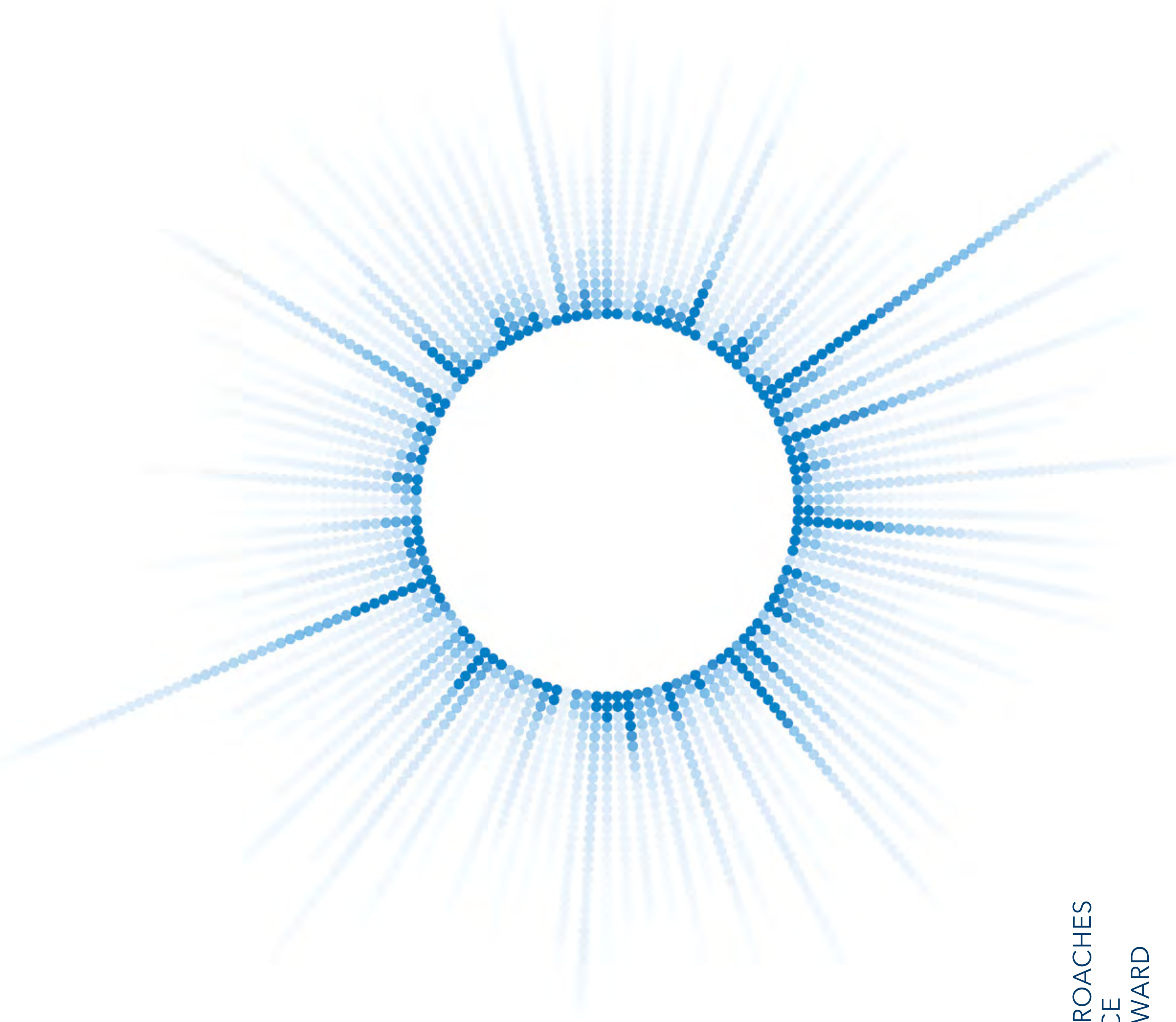
ALLEN
INSTITUTE

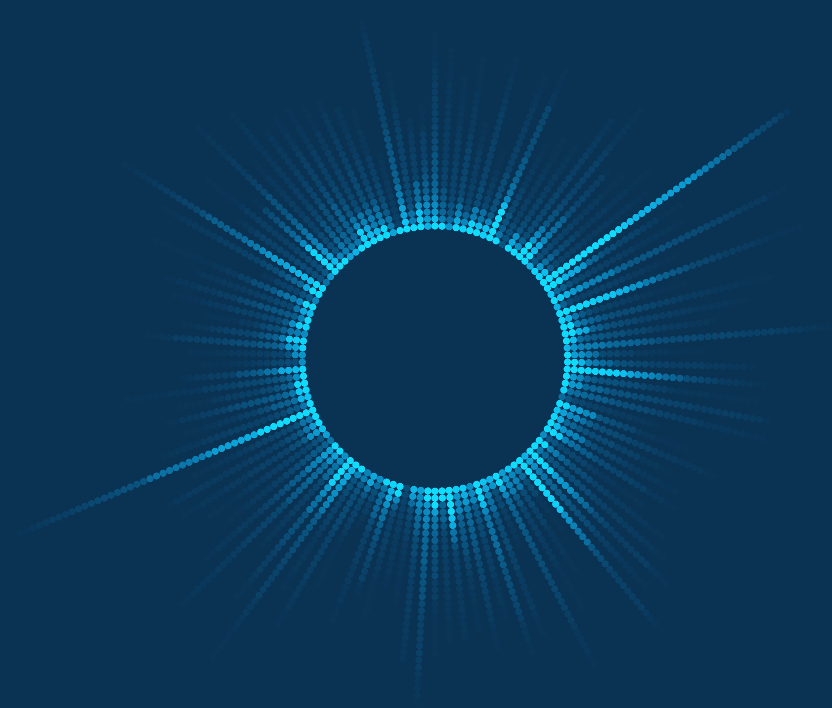
2016
ANNUAL REPORT



MULTISCALE APPROACHES TO MOVE SCIENCE FORWARD

SCIENTIFIC DISCOVERY

Scientific discovery can happen at many scales, from the impact of the smallest molecule to the behavior of entire complex systems. The Allen Institute's multiscale approach to biology gives broad insight into some of our most challenging scientific problems. Our newest resources on the brain combine many data modalities to answer old questions and uncover new ones. We are exploring the intricate machinery of cells and working to visualize them in a new, holistic way. And we are looking at the frontiers of bioscience to uncover significant problems and identify investigators willing to solve them.



COVER
A corona data plot showing the response of a single cell in the Allen Brain Observatory to natural scenes presented to a mouse.

Biology is an incredibly complex science. It comprises systems at many scales, from the interactions of small molecules and networks of cells in the brain, to the levels of entire organisms and even ecosystems. In order to truly understand any biological phenomenon, we need to examine it at each of these levels of complexity.

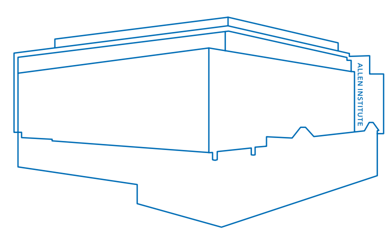
The Allen Institute has had an extraordinary year. We have settled into our beautiful new purpose-built home in the South Lake Union neighborhood of Seattle, joining all the Allen Institute teams under one skylight-filled roof. Among many other accomplishments, the Allen Institute for Brain Science debuted the Allen Brain Observatory: a singular tool to study cellular activity in the living cortex. The Allen Institute for Cell Science has launched their pipeline and is generating unique cell lines and images to capture live human cells in unprecedented ways. The newest member of our team, The Paul G. Allen Frontiers Group, kicked off this year with an event that highlighted the impact that true innovations in science can have not just on research, but on the world at large.

