2021 ANNUAL REPORT

ALLEN INSTITUTE
open for science

Who are we?

Where did we come from?

There are probably as many ways of answering those questions as there are cells in the human body (35 trillion, give or take).

Whether it's classifying the billions of neurons that make up our brain, tracing the lineages of our development or understanding the detailed ins and outs of our cells, Allen Institute scientists are making the unknown known – and ultimately helping us to understand what it means to be human.

Good science often raises just as many questions as it answers.

When I reflect on my time at the Allen Institute – more than 18 years, as of this writing – I'm especially proud of our researchers' and staff's ability to stare unflinchingly into the face of science's most difficult questions. We were founded with a goal of overcoming one singular, big challenge in neuroscience and in the years since have branched out to take on many more complex and tough research questions.

This will be my last Annual Report letter as President and CEO of the Allen Institute. As I announced early this year, I'm stepping down from this position. We're delighted to welcome Rui Costa, D.V.M., Ph.D., as our next President and CEO, and I am confident the Institute is in great hands. I'm so pleased to continue to support the Allen Institute and its transformational impact in a new role as a member of the Board of Directors.

I remain in awe of our teams' fearless approach to science. Our scientific teams are confronting some of science's hardest problems: Uncovering the cells that make up our brains, revealing the immune mysteries that underlie long-haul COVID, investigating the science behind complex behavior and decision-making.

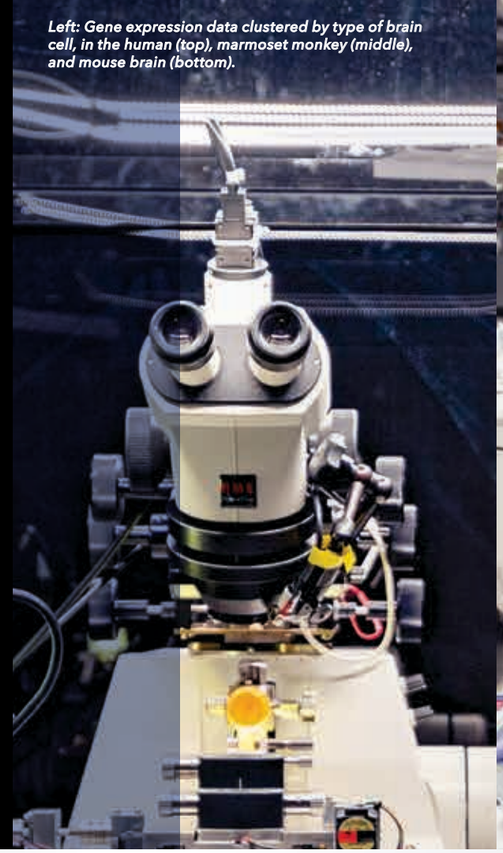
I'm thrilled to share their progress with you in this past year, which presented the additional hurdles of an ongoing deadly pandemic and all its accompanying uncertainties. It's a testament to the strength of our Institute's principles and of our stellar scientists and staff that they've made such incredible strides even under difficult circumstances.

I can't wait to see the next set of questions they will take on.

Allan Jones, Ph.D.

President and Chief Executive Officer

Left: Gene expression data clustered by type of brain cell, in the human (top), marmoset monkey (middle), and mouse brain (bottom).



What are the cells that make up our brains?

A huge collaborative effort fueled the most detailed map to date of the brain region that controls movement.

