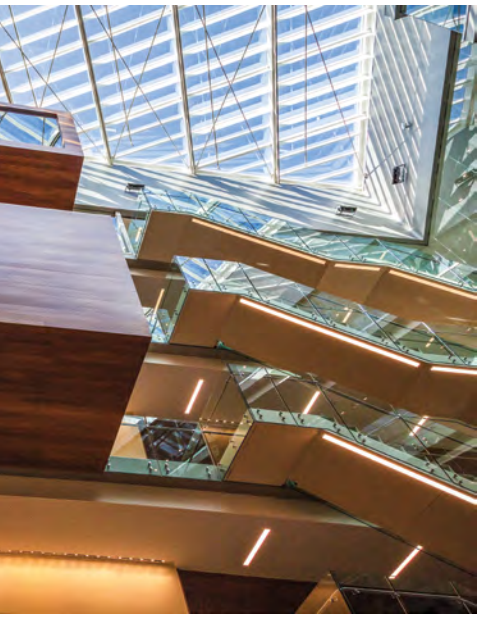
ALLEN INSTITUTE

2019 ANNUAL REPORT

UNLOCKING *the* MYSTERIES *of* US

Uncovering the biology of humanity is difficult but crucial: Our own health hangs in the balance.

At the Allen Institute, we're bringing our unique approach to bear on human biology. Across our divisions, we're exploring what it means to be human, from the building blocks of our bodies to the intricate details of our neurons to how our dynamic immune systems keep us healthy — *and what goes wrong in disease.*



At the Allen Institute, we take on the hardest problems in biology in a way that's uniquely our own, working together in carefully crafted teams and sharing everything we do with the broader scientific community and with the world.

Our research has laid the groundwork for translational work with the potential to improve human health, and we will continue to focus on such foundational research. By launching our newest scientific division, the Allen Institute for Immunology, we're also tackling a complex problem with an immediate through-line to health and disease: the human immune system. Millions of people around the world are suffering with and sometimes dying from immune-related diseases, and there's still so much to uncover about this critical system in our bodies.

At the same time, we're making incredible insights that shed light on the very nature of who we are, from how our cells divide to the individual components that make up our brains. And we're thrilled to be part of a new innovative funding initiative that is enabling cutting-edge explorations into the urgent problems of Alzheimer's disease and other age-related brain disorders.

Like everything we do at the Allen Institute, our studies of human biology honor the legacy of our founder, the late Paul G. Allen, who was dedicated to unlocking the mysteries of bioscience.

Allan Jones, Ph.D.
President and Chief Executive Officer

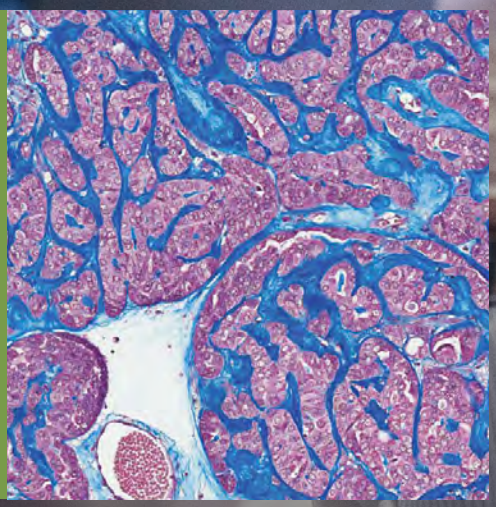
Julian Reading, a researcher at the Allen Institute for Immunology, in the Institute's new lab.

OUT OF BALANCE

When Allen Institute for Immunology Executive Director Tom Bumol, Ph.D., moved into his new office, he gave prominent placement to a set of CT scans: a tumor before treatment, and its near-absence after. Throughout his career in immunology research, Bumol has heard many heartbreaking personal stories that motivate him and his colleagues to push toward better treatments for immune-related diseases.

The story behind these scans is his own.

Bumol's experience with a life-threatening lymphoma spurred him to double down on his research, eventually bringing him to lead the Institute's new division. Read more of Tom's story and see other profiles of the patients that inspire our researchers in our new series, Out of Balance, at alleninstitute.org/outofbalance.



