Roslyn Z. Wolf Chair in International Affairs at the John Glenn College of Public Affairs, The Ohio State University; Former RAND Scholar

Large-Scale Science Working Group

Arthur Bienenstock (*Cochair*), Professor Emeritus of Photon Science, Special Assistant to the President for Federal Research Policy, and Associate Director of the Wallenberg Research Link, Stanford University; Member of the National Science Board

Peter Michelson (*Cochair*), Luke Blossom Professor in the School of Humanities and Sciences, Professor of Physics, and Senior Associate Dean for the Natural Sciences, Stanford University

Claude Canizares, Bruno Rossi Professor of Physics, Massachusetts Institute of Technology

E. William Colglazier, Editor-in-Chief of *Science & Diplomacy*; Senior Scholar in the Center for Science Diplomacy, American Association for the Advancement of Science

Inez Fung, Professor of Atmospheric Science, Department of Earth & Planetary Science, Department of Environmental Science, Policy and Management, University of California, Berkeley

Michael Holland, Vice Chancellor for Science Policy and Research Strategies, University of Pittsburgh

Kaye Husbands Fealing, Dean and Ivan Allen Jr. Chair, Ivan Allen College of Liberal Arts, Georgia Institute of Technology

Cherry Murray, Deputy Director for Research, Biosphere 2, and Professor of Physics, The University of Arizona; Former Director, Office of Science, U.S. Department of Energy

Philip Rubin, Chief Executive Officer Emeritus, Haskins Laboratories; Professor Adjunct, Department of Surgery, Yale School of Medicine; President-Elect, Federation of Associations in Behavioral & Brain Sciences; Former Principal Assistant Director for Science, White House Office of Science and Technology Policy

Gary Sanders, Project Manager, TMT International Observatory, LLC and California Institute of Technology

Diane Souvaine, Professor, Department of Computer Science, Tufts University; Chair Emerita, National Science Board

Emerging Science Partners Working Group

Shirley Malcom (*Cochair*), Senior Advisor and Director of SEA Change, American Association for the Advancement of Science

Olufunmilayo Olopade (*Cochair*), Walter L. Palmer Distinguished Service Professor in the Biological Sciences Division, Professor of Medicine & Human Genetics, and Associate Dean for Global Health, The University of Chicago

Alice Abreu, Professor Emerita, Federal University of Rio de Janeiro; Member of GenderInSITE Steering Committee

Bruce Alberts, Professor Emeritus, Biochemistry and Biophysics, University of California, San Francisco

Bernard Amadei, Distinguished Professor and Professor of Civil Engineering, University of Colorado at Boulder; Founding President, Engineers Without Borders–USA; Co-Founder, Engineers Without Borders–International Network

Arthur Bienenstock (*ex officio*), Professor Emeritus of Photon Science, Special Assistant to the President for Federal Research Policy, and Director of the Wallenberg Research Link, Stanford University; Member of the National Science Board

Jared Cohon, President Emeritus and University Professor in Civil and Environmental Engineering and Engineering and Public Policy, Carnegie Mellon University

Rita Colwell, University Distinguished Professor, University of Maryland Institute for Advanced Computer Studies, University of Maryland College Park

James W. Curran, James W. Curran Dean of Public Health, Rollins School of Public Health, Emory University; Co-Director, Emory Center for AIDS Research

Ali Douraghy, Chief Strategy Officer, Earth and Environmental Sciences Area, Lawrence Berkeley National Laboratory (concluded participation in the working group on January 19, 2021)

Nina Dudnik, Founder and CEO Emeritus, Seeding Labs

Mohamed Hassan, President, The World Academy of Sciences; President, The Sudanese National Academy of Sciences

John G. Hildebrand, Regents Professor and Professor of Neuroscience, Chemistry & Biochemistry, Ecology & Evolutionary Biology, Entomology, and Molecular & Cellular Biology, University of Arizona

Nkem Khumbah, Lecturer and Member of the STEM-Africa Steering Committee, University of Michigan

Peter Michelson (*ex officio*), Luke Blossom Professor in the School of Humanities and Sciences, Professor of Physics, and Senior Associate Dean for the Natural Sciences, Stanford University

Peggy Oti-Boateng, Director, Division of Science Policy and Capacity-Building, Natural Sciences, United Nations Educational, Scientific, and Cultural Organization

Jamil Salmi, Professor Emeritus of Higher Education Policy, Diego Portales University; Research Fellow, Boston College Center for Higher Education; Former Tertiary Education Coordinator for the World Bank

Flavia Schlegel, Former Assistant Director-General for Natural Sciences, United Nations Educational, Scientific, and Cultural Organization