ALLEN INSTITUTE *for* BRAIN SCIENCE

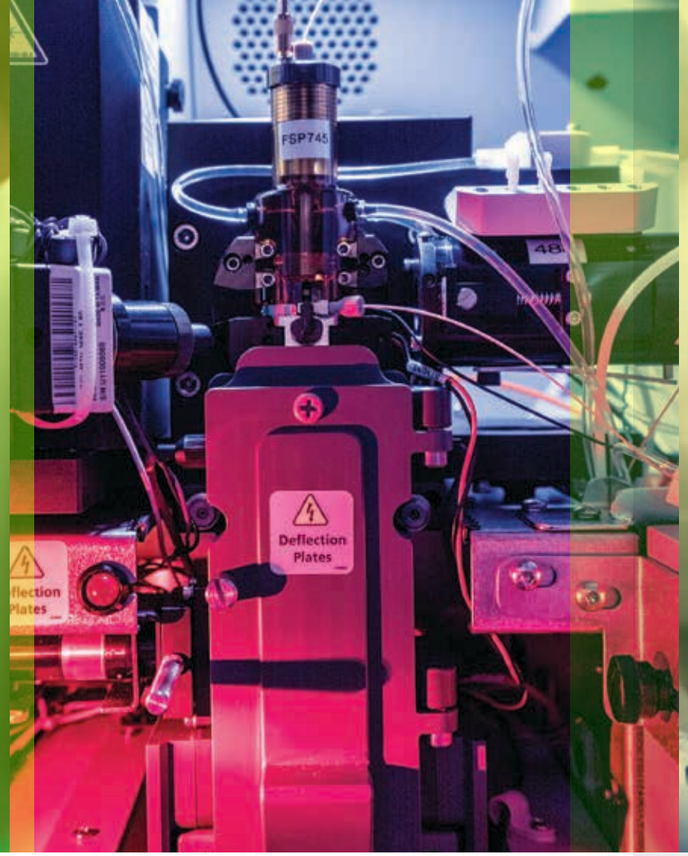
For the first time, the neurons and other cells involved in the region of the human, mouse and monkey brains that controls movement have been mapped in exquisite detail. Published in a 17-article takeover of the journal Nature, this project represents a major milestone in the effort to create a catalog of all brain cell types.

The map's creators, a large consortium of neuroscientists brought together by the National Institutes of Health's BRAIN Initiative, say this new atlas will pave the way for mapping the entire mammalian brain as well as better understanding mysterious brain diseases – including those diseases that attack the neurons that control movement, like ALS.

Dozens of research teams around the world, including several at the Allen Institute for Brain Science, worked together to complete a cell-by-cell atlas of the primary motor cortex. This region is similar across all mammalian species – while humans, monkeys and mice have many differences between our brains, the way we control movement is similar – and is part of the neocortex, the outermost shell of our brains that gives rise to cognitive function.

To define and characterize cell types, the atlas's creators used cellular features such as the complete set of genes a cell switches on; a cell's "epigenetic" landscape, which defines how genes are regulated; cells' 3D shapes; their electrical properties; and how they connect to other cells.

The result: By and large, cell types are very similar between species, but with key specializations of certain brain cell types that may have helped us adapt to our unique environments. For example, one Allen Institute team studied live human "Betz cells" for the first time; the largest neurons we have, these specialized motor cells send projections from the brain to our spinal cord and are especially vulnerable in ALS, a neurodegenerative disease.



What goes wrong in long COVID?

A collaborative study uncovers immunological fingerprint of long-haul COVID

ALLEN INSTITUTE *for* IMMUNOLOGY

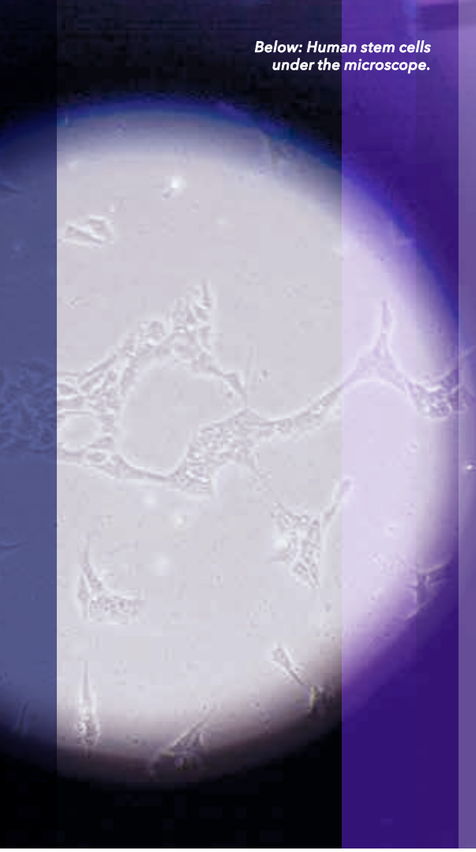
The Allen Institute for Immunology team didn't set out to study long COVID. But when the data from their newly established collaboration with Fred Hutchinson Cancer Research Center to study mild-to-moderate cases of COVID-19 started coming in, there it was staring them in the face: a handful of patients who'd enrolled in their study had ongoing symptoms that put them in the "long-haul COVID" category.