The Allen Institute has never shied away from complex questions in biology. As we have extended our view beyond the brain and into cellular machinery and research questions on the frontier, we have embraced the idea that scientific insights exist at multiple scales. The resources generated by our institutes capture these multiscale facets of biology and share them with the scientific community, recognizing that accelerating the pace of biomedical research is a global pursuit.

Biology is undoubtedly complex—but it is also finite. With the tools, creativity and insight of the team assembled at the Allen Institute, I eagerly look forward to the strides we will make in the coming year.

ALLAN JONES, PH.D.
——PRESIDENT &
CHIEF EXECUTIVE OFFICER

615 WESTLAKE—— Our new headquarters is purpose-built for life science research. The building facilitates our trademark team science approach and exemplifies our core principle of open science amid abundant natural light and with stunning views of Seattle.



270,000 Square feet

1.2 Acre footprint

2,000 Tons of reinforcing steel within the building structure

65,000 Square feet of glass on the building exterior

2,742 Individual pieces of terra cotta reinstalled

THE BRAIN IN ACTION

INTRODUCING THE ALLEN BRAIN OBSERVATORY

The brain is not just an assembly of parts—it is an intricate machine in action, performing the tasks that give rise to perception, cognition and ultimately consciousness.

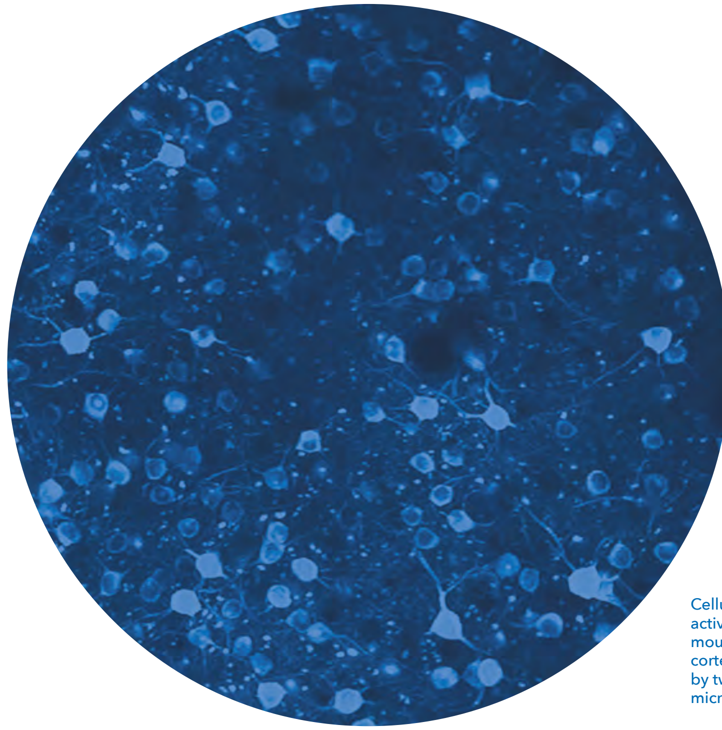
The Allen Brain Observatory is our newest and perhaps most singular resource, designed to provide a window into the brain by capturing natural dynamic brain activity as it is happening in the visual cortex of a behaving mouse.