Vaughan Turekian, Executive Director of the Policy and Global Affairs Division, National Academies of Sciences, Engineering, and Medicine; Former Science and Technology Advisor to the U.S. Secretary of State

Caroline Wagner, Ambassador Milton A. and Roslyn Z. Wolf Chair in International Affairs at the John Glenn College of Public Affairs, The Ohio State University; Former RAND Scholar

Project Staff

Amanda Vernon
Rebecca Tiernan
Islam Qasem
Tania Munz
John Randell
Gregory Savageau

Publications Staff

Phyllis Bendell
Scott Raymond
Heather Struntz
Peter Walton

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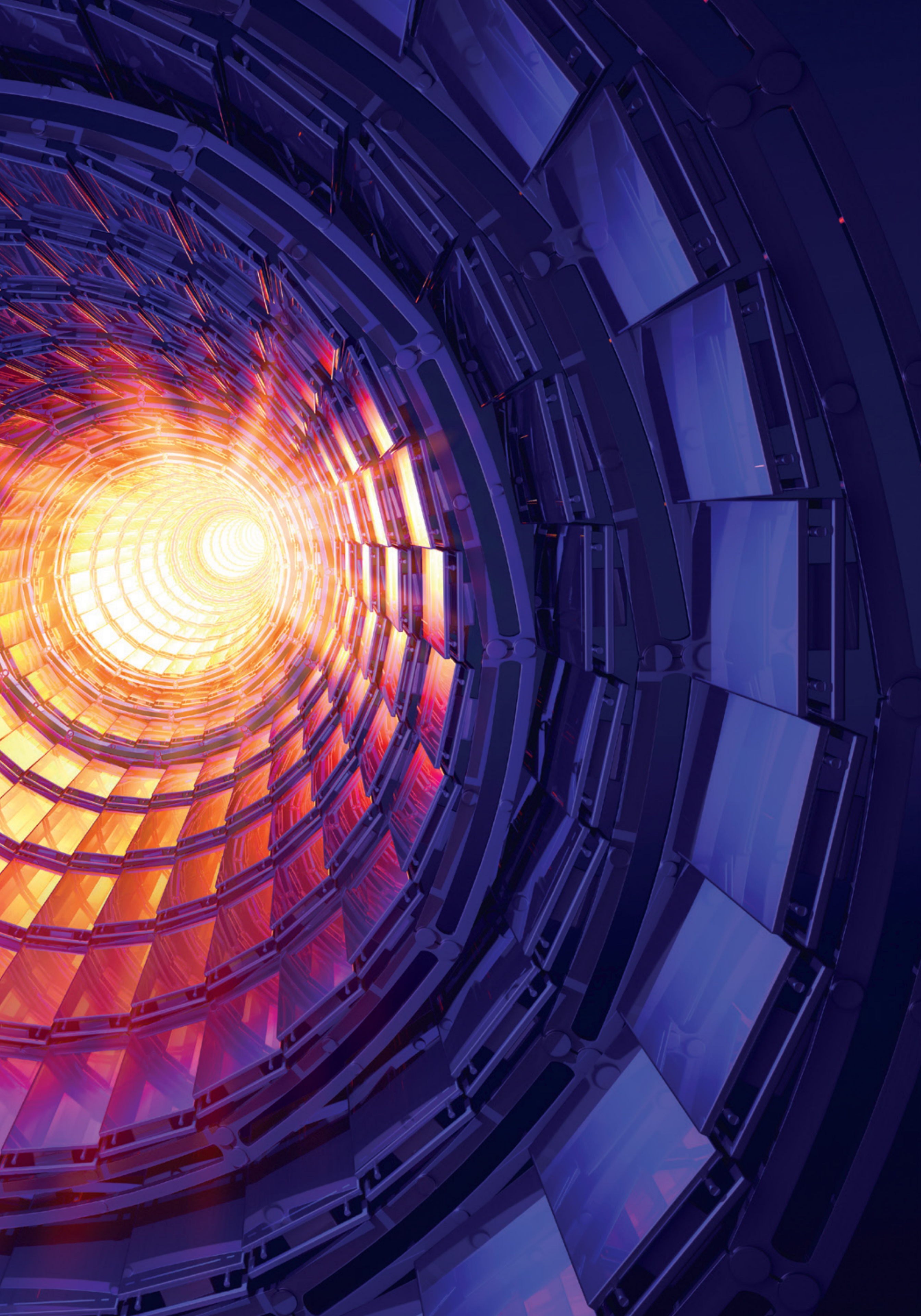

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