Looking deeper into these patients' immune systems, the team found that those with long COVID had molecular signatures in their blood indicating that their immune systems, which had ramped up to fight the infection, didn't dial down even after the virus was cleared.

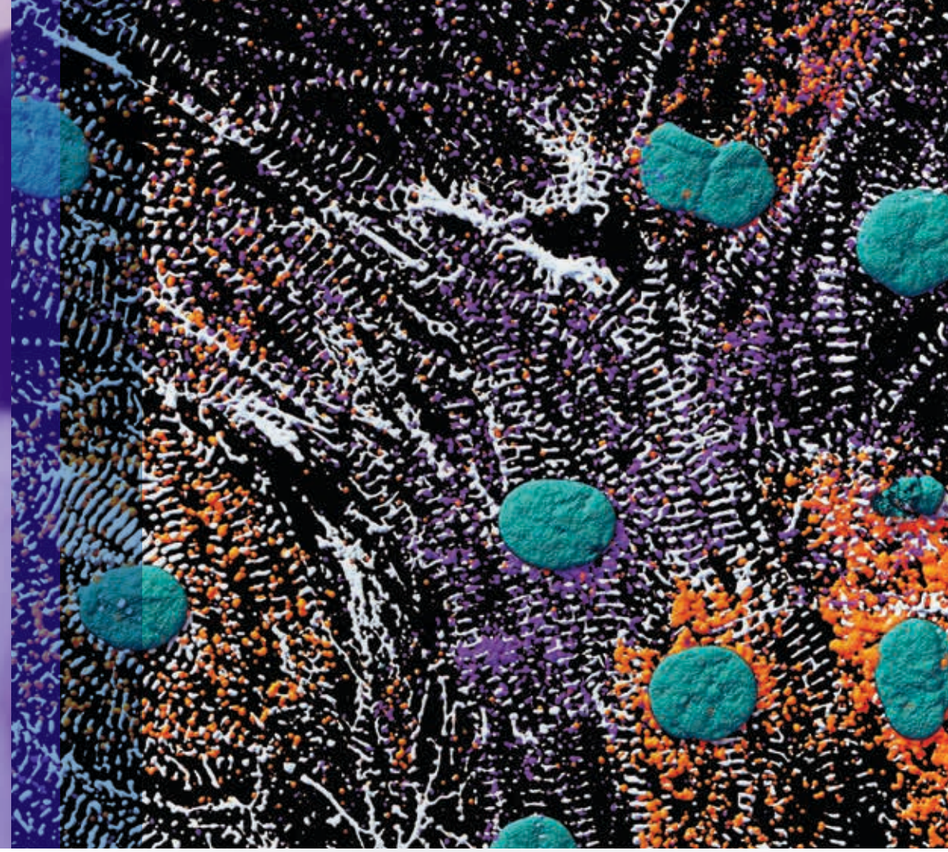
The study, established just a few months into the pandemic, aimed to gather important information about mild to moderate infections, which represent around 80% of all COVID cases but haven't been extensively studied. Understanding a "successful" immune response to the virus could yield important insights for improving future treatments and vaccines.

Unusual for studies of its kind, the Allen Institute-Fred Hutch study deeply profiles patients' immune systems over long periods of time to map the immune history of each individual from soon after diagnosis through recovery.

The detailed findings of the immune system differences that underlie long COVID – those with symptoms that lasted longer than 60 days from diagnosis, who make up at least 30% of COVID patients – are novel and need further study. The Allen Institute teams found variability in the immune systems of patients with long COVID, as might be expected given the variability of the disease itself, but there were certain signatures of inflammation that persisted in people with long COVID but faded away in those who'd recovered from their disease. This newly discovered immune signature might not have been found if the researchers hadn't been following patients over time, and it could yield new treatment targets for a mysterious disease where effective treatments are sorely lacking and which already is a major cause of illness around the world.



Below: Human stem cells under the microscope.



Right: Heart muscle cells showing the DNA-storage compartment in green and contractile structures in white.

How can we best understand our own cells?

