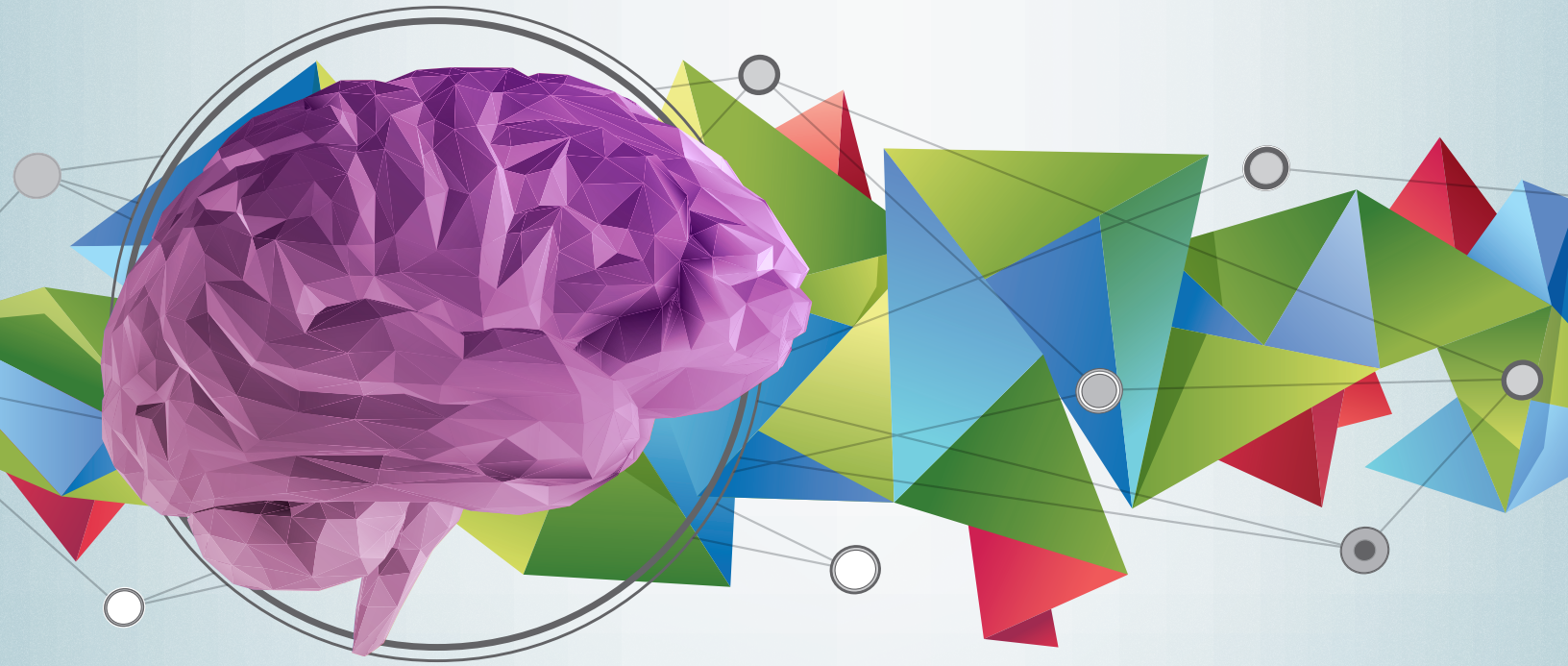
American Heart Association.

THE PAUL G. ALLEN FRONTIERS GROUP

NARRATIVE REPORT

BRAIN HEALTH AND COGNITIVE IMPAIRMENT



STRATEGIC FUNDING INITIATIVE

January 1, 2019 - December 31, 2026

In 2010, more than 35 million people worldwide were diagnosed with dementia and cognitive disorders.[1] That number increased to 46.8 million by 2015 and is expected to reach over 130 million in 2050.[2] As medical and scientific advancements have extended life expectancies, healthy aging is an urgent frontier for research. The burden of age-related cognitive impairment is growing exponentially – whether from Alzheimer's Disease, vascular dysfunction, the combination of these, or other causes. These debilitating diseases are costly, both to our health care system in terms of long-term care facilities, and to individuals and their families in terms of personal and emotional toll.

