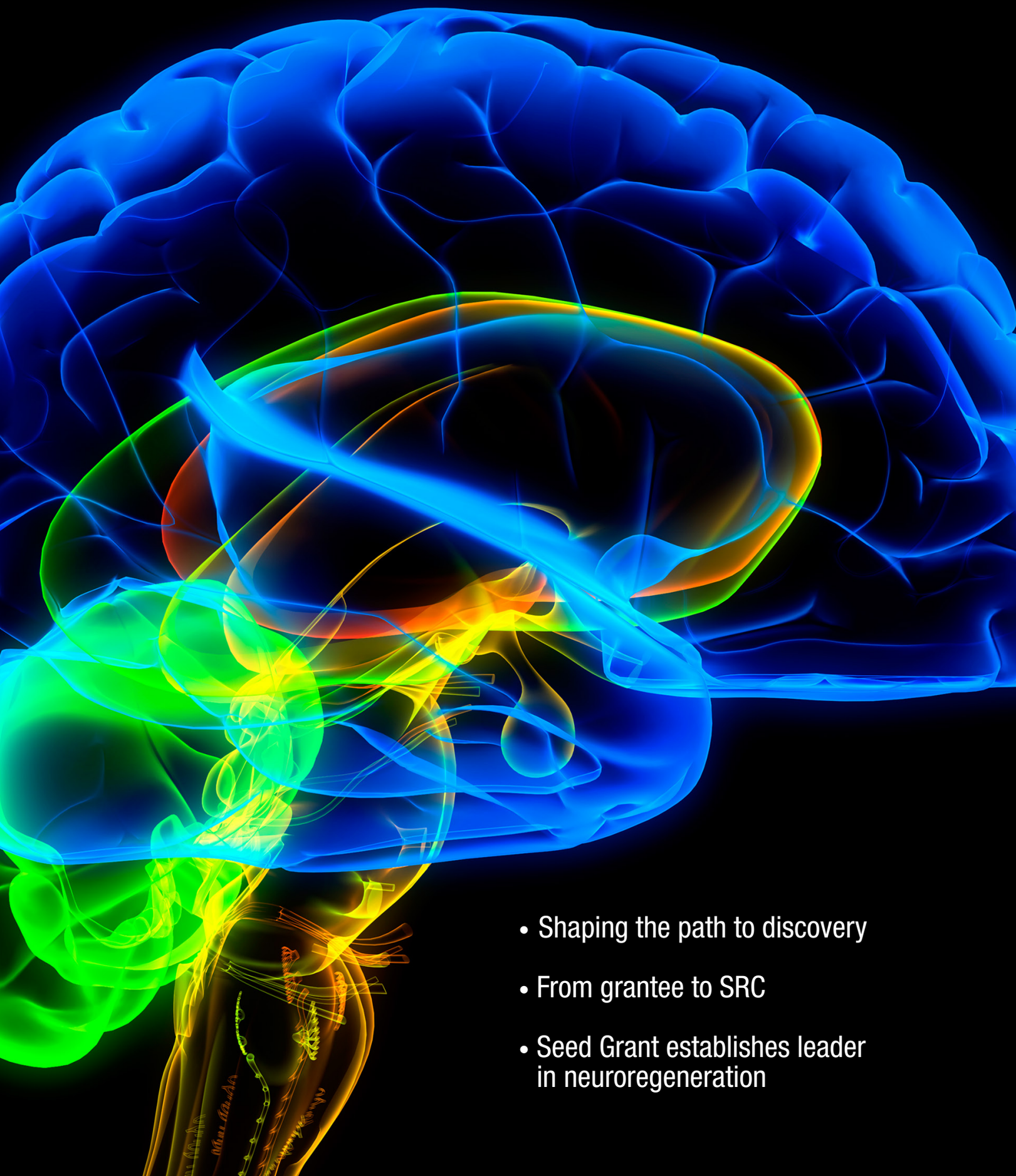
Brain Research Foundation

Spring 2020



- Shaping the path to discovery
- From grantee to SRC
- Seed Grant establishes leader in neuroregeneration

Shaping the Path to Discovery

During these unprecedented and trying times, our community, our nation and our world need to come together to fight this pandemic. We need to do our best to slow down the spread as another very important community–scientists–work tirelessly to better understand COVID-19 and develop treatments and vaccines.