ALLEN INSTITUTE *for* IMMUNOLOGY

Our immune system's dynamic balance

Late last year, we debuted the Allen Institute for Immunology to the world, seeded by a commitment of $125 million by our founder, the late Paul G. Allen. Researchers at this new scientific division of the Allen Institute are working to understand the dynamic balancing act of the human immune system, how it senses friend from foe and what goes wrong when we're ill.

Their work will lay the foundation to improve human health and treatments for immune-related diseases.

The researchers work directly with samples and data from patients and healthy volunteers, thanks to a unique partnership with leading research organizations: Benaroya Research Institute at Virginia Mason, Fred Hutchinson Cancer Research Center, the University of California San Diego with the University of Colorado Anschutz Medical Campus, and the University of Pennsylvania.

The researchers will initially focus on cancer and the autoimmune diseases rheumatoid arthritis and inflammatory bowel disease. They will also study healthy volunteers, with the goal of understanding what makes a "normal" immune baseline and how to help patients return to that healthy state.

ALLEN INSTITUTE *for*
BRAIN SCIENCE

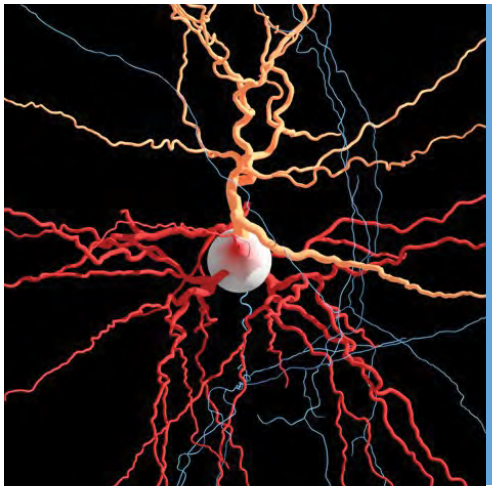
The cells that build our brain

A recent discovery has captured crucial differences between human and mouse brain cells that could explain why many drugs that work in the lab don't work in us. The study, which was led by the Allen Institute for Brain Science and published in the journal Nature, describes the most detailed "parts list" of the human brain to date.

The team's ultra-high-resolution comparison showed that many of our brain cell types can be matched to those in the mouse brain – with key differences that could explain why so many psychiatric drugs developed in mouse studies don't work in humans. For example, they found that the proteins that allow our neurons to react to the brain chemical serotonin are used differently in mice and human neurons. This finding could explain why it's been so difficult for clinical researchers to develop new therapies for depression and other disorders related to serotonin: A drug that acts on this chemical, which plays a starring role in mood, appetite and sleep, could affect a mouse very differently than it would us.

The researchers looked to our genes to tell the story of how our brains evolved away from mouse brains over the past 75 million years, using the genes that are switched on in single cells to sort nearly 16,000 cells from part of the temporal lobe of the human cortex and comparing them with those from mice.

As part of the NIH-funded BRAIN Initiative, the team is now working on the ambitious goal to develop a complete parts list of the entire human brain.



NEW CLUES ABOUT WHAT MAKES OUR BRAINS TICK

Our researchers are also probing the behavior of living human neurons in the lab, a rare opportunity to delve into the inner workings of our own brains. These precious cells come from generous patients who donate healthy tissue removed during the course of surgery, coordinated by Seattle-area neurosurgeons.

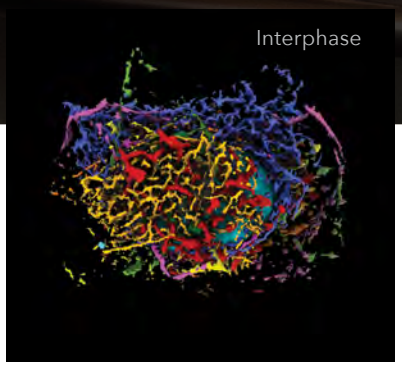
Our scientists have found intriguing electrical properties of human von Economo neurons, a rare brain cell type that doesn't exist in mice and which plays a still-mysterious role in human neurological and psychiatric disorders. They've also found that another type of neuron, one that exists in both mice and us, filters electrical signals differently in mice and in humans, a finding that could have implications for epilepsy drug development.