The Allen Brain Observatory is built on the teamwork of over 100 people representing a wide variety of fields, including software developers, animal care technicians, neuroscientists, engineers, microscopy experts, optical physiologists, physicists, mathematicians and theorists.

FAR RIGHT
A sample of data visualizations from the Allen Brain Observatory.

Measurements from thousands of individual cells and populations of cells in the mouse cortex as they respond to visual stimuli allow researchers to determine the "tuning" of individual cells to visual features like motion and shape orientation. The data also allow researchers to investigate how networks of cells encode information and enable the brain to translate visual input into the complex images, natural scenes and movies that we experience. Information in the Allen Brain Observatory is presented using novel visualization formats and is accompanied by online and downloadable analysis toolkits, as well as access to raw data and user tutorials.

The Allen Brain Observatory is the first publicly available resource of its kind to provide a highly standardized survey of brain activity at the cellular level. Like all Allen Brain Atlas resources, the data and tools are shared openly with the entire scientific community, empowering scientists around the world to make novel discoveries about how information is computed in the brain.



Cellular-level activity in the mouse visual cortex, captured by two-photon microscopy.

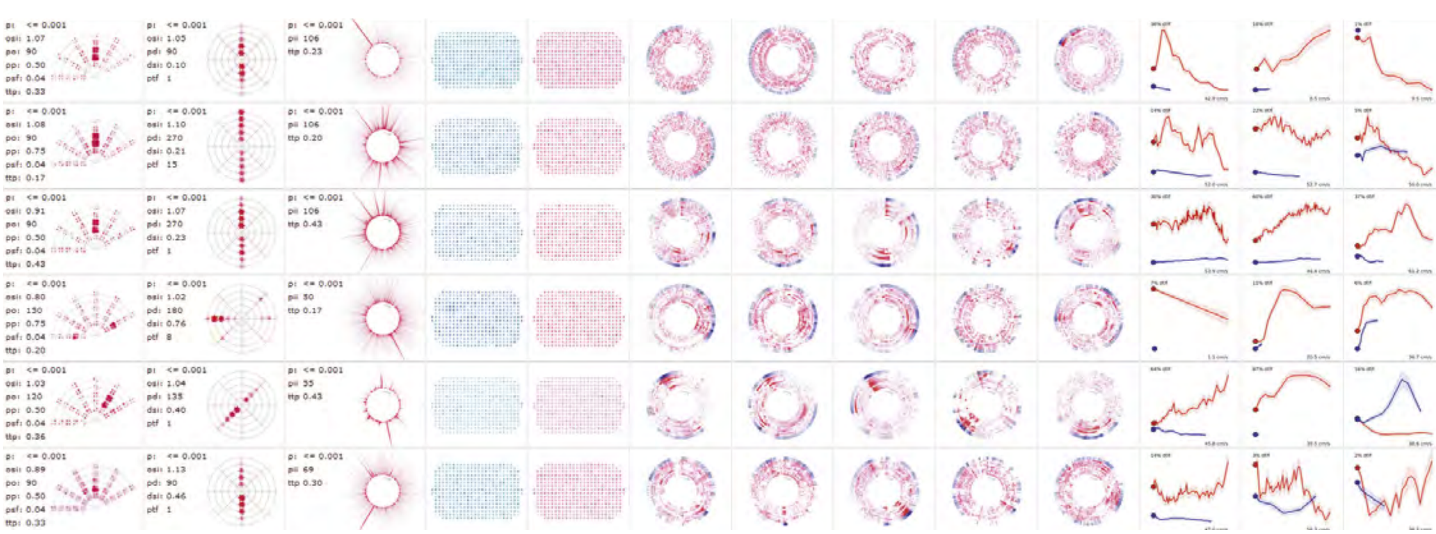
OBSERVING THE BRAIN IN ACTION——— In 2016 we released the first two updates to the Allen Brain Observatory.

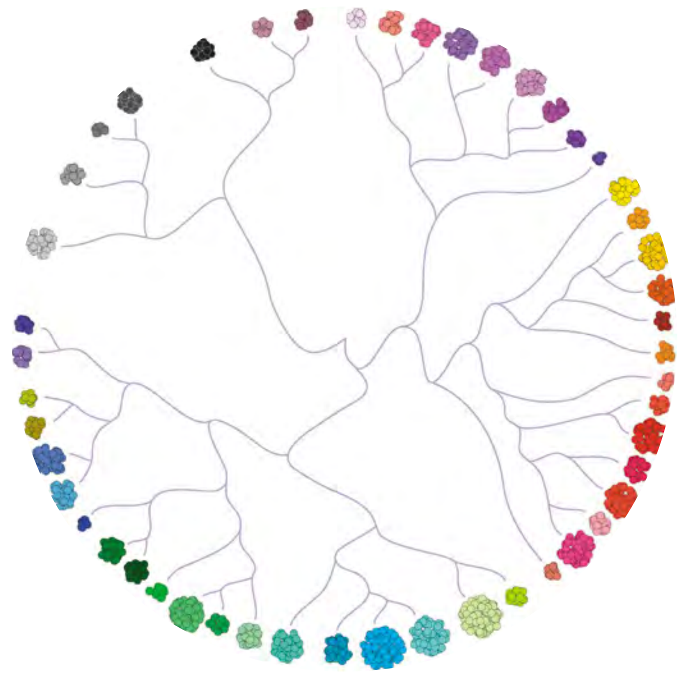
116
Locations recorded

4
Areas and 3 depths of the visual cortex

348
Two-photon experiments

6
Engineered mouse lines





BUILDING BLOCKS OF THE BRAIN

A graphical representation of the cellular taxonomy of the mouse visual cortex created by clustering cells with similar gene expression patterns.