Cerebrovascular diseases and neurodegenerative diseases were once considered mutually exclusive conditions. This traditionally rigid distinction has made it more difficult to understand and mitigate

Dr. Kathryn Richmond

these disorders. In 2018, the American Heart Association (AHA) and the Paul G. Allen Frontiers Group (Frontiers Group) came together to confront this historical divide in the scientific and medical community by creating the **American Heart Association - Allen Initiative in Brain Health and Cognitive Impairment (BHCI)**. "By catalyzing fundamental research that bridges across fields, we aim to advance our understanding of these diseases in service of human health," stated **Kathryn Richmond, Ph.D., M.B.A.**, Executive Vice President and Director Frontiers Group and Office of Science and Innovation at the Allen Institute. Dr. Richmond also serves as a member on the Joint Leadership Group, which provides oversight for the awards.

AHA and the Frontiers Group, together with additional contributors including the Oskar Fischer Project and Henrietta B. and Frederick H. Bugher Foundation, have committed over $43 million to disrupt the incremental trajectory of brain health science and open new frontiers of discovery that will improve and lengthen lives.

"During my tenure as president of the AHA, I was especially pleased to witness strategies to bridge the science of vascular health and brain health through revolutionary approaches to make new discoveries and to forge timely advances," said **Ivor Benjamin, M.D., FAHA,** AHA Past President, physician scientist, and co-chairperson of the Joint Leadership Group.

This Initiative supports highly promising teams of biomedical investigators pursuing creative, transformative ideas with the potential to move brain health and cognitive impairment science forward. The initiative has granted three competitive basic science research awards that started on January 1, 2019, to study brain health over eight years.

Dr. Ivor Benjamin

The AHA-Allen BHCI research teams are led by the following:

- **Fred "Rusty" Gage, Ph.D.** at the Salk Institute in La Jolla, California – Understanding the cell biological drivers of aging as risk factors for cognitive impairment
  Jan 1, 2019 - Dec 31, 2026
- **Tony Wyss-Coray, Ph.D.** and **Marion Buckwalter, MD., Ph.D.** at Stanford University, in Palo Alto, California – Studying immunomodulation to promote cerebrovascular and cognitive health
  Jan 1, 2019 - Dec 31, 2022
- **Andrew Pieper, M.D, Ph.D.** at University Hospitals in Cleveland Ohio - Optimizing the function of a redefined neurovascular unit to prevent age-related dementia
  Jan 1, 2019 - Dec 31, 2022

[1]Alzheimer's Disease International. (2009). World Alzheimer Report 2009 Executive Summary. In alzint.org/u/WorldAlzheimerReport-ExecutiveSummary.pdf

[2]Alzheimer's Disease International. (2015). World Alzheimer Report 2015 Executive Summary. In alzint.org/u/WorldAlzheimerReport-ExecutiveSummary.pdf

INSTITUTION SPOTLIGHT

Salk Institute

Team Director: Fred "Rusty" Gage, Ph.D.

Project Title: Understanding the cell biological drivers of aging as risk factors for cognitive impairment

'What makes one person decline into Alzheimer's Disease at age 68 while others seem sharp as a tack when they're 100 years old?'

To answer such a complex question, the Salk Institute put together a wide-ranging research project that included genomiscists, mathematicians, cell biologists and even a colony of silky-furred monkeys known as marmosets.

Scientists gave the tiny monkeys iPads and watched them excitedly play games, which were cognitive tests.

"Marmosets are fantastic," said **Fred "Rusty" Gage, Ph.D., Salk Institute team director**. "They're smart, social primates, but they age really quickly, which lets us take a deep dive and map all these molecular mechanisms" to produce a drug for humans that can stop mental decline.