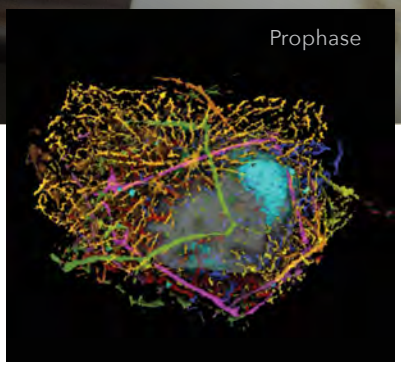
Rebecca Hodge, Ph.D., a scientist at the Allen Institute for Brain Science, holds a section of postmortem human brain used to study brain cell types.

Megan Riel-Mehan, Ph.D., and Matheus Viana, Ph.D., two researchers at the Allen Institute for Cell Science who worked on the Integrated Mitotic Stem Cell.

THE STAGES OF MITOSIS

Our researchers have developed new ways to visualize the major parts of a human cell as it passes through four different stages of cell division and the non-dividing state, also known as interphase.





ALLEN INSTITUTE *for*
CELL SCIENCE

How our cells divide

This spring, the Allen Institute for Cell Science debuted the Integrated Mitotic Stem Cell, a model and visualization tool that captures – for the first time – a holistic view of human cell division. This new window on human stem cell division, a process also known as mitosis, will enhance basic biology research and studies of cancer.

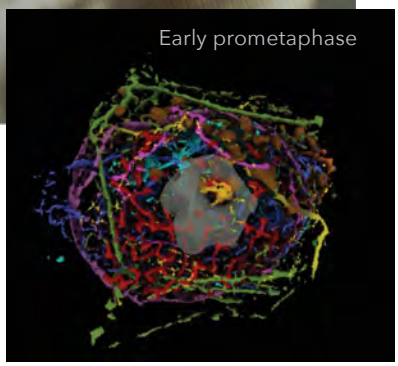
Many of us learned about cell division in school through cartoonish illustrations in a textbook. But scientists still don't have a complete view of everything that happens as our cells go from one to two.

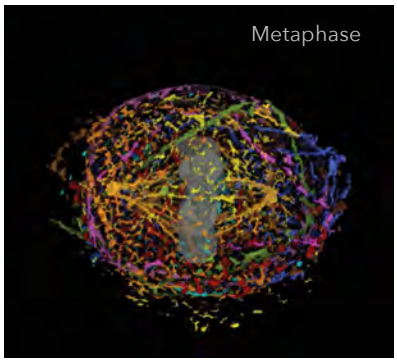
That process is literally vital. Cell division is integral to humanity and all living things. It's how we grow from one fertilized egg into the trillions of cells that make up our adult bodies, why we have specialized cells that form our organs, and how we repair wounds.

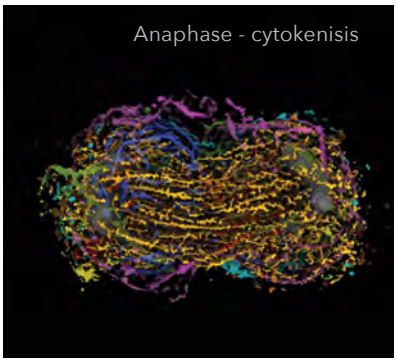
It's also essential to human health: Tumors can form when a cell fails to divide correctly.

The tool captures changes in size, shape and location of the major components of cells as they undergo mitosis. Our researchers generated the model using images from live human stem cell lines that they gene-edited to highlight different structures with glowing fluorescent tags.

With a completely new way to visualize and explore mitosis, our scientists have already made new observations about coordinated behaviors many structures undergo during human stem cell division – with more to come.







THE
PAUL G. ALLEN
FRONTIERS GROUP

Keeping our brains healthy as we age

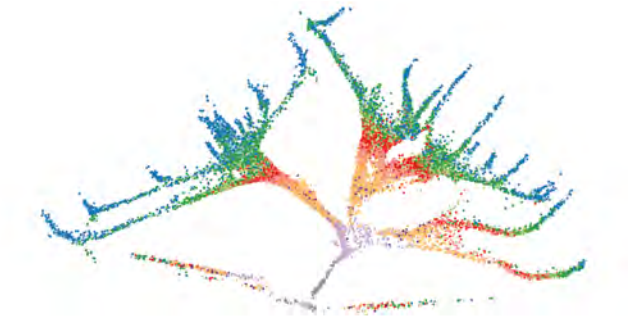
Three research teams are tackling healthy brain aging and age-related dementia thanks to a new $43 million collaborative funding initiative from the American Heart Association and The Paul G. Allen Frontiers Group, a division of the Allen Institute that looks for new ideas in bioscience and directs research funding to help advance human health.