(LEFT TO RIGHT)
Thuc Nguyen, Senior Research Associate

Bosiljka Tasic, Ph.D., Associate Director, Molecular Genetics

The Allen Institute for Brain Science is committed to understanding the fundamental units that make up the brain, including its wide variety of neuronal cell types and the intricate interfaces where cells share information.

A PERIODIC TABLE OF CELLS——— As part of our quest to understand the brain's fundamental components, Allen Institute scientists have adapted new technology to investigate gene expression in individual cells in the brain, identifying 49 distinct types of cells in the visual cortex. This data-driven approach to sorting individual neurons based on their genome-wide gene expression was heralded on the cover of *Nature Neuroscience*.

REVERSE-ENGINEERING THE BRAIN——— Allen Institute researchers are working as part of a collaborative team to digitally reconstruct an entire cubic millimeter of the mouse visual cortex: smaller than a grain of sand, but what will be the largest piece of brain studied this way to date. The project is part of a contract from IARPA (Intelligence Advanced Research Projects Activity) that leverages the unique high-throughput capabilities of the Allen Institute,

A network of cortical neurons whose connections were traced from a multi-terabyte 3D data set.

(LEFT TO RIGHT)
Adam Bleckert, Ph.D., Scientist II

Nuno da Costa, Ph.D., Assistant Investigator

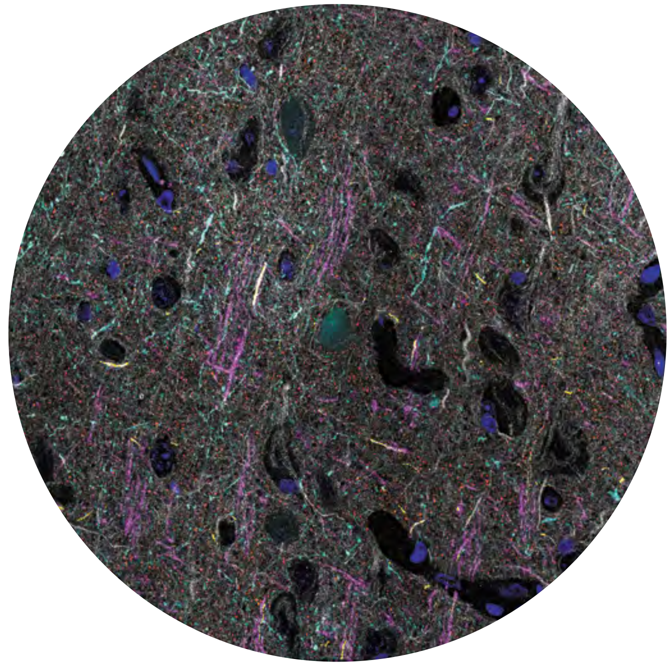
Dan Bumbarger, Ph.D., Scientist II

Clay Reid, Ph.D., Senior Investigator

Lynne Becker, Ph.D., Senior Scientific Program Manager

Shelby Suckow, Ph.D., Project and Alliance Manager

Tom Keenan, Ph.D., System Design Engineer III



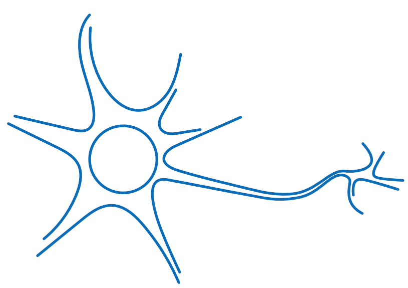
Array tomography of human lateral temporal cortex highlighting synapses, cytoskeleton and myelin.

(LEFT TO RIGHT)
Forrest Collman, Ph.D., Scientist II

Stephen J. Smith, Ph.D., Senior Investigator

where brain circuits are being sliced 1,000 times thinner than a human hair and arranged on a tape for imaging in an array of electron microscopes. With virtually no margin for error, the project is pushing the limits of large-scale brain imaging at incredibly high resolution.

VISUALIZING COMPLEXITY——— The brain's networks are built on an extremely intricate architecture of molecules and membranes. Array tomography is a powerful new microscopy method that enables researchers to capture and visualize this architecture in three dimensions. Allen Institute researchers are now building automated high-throughput systems to scale up array tomography, in order to study the relationship between network structure and function in entire live slices of human brain and provide insight into the brain's most fundamental mechanisms.



CELL BY CELL——— Our *in vitro* single cell characterization pipeline generates huge amounts of data on individual cells in slices of brain.

300+
Neuron shapes digitally reconstructed

1,228,205
Microns of dendritic and axonal branches reconstructed

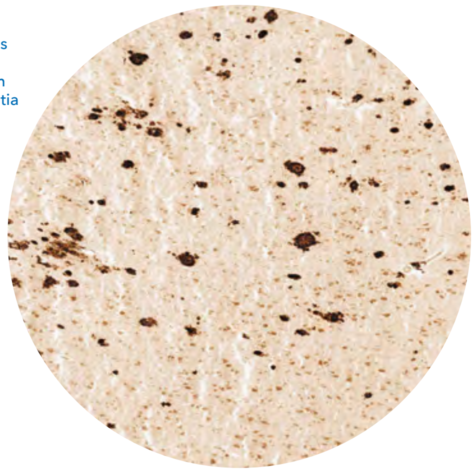
1,435
Mouse neurons' signals recorded

3
Mouse brain regions targeted (primary visual, lateral geniculate and anterior lateral motor cortex)

16,029
Cells and nuclei—both mouse and human—for which we have single-cell gene expression data