Scientists take a deep dive into the genes and cellular structures of human heart muscle cells

ALLEN INSTITUTE *for* CELL SCIENCE

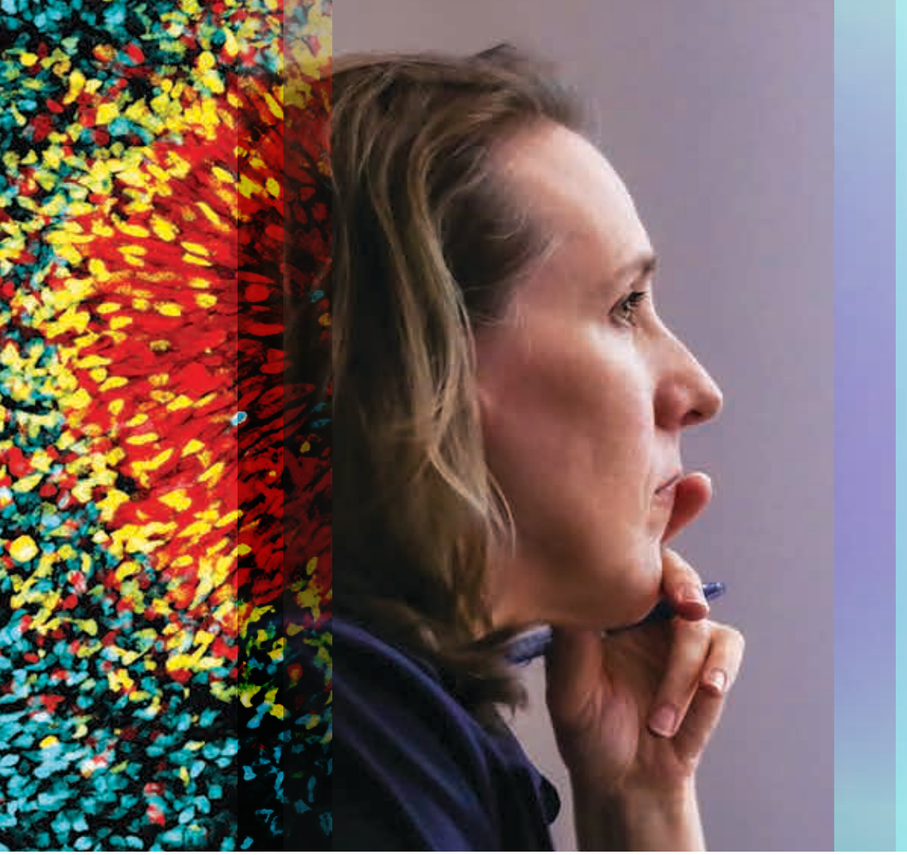
Researchers at the Allen Institute for Cell Science have found that there's more to our cells than genes alone reveal. In the quest to understand human cells, many scientists turn to gene expression, or the genes each cell switches on. But a study published this year suggests that if you want to really understand what a cell is doing, studying its genes might not tell you the entire story.

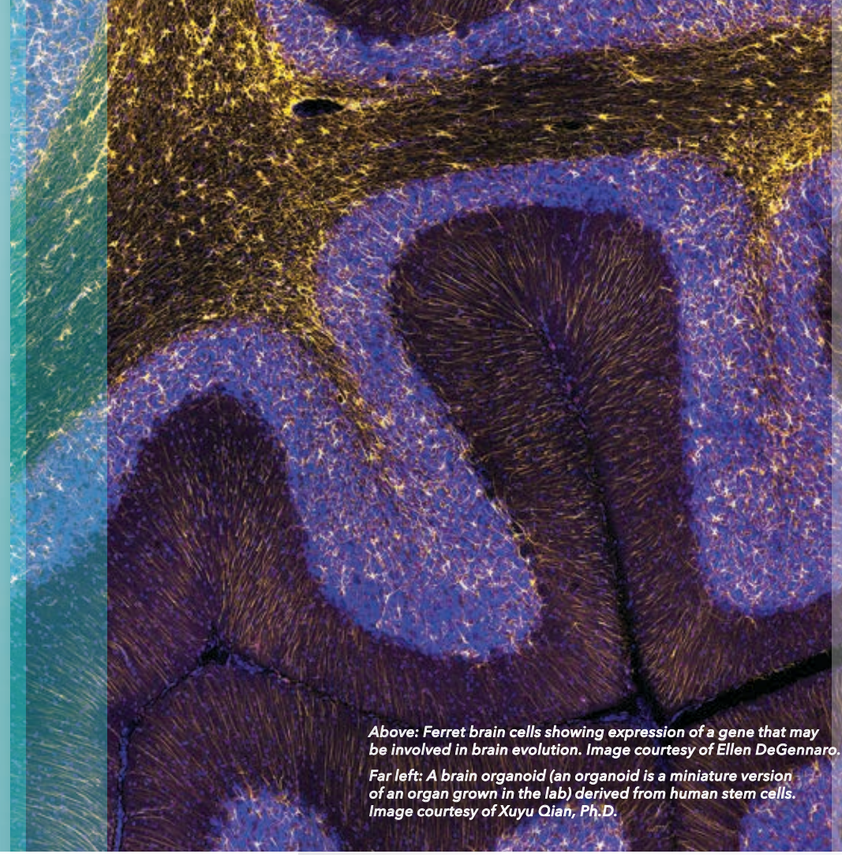
Looking at human cardiomyocytes, or heart muscle cells, the scientists compared individual cells' gene activity with their structural features. They developed a computational method to automatically capture visual characteristics from thousands of images of heart muscle cells generated from human stem cells. The team captured a score for how "organized" the muscle cells' contracting machinery was, which is a measure of the cells' progress on the path to maturity, and expression of key genes responsible for that maturity. When they compared these two measures, they discovered a wide range of variability in both measurements with little correlation between the measurements in any given cell.