The teams, announced late last year, will tackle tough questions:

Are age-related brain diseases caused not by a single event, but by a failure of interconnected systems? Rusty Gage, Ph.D., a neuroscientist and president of the Salk Institute for Biological Studies, is leading a team working to understand the complex, multi-part network that keeps our brains healthy – and how that network goes wrong in disease.

Could blood hold the molecular secrets to preventing Alzheimer's and related disorders? Tony Wyss-Coray, Ph.D., Professor of Neurology at Stanford University School of Medicine, has found in his studies that blood or plasma from young animals or humans can slow brain aging in mice and improve symptoms of mild Alzheimer's disease. Now, he is leading a research team aiming to unlock the beneficial effects of young blood to create new therapeutics for vascular dementia, Alzheimer's disease, and related brain disorders.

Can targeting red blood cells and blood vessels jointly keep our brains healthy and prevent dementia? Mukesh K. Jain, M.D., a cardiologist at University Hospitals Cleveland Medical Center and Professor of Medicine at Case Western Reserve University School of Medicine, is leading a team of investigators exploring how red blood cells, the most abundant cells in our body, and the inner lining of small blood vessels called the endothelium work together as a unit to drive brain health and age-related cognitive disease.



A SINGLE-CELL BREAKTHROUGH

Studies from the Allen Discovery Center at UW Medicine tracing development at the single-cell level in the zebrafish, showing the lineage of how one cell gives rise to many, were among those named Science Magazine's 2018 Breakthrough of the Year.

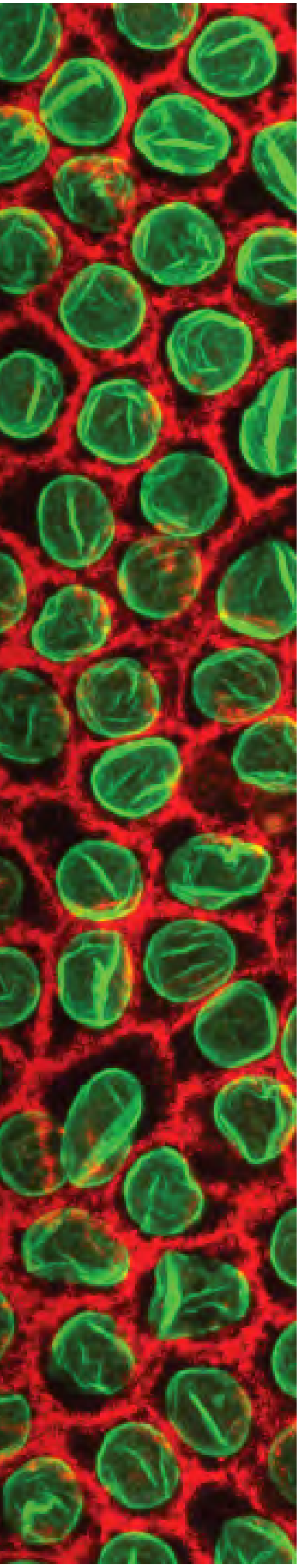
Rusty Gage, Ph.D., a neuroscientist who leads one of the recently announced AHA-Allen Initiative teams, presents his research at the Allen Institute.

The foundation to better health

At the Allen Institute, open science is one of our founding credos. We share our data, knowledge and tools with the world because we know scientific progress accelerates when we all work together. As a true testament to the power of foundational research, we've seen scientists around the world using our resources in ways we never could have imagined.