While the Salk team is several years away from completing all the studies in its eight-year project, its research has already been highly productive in providing a better understanding of what goes wrong as brain cells age. The project has multiple components, with numerous researchers working on each. Scientists are zeroing in on flaws in the relationship between five interconnected cellular systems: genome integrity, proteostasis, inflammation, epigenetics, and energy metabolism and stress. Researchers

Dr. Fred "Rusty" Gage

treated neurons from Alzheimer's patients with a therapeutic cocktail that can remove aging cells, which successfully reduced the number of problematic neurons. Additionally, other Salk scientists created effective new approaches to treating human neurons in vitro, a discovery that could provide new ways to slow cognitive decline in Alzheimer's patients. Further research sheds new light on how sections of chromosomes known as telomeres trigger an inflammatory response that damages cells. Salk scientists also discovered natural compounds that can treat inflammatory disease.

The goal of all these studies "is to stratify the population and get biomarkers to see what your aging style is, or what somebody else's aging style is," Gage said, "because the interventions for them will be different."

He commended the AHA for taking a "new perspective" on researching brain health and cognitive impairment.

"We're not looking at a single target or searching for a magic bullet," Gage said. "We are coming at it with experts in multiple areas, from multiple perspective, so we will have a comprehensive understanding of it.

"By the end of this project, we'll be working our way toward new therapies that help millions and millions of people live healthier lives as they age."

Dr. Tony Wyss-Coray

Stanford University

Team Co-Directors: Tony Wyss-Coray, Ph.D. & Marion Buckwalter, M.D., Ph.D.

Project Title: Immunomodulation to promote cerebrovascular and cognitive health

As we age, it is easy to notice our skin wrinkling and our hair turning gray. What is not so apparent are the age-induced changes to our blood that affect brain function.

Scientists at Stanford University identified new mechanisms behind the domino effect in which changes in the blood trigger changes in brain blood vessels — which then damage brain cognition. They also clarified the role blood plays in the brain's response to a stroke.

"How does the brain heal after a stroke?" said **Marion Buckwalter, M.D., Ph.D., team co-director**, "and what process might a stroke trigger that causes dementia later? The answers are important because strokes are more common in people with memory problems, and having a stroke doubles your chance of getting dementia later in life."

Collaborating with human volunteers, researchers discovered post-stroke blood proteins that may cause dementia, a finding that has led the National Institutes of Health (NIH) to fund additional research. Working with mice, Stanford scientists also found key proteins that can be altered to improve cognitive function after a stroke.

Team co-director Tony Wyss-Coray, Ph.D. added, "The initiative facilitated the collaboration among a larger group of people and synergized efforts to understand the role of vasculature and vascular inflammation in cognitive impairment and dementia.

"It allowed us to develop the first survey of gene expression in the human vasculature at a cellular resolution which led to multiple discoveries and spawned a growing number of follow-up studies in the community."

"Stroke research is really important because it offers proof for a new paradigm," Buckwalter said. "Now we're poised to develop new treatments."

The researchers then developed new ways to grow blood vessel cells to study why blood vessel diseases occur and cause strokes. They also created several tools for global researchers, including the first online "atlas" of brain blood vessel cells that details how the cells change with age.

So far, Stanford's work on the AHA-Allen Initiative in Brain Health and Cognitive Impairment has led to more than thirty publications, including papers in *Nature*, *Neuron*, *Circulation* and *Cell*.

"It's been a really big effort, and we made a lot of exciting discoveries and progress in finding new ways to prevent dementia," Buckwalter said. "Pursuing these more creative, innovative types of research can have big rewards. None of this would be possible without the Brain Health and Cognitive Impairment Initiative."

Dr. Marion Buckwalter

University Hospitals Cleveland Medical Center

Team Director: Andrew Pieper, M.D., Ph.D.

Project Title: Optimizing the function of a redefined neurovascular unit to prevent age-related dementia

Unlike a battery, the brain cannot store energy. If its constant blood flow from the heart is interrupted, the brain starts to die.

Scientists at University Hospitals set out to learn more about energy and the brain-blood flow connection as they figured out new ways to potentially prevent age-related dementia.

"A broken bone heals more quickly when you're a kid than it does when you're 70, and it's the same principle with the brain: We showed that if you can preserve the energy levels of the brain, it's equipped to keep things in check just like a younger brain can," said **Andrew Pieper, M.D., Ph.D., team director**.