The researchers focused on a key structure in heart muscle cells known as the sarcomere. These tiny cellular structures allow the cells to contract – the driving force behind your heartbeat. As stem cells develop into cardiomyocytes, sarcomeres form and become more organized. At first, the structures look like scattered dots, but they later elongate and line up in stripes that run perpendicular to the long, skinny cells, like slats on a tiny railroad track.

The Allen Institute team quantified that railroad-like organization computationally, and then married those measures with gene expression data from the same cells. This work required a massive data-collection effort – capturing images and gene expression information from 30,000 single cells, all of which is openly available to the public.

Looking beyond genes gives the researchers a roadmap to best understand our own cells, one they hope will ultimately lead to a more complete picture of how our cells work in health and change in disease.





Above: Ferret brain cells showing expression of a gene that may be involved in brain evolution. Image courtesy of Ellen DeGennaro.

Far left: A brain organoid (an organoid is a miniature version of an organ grown in the lab) derived from human stem cells. Image courtesy of Xuyu Qian, Ph.D.

How do animals grow from one cell to many? How did the human brain evolve?

Two Allen Discovery Centers enter their next phase of discovery, poised to address large questions about biology

THE
PAUL G. ALLEN
FRONTIERS GROUP

This year, The Paul G. Allen Frontiers Group recommended the next four-year phase of funding for two Allen Discovery Centers, large-scale collaborative research groups established in 2017 and headquartered at UW Medicine and at Boston Children's Hospital and Harvard Medical School.

The Allen Discovery Center for Human Brain Evolution, led by investigators at Boston Children's Hospital and Harvard Medical School, aims to answer a deeply important question about humanity: How did our unique brains evolve? Their work over the past four years has established a huge database of ancient human DNA that has given rise to new insights not only about our biology and evolution, but our cultural and social histories as well.

In the next phase of the center, the teams will mine the database for regions of the human genome that evolved to endow new cognitive traits along with major cultural shifts in human history, such as the shift from hunter-gatherer to agricultural societies. They will also characterize how these DNA sequences work, using cell biology and animal models to understand the changes that drove our brain evolution.

The Allen Discovery Center for Cell Lineage Tracing, led by investigators at UW Medicine, the California Institute of Technology and the University of Basel, wants to understand how we and other animals grow from one cell to many. Animal development is a highly regulated process with a lot of natural variation—in healthy development, we all end up with the same body plan but none of us are carbon copies of each other. Understanding how our genes and environments influence development will also help researchers better understand developmental diseases.

In the center's first phase, they developed several cutting-edge techniques to speed progress in mapping developmental biology. In the next phase, they will apply these technologies to map cell-by-cell development in two model animals, mice and zebrafish, with the goal of understanding how a single fertilized egg develops into the specialized cells that build an entire animal's body. The scientists will also disrupt genes and perturb the environment to understand how our genes and surroundings affect development.

How do we make complicated decisions?