While we are familiar with the respiratory symptoms of COVID-19 there is a new symptom that has emerged–loss of smell. Dr. Sandeep Datta, a neuroscientist at Harvard Medical School, studies how the brain extracts smells from the environment and converts it into behaviors. As an expert in olfaction he is now researching the possible mechanisms through which COVID-19 may lead to anosmia (partial or complete loss of smell). If a link can be established, perhaps smell tests could be given to screen for the virus much earlier and faster.

I specifically mention Dr. Datta because in January of this year he was granted a Scientific Innovations Award by this Foundation. Our Scientific Review Committee felt that Dr. Datta's proposed project, looking at sense of smell and social interactions in mice with mutations linked to autism in humans (see page 7) was truly groundbreaking. And now, just four months later, we are learning sense of smell may be affected in COVID-19.

It is particularly rewarding to see Dr. Datta's efforts being covered by the news and scientific community. Not only does it offer hope in this time of crisis, but it also reinforces BRF's mission to fund the most innovative neuroscience research that studies the entire brain and nervous system. More than ever before, the work we fund has wide-ranging and critical implications and the case for supporting science and scientific research has never been stronger.

In this issue, we feature examples of research projects we're funding that are making a difference in many areas of disease, including Alzheimer's, autism, schizophrenia and potentially even heart disease and inflammatory bowel disease. The back cover illustrates how BRF is hastening science through our Seed Grant Program which provides start-up money for innovative, daring research projects.

Without BRF's initial investment, many projects may have been hindered or perhaps never been funded at all. The BRF Seed Grant Program has contributed $13,507,930 to extraordinary research projects. With the data BRF funding has enabled our grantees to gather, most have been able to obtain significant, larger NIH grants. To date, these scientists have generated an additional **$350,035,890** to continue their impactful work.

At our Discovery Dinner last fall, we honored Dr. Rudolph Tanzi from Harvard University with the Dr. Frederic A. Gibbs Award in Scientific Achievement. Dr. Tanzi has dedicated his entire scientific career to studies aimed at preserving and promoting brain health and preventing brain disease and has played a key role in Alzheimer's research.

That evening he gave our audience a plan to promote brain health and prevent Alzheimer's disease. However, the overall message was how to keep your brain healthy. And at this time of stress and isolation, I think that this plan–called S.H.I.E.L.D.–to keep physically and mentally healthy is so topical that I wanted to share it with you. It appears at the top of the facing page.

I thank you for being part of the BRF community. You have my promise that we will continue to support research projects that succeed in opening future opportunities for research, collaboration and scientific advancement.

–Terre A. Constantine, Ph.D.
Executive Director and CEO
Brain Research Foundation

Sleep 8 Hours During deep night sleep amlyoid production is turned down and the brain cleans itself out.

Handle Stress Take 20 minutes each day to do something that relaxes you.

Interact With Others (virtually, for now) Loneliness causes stress that can lead to chemical changes in the brain that kill nerve cells.

Exercise Walking 8,000-10,000 steps a day helps grow new nerve cells.

Learn New Things This strengthens the connections between nerve cells called synapses.

Diet Nothing is better for the brain than the Mediterranean diet.

Dr. Rudolph Tanzi's S.H.I.E.L.D. plan to keep physically and mentally healthy.

From Our Young Leadership Board

Like many people, I have had loved ones suffer from brain disorders. Through my Grandfather's battle with Alzheimer's disease, I witnessed firsthand the impact that a neurological disease can have on the afflicted individual and their family. Watching a loved one struggle with a disorder for which you cannot provide sufficient treatments, or any hope of a readily available cure, is a demoralizing experience. These sentiments are what motivate me to do my part in helping to alleviate the hardships faced by individuals with neurological disorders and those who support them.

When the opportunity to become involved with the Brain Research Foundation through the Young Leadership Board (YLB) was presented, I leapt at the chance. On the YLB, I find myself surrounded by like-minded, motivated young professionals who recognize the importance of getting involved with an organization like BRF. Importantly, the BRF leaders listen to our ideas, support us, and recognize the tremendous benefits of receiving input from young professionals.