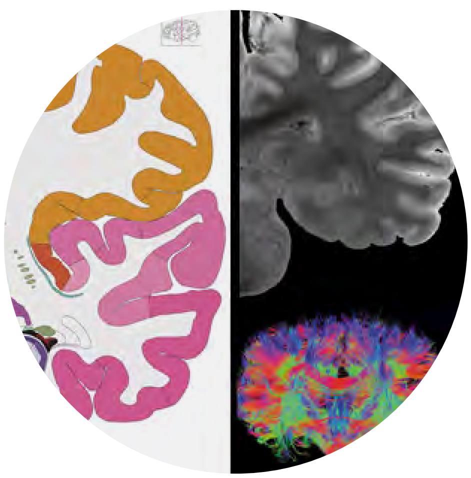
HUMAN SCALE

Our ultimate goal is to understand how the human brain works. To that end, we are using novel techniques and large-scale approaches to study human brain tissue to generate insights that directly impact our understanding of the uniquely human brain.



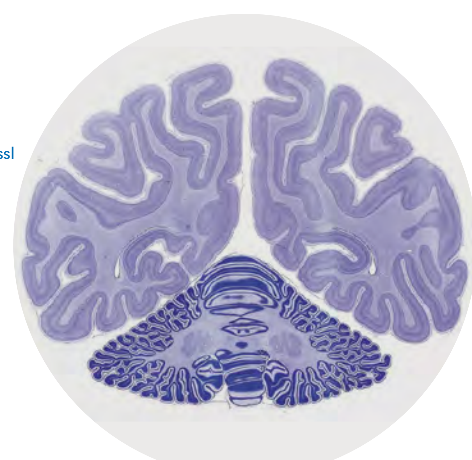
Antibody labeling of amyloid plaques in a sample of human cortex from the Aging, Dementia and TBI Study.

THE AGING BRAIN — Understanding how our brains change as we age normally, or as a result of disease or injury, has been a long-standing challenge in neuroscience. In collaboration with researchers and physicians at UW Medicine and Group Health Research Institute, the Allen Institute has created a new online resource on Aging, Dementia and Traumatic Brain Injury (TBI): a one-of-a-kind tool that collects and shares a wide variety of anatomical, molecular and pathological analyses on a large cohort of aged brains, complete with mental health histories and clinical diagnoses. The large number of patients combined with systematic characterization using a variety of types of data makes this resource a powerful way to investigate ways the human brain can change as we age.



Annotated plate from the Allen Human Brain Reference Atlas (left) with corresponding images of structural MRI and DWI tractography (right).

A REFERENCE MANUAL FOR THE HUMAN BRAIN — Navigating the brain requires a detailed map. This year, the Allen Institute published the highest resolution atlas of the entire human brain to date, both as an interactive, freely available part of the online Allen Human Brain Atlas and as a stand-alone issue of the *Journal of Comparative Neurology*. The atlas, which is based on a single human brain and imaged at micrometer resolution, combines neuroimaging with cellular resolution microanatomy analysis and expert structural annotation. This comprehensive digital human brain atlas allows users to navigate from the level of entire brain sections all the way to the detailed microstructure of individual neurons, creating a foundational resource for understanding brain structure and function.



Coronal section through the neocortex and cerebellum of an adult rhesus monkey brain labeled with a Nissl stain that labels all neuronal and glial cell bodies.

PRIMATE BRAIN DEVELOPMENT — Studying brain development in our close evolutionary relatives can shed valuable light on mechanisms that make the human brain distinct. Allen Institute researchers have published a comprehensive atlas of non-human primate brain development in the journal *Nature*, revealing key features of the primate genetic code that characterize brain development and identifying distinct molecular patterning in the human brain. The study is based on the NIH Blueprint Non-Human Primate (NHP) Atlas, a publicly available resource created by the Allen Institute and colleagues at the University of California, Davis and the California National Primate Research Center.

(LEFT TO RIGHT)
Susan Sunkin, Ph.D., Senior Scientific Program Manager

Song-Lin Ding, M.D., Senior Scientist

Ed Lein, Ph.D., Investigator

Jeremy Miller, Ph.D., Scientist II

Josh Royall, Senior Research Associate

Trygve Bakken, M.D., Ph.D., Scientist II

Amy Bernard, Ph.D., Product Architect

HUMAN CELLS—— Our human *in vitro* single cell characterization pipeline generates data from human tissue that would typically be discarded as medical waste from neurosurgeries. This unique and rare opportunity is a direct portal into understanding the fundamental units of computation in the human brain.

549
Human neurons' signals recorded

25
Human surgical cases processed

174
Human slices recorded

7
Maximum cells recorded from a single human slice

SCIENTIFIC PUBLICATIONS—— Our scientific publication record demonstrates our impact in the field of neuroscience. We remain committed to openly sharing our data and tools with the global scientific community, even before we publish on them.