Newly launched Allen Institute for Neural Dynamics will study complex behavior, decision making, memory

ALLEN INSTITUTE *for*
NEURAL DYNAMICS

Late this year, we announced the Allen Institute for Neural Dynamics, a new neuroscience research division focused on the mammalian brain's computations that give rise to complex behaviors like decision making, learning and memory. The new Institute becomes the Allen Institute's fifth division and is led by renowned neuroscientist Karel Svoboda, Ph.D.

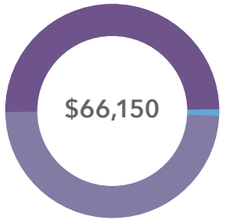
The newly established team of scientists, engineers and other staff will explore the brain's neural circuits and electrical activity, at the level of individual neurons and the whole brain, to reveal how we interpret our environments to make decisions. The division's experiments and openly shared resources will shed light on behavior, memory, how we handle uncertainty or risk, how we chase rewards – and how some or all of these complex cognitive functions go awry in neuropsychiatric disorders such as depression, ADHD or addiction.

The new division will study the laboratory mouse as a model for the mammalian brain, focusing first on food foraging. As an animal forages, it must make real-time decisions about risk and reward, as well as learn new information about its environment. Foraging, which is a basic survival behavior shared across all mammalian species, holds deep parallels with the risks and rewards of economic decision making, such as stock market trading. Deficits in foraging have been linked to behaviors reminiscent of human psychiatric disorders such as major depressive disorder and attention deficit disorder.

By answering pressing questions about the dynamics and circuits of the mouse brain during complicated behaviors, the researchers hope to shed light on how our own brains function to allow us to survive in complex and ever-changing environments.

Financial Summary

Support & Revenue (In Thousands)



	2020 (Audited)	2019 (Audited)
Contributions	$33,102	$31,242
Research Grants & Contracts	$32,521	$32,648
Other	$527	$11,479

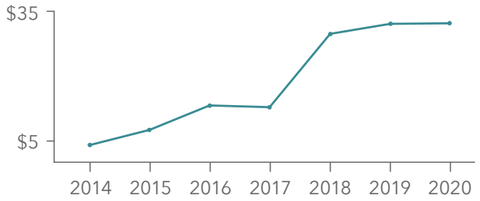
Total Expenses (In Thousands)

	2020 (Audited)	2019 (Audited)
Program Services	$108,972	$107,666
Management & General	$24,801	$23,823

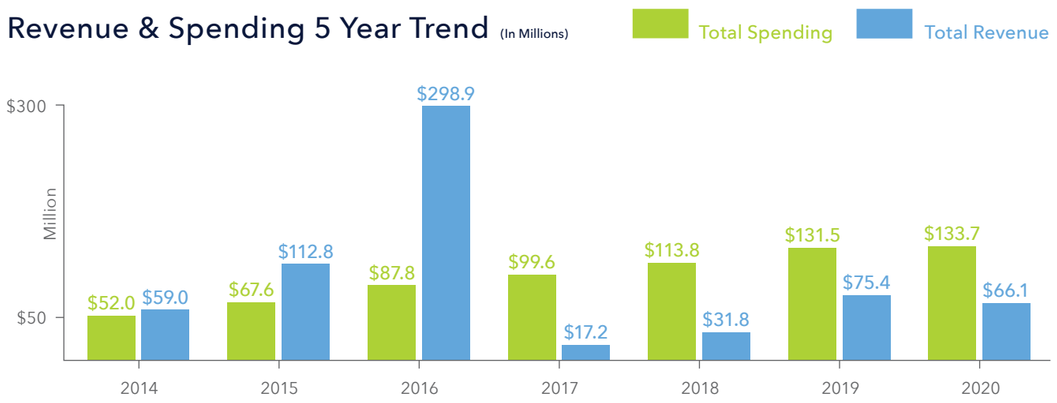
Change in Net Assets

	2020 (Audited)	2019 (Audited)
Change in Net Assets	(67,623)	(56,120)
Net Assets, Beginning of Year	206,918	263,038
Net Assets, End of Year	**139,295**	**206,918**

Research Grants & Contract Revenue (In Millions)



Revenue & Spending 5 Year Trend (In Millions)



The Allen Institute, comprising the Allen Institute for Brain Science, the Allen Institute for Cell Science, the Allen Institute for Immunology, the Allen Institute for Neural Dynamics and the administrative portion of The Paul G. Allen Frontiers Group, continues to grow. A large contribution in 2016 will support the Institute for multiple years.

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