Researchers focused on several areas, including the blood-brain barrier, a layer of cells that filters out harmful substances, maintaining the organ's health. The team's research found new ways to protect the brain's endothelial cells and clarified how important red blood cells are in transporting gasses such as nitric oxide to the brain. They also discovered new insights into the connection between traumatic brain injury and dementia.

"We're pretty excited about it," Pieper said. "People have always assumed that a traumatic brain injury starts a chronic neurodegenerative process, and there's nothing you can do. We generated

Dr. Andrew Pieper

evidence that if you can fix the blood-brain barrier and prevent this energy deficit in animals, then you can protect them from developing Alzheimer's disease." The research paves the way for the development of new medicines and therapies to optimize brain health. "The take-home message is that we don't need to be thinking of neuro-degeneration as an irreversible condition for which there's no hope – which is what a lot of people have thought for a century," Pieper said.

"The brain is a difficult organ to study, and we don't understand it as well as other organs. But as we work in an interdisciplinary way, toward this common goal, we're shedding new light on these neurodegenerative conditions with the hope that we'll be able to treat them in the not-too-distant future."

EARLY CAREER TRAINEES

The BHCI is taking a crucial step into the future by training pre- and post-doctoral scientists to be part of an innovative new generation of brain health investigators.

These early-career trainees forged key relationships with scientists and mentors inside and outside their teams as they researched new ways to prevent cognitive impairment.

"Networking is critical for them," said Stanford University team co-director **Marion Buckwalter M.D., Ph.D.** "They meet people at other institutions, get new ideas and see how scientists working together can discover big things."

Salk Institute researcher **Joseph Herdy** helped uncover new understandings of the relationship between neurons in the brain, inflammation, and neurodegeneration. He said he was energized by feedback from mentors in group meetings, which led him to conduct new experiments.

"The Initiative gave me the chance to interact with experts in fields I otherwise wouldn't have interfaced with," Herdy said. "It's these perspective-changing moments that I think is a strength of a multi-institute effort."

Herdy also acquired key skills in project management and learned the best strategies for sharing resources. "It is not easy to corral so many scientists. "Seeing what works has been helpful," he said.

Stanford University researcher **Chinyere Agbaegbu Iweka, Ph.D.**, said the Initiative inspired her to take a deep dive into how immune cell mechanisms contribute to brain aging. She singled out the mentor-mentee meetings as particularly helpful.

"Just being part of this community and receiving positive guidance has taught me the importance of collaboration and sharing data. It has exposed me to interesting new areas I can investigate."

M.D./Ph.D. candidate and University Hospitals researcher **Sarah Barker** is examining the link between traumatic brain injury and Alzheimer's Disease and testing drugs that might slow

Joseph Herdy

Dr. Chinyere Agbaegbu Iweka

Dr. Sarah Barker

dementia. She said Team Director Andrew Pieper has had " a significant impact on my training. He encourages me to think big and to try risky experiments at this early point in my career."

Barker was also inspired by investigators she met while presenting her work at the American Heart Association's International Stroke Conference. Overall, the Initiative is preparing her for a lifetime of developing new strategies to improve brain health, she said.

"I am consistently humbled by science. By collaborating with so many experts in the field, I am expanding my toolkit and learning there are many ways to approach a problem such as Alzheimer's Disease."

COLLABORATIONS

Collaboration was a key element of the American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment. The goal was to share the best methods, models, and approaches for studying healthy cognitive function.

"Scientists from the three teams partnered whenever and wherever they could," said University Hospitals Team Director **Andrew Pieper, M.D., Ph.D.** "We've had some very important collaborations, including working with the Salk team on how primates can learn to use touchscreens for particular tasks."

Additional teamwork is taking place among the three pairs of scientists who received BHCI Collaborative Grants to expand the research being done in the Brain Health Initiative. "Working together is really beneficial for coming up with novel ways of problem solving," said Salk Institute's **Jeffrey Jones, Ph.D.**, who teamed up with Stanford's **Travis Conley, Ph.D.**, to study the role of kynurenine in Alzheimer's Disease in a one-year award.