OVER 560 SCIENTIFIC PUBLICATIONS TO DATE

In the past year, we published 1 cover (*Nature Neuroscience*), 1 dedicated issue (*Journal of Comparative Neurology*), and 41 articles in 28 journals:

Nature
Science
Cell
Nature Neuroscience
Nature Reviews Neuroscience
Nature Protocols
Nature Methods
Journal of Neuroscience
Journal of Comparative Neurology
PNAS
Neuron
PLoS ONE
Journal of Neurophysiology
Neuroinformatics
eLife
Focus on Bio-Image Informatics
arXiv
Cerebral Cortex
eNeuro
Frontiers in Neural Circuits
Brain Informatics
Photoacoustics
Trends in Neurosciences
Journal of Vision
Scientific Reports
BMC Neuroscience
Neuro-Oncology
Neural Computation

ALLEN INSTITUTE FOR CELL SCIENCE

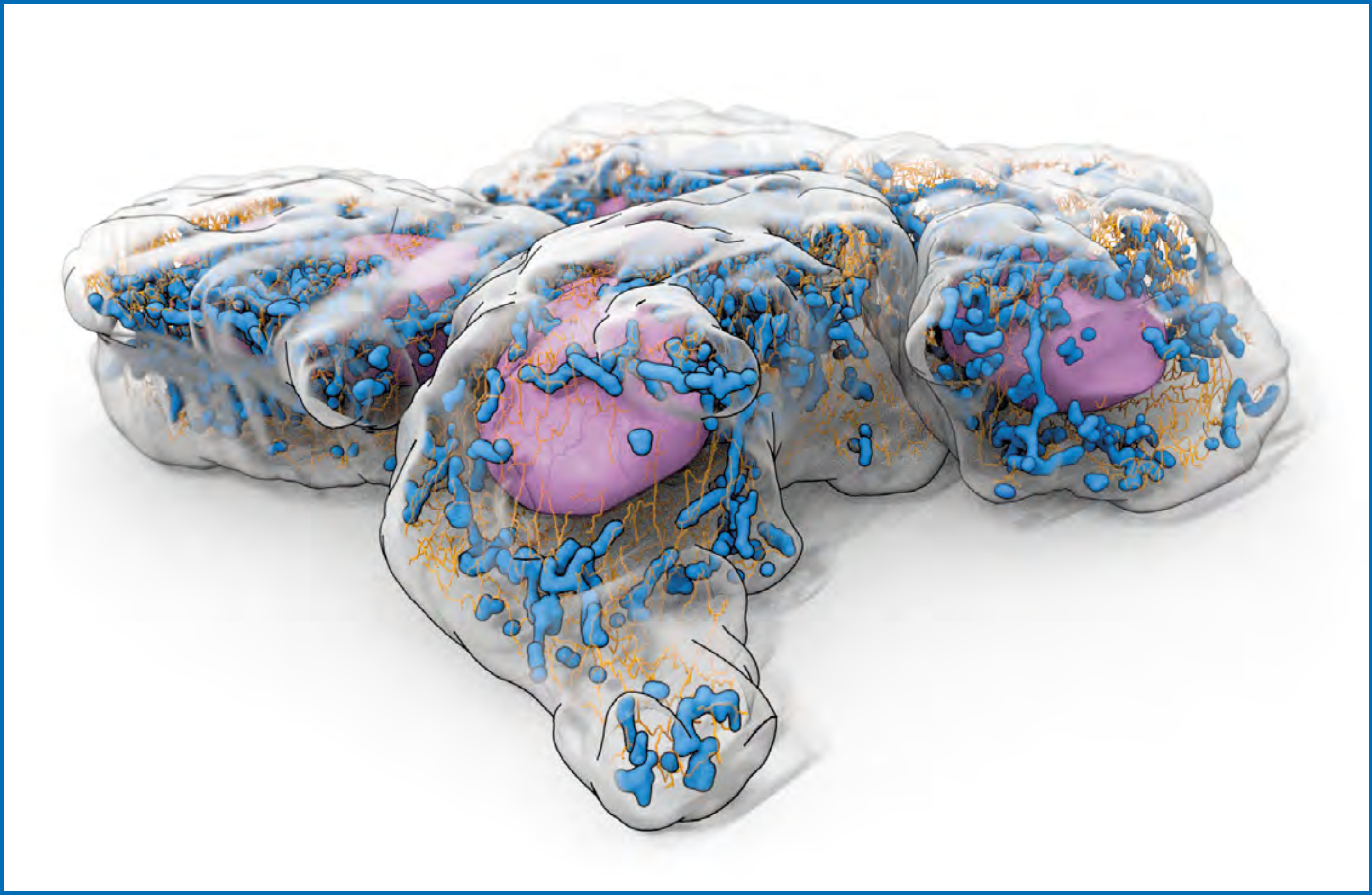
The Allen Institute for Cell Science has kicked off its inaugural project to understand the organization and shapes of major structures inside both undifferentiated human stem cells and in derived heart muscle cells.

Understanding and predicting the dynamic structure of cells is a fundamental step toward being able to analyze and address how cells change in disease.

Scientists at the Allen Institute for Cell Science are creating and sharing a novel collection of powerful tools, including gene edited stem cell lines with fluorescent tags on key organelles. Researchers around the world will be able to use these cells, along with light microscopy, to determine the numbers, locations and dynamic changes of structures and regulatory complexes inside normal human cells. Several of these gene edited cell lines are already available for the greater scientific community, and include extensive documentation and quality control standards.

The data generated from these human cell lines will be used to develop novel algorithms that can predict positions of structures within the cell and to model how the cell's components reorganize as it goes through its cycles of division and differentiation.

All these efforts will culminate in the Allen Cell Explorer: an online image database with tools to visualize, interrogate and annotate dynamic three-dimensional images, cellular models and other computational outputs of the cell.



PIPELINE KICKOFF——— With this year's launch of the pipeline to generate cell lines and image data, the Allen Institute for Cell Science is in full-scale production mode.