More than 600 vials from the Allen Cell Collection's gene-edited human stem cell lines have been distributed to labs in 19 different countries around the world, studying diseases and model systems ranging from human cell differentiation to kidney disease, Alzheimer's and heart regeneration. Researchers at the National Eye Institute at the National Institutes of Health are using these cell lines in their work studying eye disease. The team studies a structure in the eye known as the retinal pigment epithelium which, in healthy eyes, sustains photoreceptor cells. In patients with age-related macular degeneration, a type of eye disease, that structure dies off, leading to the loss of photoreceptor cells and vision loss. The Allen Institute's cell lines are helping the team understand how these critical retinal cells work, with the ultimate goal of developing a stem cell therapy that could reverse macular degeneration.

Researchers from the National Eye Institute in the lab.



A type of retinal cells derived from a human stem cell line gene-edited at the Allen Institute for Cell Science. Researchers are using these cells to better understand eye disease.

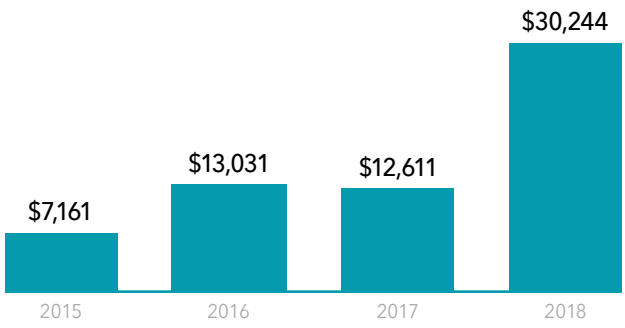
Neuroscientist Emily Sylwestrak, Ph.D., speaks at the Allen Institute for Brain Science's 2018 Showcase Symposium.

Neuroscientist Emily Sylwestrak, Ph.D., studies the habenula, a tiny brain structure that plays a role in addiction, depression, pain and sleep. Sylwestrak, who just launched a lab at the University of Oregon and is also an Allen Institute for Brain Science Next Generation Leader, turned to the Allen Mouse Brain Atlas to find genes whose expression is specialized to this structure. Her research that followed from that observation is shedding light on the roles different cell types in the habenula play in reward seeking and response – a phenomenon that could go awry in human drug-seeking and addiction.

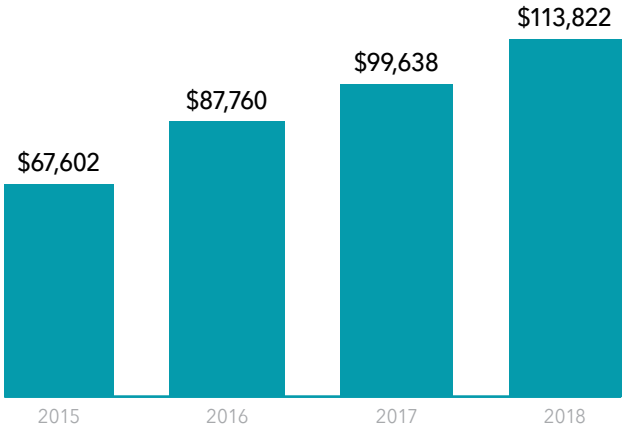
In the coming years, as the Allen Institute for Immunology generates publicly available resources and as our other divisions continue to share their data, knowledge and tools, the potential for impact on human health will only continue to grow. We can't wait to see where the scientific community takes our resources next.

Financial summary

Research Grants & Contract Revenue
(in Thousands)



Total Spending
(in Thousands)



Allen Institute Fiscal Years 2018 and 2017
(in Thousands)

	2018 (Audited)	2017 (Audited)
Support and Revenue		
Contributions	290	109
Research Grants and Contacts	30,244	12,611
Other	1,312	4,485
Total Support and Revenue	**31,846**	17,205
Expenses		
Program Services	92,991	80,082
Management and General	20,831	19,556
Total Expenses	**113,822**	99,638
Change in Net Assets	(81,976)	(82,433)
Net Assets, Beginning of Year	345,014	427,447
Net Assets, End of Year	**263,038**	345,014

The Allen Institute, comprising the Allen Institute for Brain Science, the Allen Institute for Cell Science, the Allen Institute for Immunology 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.

Our team

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Paul G. Allen

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Chief Operations Officer

Todd Peterson, Ph.D.
Chief Scientific Officer

Marjorie Thomas
Chief Financial Officer

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