Jones' research focused on cell culture models of Alzheimer's Disease (AD) and next generation sequencing, while Conley's zeroes in on modeling AD in mice. The two labs have already identified important metabolic deficits in AD and a drug to correct them. "The award has been a much-needed resource to drive this project across the finish line," Jones said.

Salk Institute's **Courtney Glavis-Bloom, Ph.D.**, initially teamed up with Stanford's **Robert Palovics, Ph.D.**, to study the protein in the blood of marmoset monkeys to better understand the "aging clock" in primates in a two-year award. When Dr. Palovics left Stanford for another role in July 2024, **Patricia Moran Losada, Ph.D.**, replaced him on the project.

"This type of project requires deep expertise from two very disparate areas of science: behavioral neuroscience and machine learning. Having a collaborator is really the only way to effectively complete a project of this type," said Glavis-Bloom.

Stanford's **Nannan Lu, Ph.D.**, joined forces with Salk's **Lara Labarta-Bajo, Ph.D.** to explore how plasma proteins influence two types of brain cells in both healthy conditions and states of inflammation in a two-year award. The pair hopes their research can be used to develop new therapies to prevent dementia.

"This collaboration offers a unique opportunity for mutual learning, the exchange of techniques, and the potential for more efficient discovery," Lu said. "It enhances the likelihood of making novel and impactful discoveries."

Lu said the BHCI grant is part of a bigger picture in science, where collaboration across diverse labs and disciplines has become the standard, not an outlier. "By combining resources, knowledge, and perspectives, we can tackle complex scientific challenges and ultimately push the boundaries of discovery."

Dr. Ivor Benjamin added, "I think the BHCI represents an excellent example of the avantgarde thinking and approach to overcoming the silos between brain-heart interactions for the foreseeable future."


Dr. Jeffrey Jones


Dr. Courtney Glavis-Bloom


Dr. Travis Conley


Dr. Patricia Moran Losada


Dr. Nannan Lu


Dr. Lara Labarta-Bajo

CONCLUSION

Alzheimer's Disease and other causes of cognitive impairment affect more than fifty million people worldwide today. The need to better understand brain health has never been more important. In addition to the devasting human toll of neurological disease, the Alzheimer's Association has reported that the 2024 financial burden of Alzheimer's and other dementias will be approximately $360 billion.

"In 2050, the number of people who will be diagnosed with Alzheimer's Disease and age-related dementia is expected to at least triple. It is an enormous cost to society and a huge burden on families," said Salk Institute Team Director **Fred "Rusty" Gage, Ph.D.**

"The problem is so immense and so important that we need to work together to produce new understandings and new therapies in the years and decades to come. It is the only way we can have a real impact and ensure people live healthier lives as they age."

To reach that goal, funding through the American Heart Association-Allen Initiative in Brain Health and Cognitive Impairment is producing compelling new research about brain health and the causes, treatment, and prevention of age-related dementia.

Throughout the eight-year project, dozens of scientists at the Salk Institute, Stanford University and University Hospitals Cleveland Medical Center, and their partners at other institutions, are identifying mechanisms that cause dementia and discovering key strategies to maintaining brain health as people age.

"Working together, all three centers are making a lot of progress in developing treatments that will prevent Alzheimer's Disease and other causes of dementia," said Stanford University Team Co-Director **Marion Buckwalter, M.D., Ph.D.** "We're right on the cusp of making a big difference."

"The foundational work from this initiative has empowered the field to expand efforts in high-risk interdisciplinary studies that span neuroscience, vascular biology, immunology, and biochemistry," said **Kathryn Richmond, Ph.D., M.B.A.**

"To date, the teams have created new data atlases and developed innovative technologies and platforms that shed light not only on key aspects of brain health and cognitive impairment, but also address challenges in adjacent fields, ranging from COVID treatments to stroke.

"The widespread impact of this initiative is a true testament to the bold approaches taken by these frontier teams."

American Heart Association

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