15
Gene edited human stem cell lines created

1,434
Clones generated

5 TB
Image data generated

9
Microscope systems established for research and development and the data production pipeline

1,000,000+
3D live cells imaged

LEFT
The Allen Institute for Cell Science team building the pipeline.

ABOVE
An epithelial sheet with four representative human induced pluripotent stem cells showing locations of mitochondria (blue), gene edited microtubules (orange) and the nucleus (pink).

EXPLORING FRONTIERS OF BIOSCIENCE

Launched in 2016 with a $100 million commitment toward a larger 10-year plan, The Paul G. Allen Frontiers Group will discover and support scientific ideas that change the world. By surveying the global scientific landscape, the Frontiers Group seeks to find the pioneering investigators who can cross disciplines and take novel approaches to hard problems in the biological sciences.

The most transformational discoveries are being made at the intersections of fields, where creative researchers find fresh perspectives and develop new insights. The Frontiers Group is committed to a continuous dialogue with scientific visionaries around the world in order to remain at the forefront of knowledge.

ALLEN DISTINGUISHED INVESTIGATORS——— The Allen Distinguished Investigators program provides three years of funding to individual researchers or small teams with groundbreaking ideas. As part of the launch, the Frontiers Group named four new Allen Distinguished Investigators. Their explorations range from investigating the genetic programs that guide major leaps in evolution to applying synthetic biology to solve the problem of antibiotic resistance.

ALLEN DISCOVERY CENTERS——— The Allen Discovery Centers provide larger-scale, longer-term funding to coherent, leadership-driven teams, typically located at major research organizations and universities. The first two Allen Discovery Centers are located at Stanford University, where scientists are creating multiscale, systems models of infection, and Tufts University, where researchers are uncovering the code for biological shape control and regeneration.

Allen Distinguished Investigators and leaders of Allen Discovery Centers gather at the launch of The Paul G. Allen Frontiers Group.

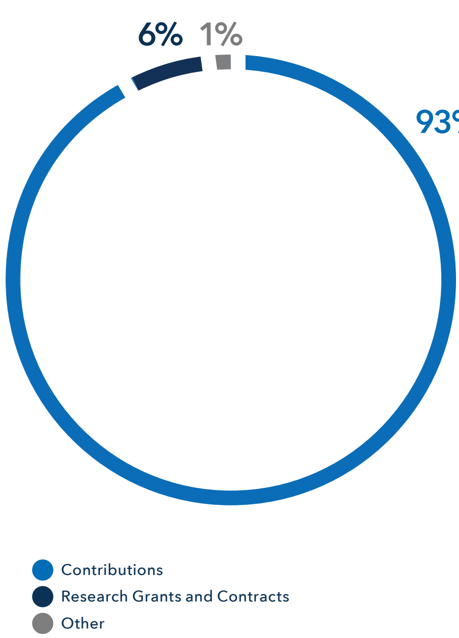
Paul Allen announces The Paul G. Allen Frontiers Group at the National Academy of Sciences in Washington, D.C.

FINANCIAL SUMMARY

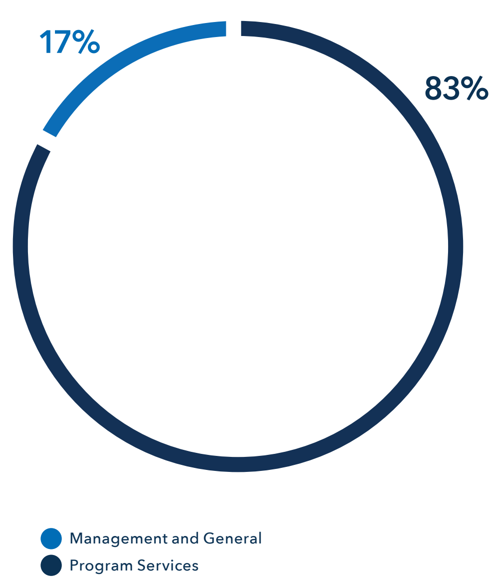
ALLEN INSTITUTE FISCAL YEARS 2015 AND 2014 (IN THOUSANDS)

	2015 (AUDITED)	2014 (AUDITED)
SUPPORT AND REVENUE		
Contributions	**$ 105,059**	$ 52,878
Research Grants and Contracts	**7,161**	3,499
Other	**558**	2,671
TOTAL SUPPORT AND REVENUE	**112,778**	59,048
EXPENSES		
Program Services	**55,891**	43,534
Management and General	**11,711**	8,451
TOTAL EXPENSES	**67,602**	51,985
CHANGE IN NET ASSETS	**$ 45,176**	$ 7,063
NET ASSETS, BEGINNING OF YEAR	**171,133**	164,070
NET ASSETS, END OF YEAR	**$ 216,309**	$ 171,133

FUNDING SOURCES 2015



EXPENSES 2015



OUR TEAM

FOUNDERS
Paul G. Allen
Jody Allen

LEADERSHIP
Allan Jones, Ph.D.
President & Chief Executive Officer

Chinh Dang
Chief Administrative Officer

David Poston
Chief Financial Officer

Christof Koch, Ph.D.
President & Chief Scientific Officer,
Allen Institute for Brain Science

Rick Horwitz, Ph.D.
Executive Director,
Allen Institute for Cell Science

Tom Skalak, Ph.D.
Executive Director,
The Paul G. Allen Frontiers Group

BOARD OF DIRECTORS
Jody Allen
Board Chair,
Allen Institute

Barbara Bennett
President & Chief Operating
Officer, Vulcan, Inc.

Nathaniel T. "Buster" Brown
Executive Vice President, CFO
Rain City Capital, LLC

Thomas Daniel, Ph.D.
Professor of Biology, Neurobiology
and Behavior, Komen Endowed
Chair, University of Washington

Stephen Hall
Managing Director, Venture
Capital, Vulcan Inc.

Allen D. Israel
Member, Foster Pepper LLC

Michael Stryker, Ph.D.
University of California,
San Francisco

BECOME A FAN OR FOLLOW US!

@allen_institute

alleninstitute

alleninstitute

ALLEN INSTITUTE FOR BRAIN SCIENCE SCIENTIFIC ADVISORY BOARD
David Anderson, Ph.D.
California Institute of Technology

Edward Callaway, Ph.D.
Salk Institute for Biological Studies

Thomas Daniel, Ph.D.
University of Washington

Catherine Dulac, Ph.D.
Harvard University

Daniel Geschwind, M.D., Ph.D.
University of California,
Los Angeles

Story Landis, Ph.D.
Former Director, National
Institute of Neurological
Disorders and Stroke

Marc Tessier-Lavigne, Ph.D.
Stanford University

Giulio Tononi, M.D., Ph.D.
University of Wisconsin – Madison

David Van Essen, Ph.D.
Washington University
School of Medicine

ALLEN INSTITUTE FOR BRAIN SCIENCE ADVISORY COUNCIL MEMBERS
Larry Abbott, Ph.D.
Columbia University

Hollis Cline, Ph.D.
Scripps Research Institute

György Buzsáki, M.D., Ph.D.
New York University

Yang Dan, Ph.D.
University of California, Berkeley

Adrienne Fairhall, Ph.D.
University of Washington

Kristen Harris, Ph.D.
University of Texas at Austin

Patrick Hof, M.D.
Mount Sinai School of Medicine

Arnold Kriegstein, M.D., Ph.D.
University of California,
San Francisco

John H.R. Maunsell, Ph.D.
Harvard Medical School

David McCormick, Ph.D.
Yale University

Markus Meister, Ph.D.
California Institute of Technology

Carl Petersen, Ph.D.
École Polytechnique
Fédérale de Lausanne

Michael Stryker, Ph.D.
University of California,
San Francisco

Botond Roska, M.D., Ph.D.
Friedrich Miescher Institute
for Biomedical Research

Peter Somogyi, Ph.D.
University of Oxford

David Tank, Ph.D.
Princeton University

Christopher Walsh, M.D., Ph.D.
Harvard Medical School

Rafael Yuste, M.D., Ph.D.
Columbia University

ALLEN INSTITUTE FOR CELL SCIENCE SCIENTIFIC ADVISORY BOARD
Bruce Alberts, Ph.D.
University of California,
San Francisco

Sangeeta Bhatia, M.D., Ph.D.
Massachusetts Institute
of Technology

Joan Brugge, Ph.D.
Harvard Medical School

Peter Devreotes, Ph.D.
John Hopkins School of Medicine

David Drubin, Ph.D.
University of California, Berkeley

Michael Elowitz, Ph.D.
California Institute of Technology

Larry Goldstein, Ph.D.
University of California, San Diego

Anthony Hyman, Ph.D.
Max Planck Institute of Molecular
Cell Biology and Genetics

Douglas Lauffenburger, Ph.D.
Massachusetts Institute
of Technology

Jennifer Lippincott-Schwartz, Ph.D.
Janelia Research Campus

Charles Murry, M.D., Ph.D.
University of Washington

Thomas Pollard, M.D.
Yale University

Sandra Schmid, Ph.D.
University of Texas Southwestern
Medical Center

Julie Theriot, Ph.D.
Stanford University
School of Medicine

ALLEN INSTITUTE FOR CELL SCIENCE ADVISORY COUNCIL MEMBERS
Brenda Andrews, Ph.D.,
C.C., F.R.S.C.
University of Toronto

Anne E. Carpenter, Ph.D.
Broad Institute

Bruce R. Conklin, M.D.
Gladstone Institutes and
University of California,
San Francisco

Gaudenz Danuser, Ph.D.
University of Texas
Southwestern Medical Center

Tom Goddard, Ph.D.
University of California,
San Francisco

David S. Goodsell, Ph.D.
Scripps Research Institute

Erico Gratton, Ph.D.
University of California, Irvine

Wallace Marshall, Ph.D.
University of California,
San Francisco

Tom Misteli, Ph.D.
National Cancer Institute

Torsten Möller, Ph.D.
Universität Wien

Charles E. Murry, M.D., Ph.D.
University of Washington

David W. Piston, Ph.D.
Washington University
in St. Louis

William C. Skarnes, Ph.D.
Wellcome Trust Sanger Institute

Jason Swedlow, Ph.D.
University of Dundee, Scotland

Ron Vale, Ph.D.
University of California,
San Francisco

THE PAUL G. ALLEN FRONTIERS GROUP ADVISORY COUNCIL
David Baltimore, Ph.D.
California Institute
of Technology

Vicki Chandler, Ph.D.
Minerva Schools at KGI

Marc W. Kirschner, Ph.D.
Harvard Medical School

Andrew D. McCulloch, Ph.D.
University of California,
San Diego

STAFF
More than 345 dedicated
employees

More than 125 researchers
with Ph.D. degrees

ALLEN
INSTITUTE

615 WESTLAKE AVENUE N
SEATTLE, WASHINGTON 98109

ALLENINSTITUTE.ORG

BRAIN-MAP.ORG