BRF's mission to advance neuroscience by funding breakthrough research is one that should resonate with everyone, especially young professionals. At our age, there is concern over the neurological health of aging parents and, as we begin starting families of our own, concern over our own health and that of our future children.

In my opinion, the scariest thing about neurological disorders is that we never know who will be afflicted with a given disorder or what the future holds for us, our friends, and our loved ones. We owe it to ourselves, our children, and our children's children to push the understanding of the human brain forward in an effort to improve the world for future generations, just as we have reaped the rewards brought on by the efforts of the generations that preceded us.

As the scientific community has successfully developed treatments and cures for a variety of conditions, I believe we will find treatments, and ultimately cures, for all of the neurological diseases for which BRF funds groundbreaking research. Nobody can be sure how many years or decades it may take to fully understand all of these neurological diseases. However, I take solace in knowing that my peers and I have done our part to join BRF in making a positive difference in the world by supporting early stage innovative neuroscience research to help treat and eventually cure diseases and conditions of the brain and nervous system in children and adults.

–Myles Kaluzna
Treasurer
Brain Research Foundation Young Leadership Board

High Impact

A BRF grant helped propel Dr. Yamuna Krishnan's work to develop a novel device that measures brain health—and more. Now she's giving back as a member of the Scientific Review Committee.

In 2016, Yamuna Krishnan, Ph.D., professor of chemistry at The University of Chicago, submitted a grant proposal to the Brain Research Foundation to support a daring idea. She wanted to build devices out of synthetic DNA that could be used to measure nitric oxide, a chemical messenger that plays key role in brain health.

At the time, scientists knew that excessive nitric oxide levels contribute to brain degeneration in diseases like Alzheimer's disease, Parkinson's disease, dementia, and stroke, but they had no way of measuring it in living cells. BRF's Scientific Review Committee (SRC) awarded Dr. Krishnan a BRF Scientific Innovations Award (SIA) to pursue the work. Dr. Krishnan recently followed up with BRF about what's happened since.

Q How did the BRF Scientific Innovations Award (SIA) help your research?

A The SIA award really allowed us to do bold work for which there was no precedent. That led to us publishing an impactful paper in *Nature Chemical Biology* in March of 2020 showing how our synthetic DNA technology is capable of measuring nitric oxide at sub-cellular resolution in living cells. The work has also led to several follow up studies.

Q How will this technology help scientists learn more about nitric oxide?

A Nitric oxide is a signaling molecule in the brain. Too much of it causes neurodegeneration and too little of cannot initiate brain cell communication and impairs normal brain function. So you can see that the amount of nitric oxide is really critical. Being able to accurately measure nitric oxide allows us to find out if it is dysregulated in many diseases and to identify ways to correct it. I can see this tool being used to study **immune disorders, heart disease, and neurobiology,** all of which involve nitric oxide levels.

Q What are the next steps for your research?

A Now that we have a tool for measuring nitric oxide, we can start thinking about whether we could get drug molecules to correct nitric oxide levels in the brain when they are either too high or too low. Our technology might also help in heart disease because an enzyme called nitric oxide synthase 2 (NOS2) is dysregulated in such diseases. We can use our tool to help find molecules or proteins that are responsible for NOS2 misbehaving and develop molecules to counteract that and treat heart disease. We are also using this technology to build a diagnostic for **inflammatory bowel disease (IBD)** where an enzyme called nitric oxide synthase 3 (NOS3) is dysregulated in IBD. By measuring nitric oxide levels we are trying to build a test that predicts when a person with IBD will have immune flares to allow more timely treatment.

A technique for measuring nitric oxide in the brain developed in Dr. Krishnan's lab will yield new insights on many neurodegenerative diseases.

Q What are the implications for brain disease?

A Nitric oxide synthases are essential for signaling in the brain. The brain also has immune cells that interact with neurons and nitric oxide generated by these immune cells is implicated in neurodegeneration. So this work has significant implications for brain health.

Q After the completion of your SIA project, you were asked to the SRC, which reviews the grant proposals submitted to BRF for funding. What is it like being on the other side of the grant application process?

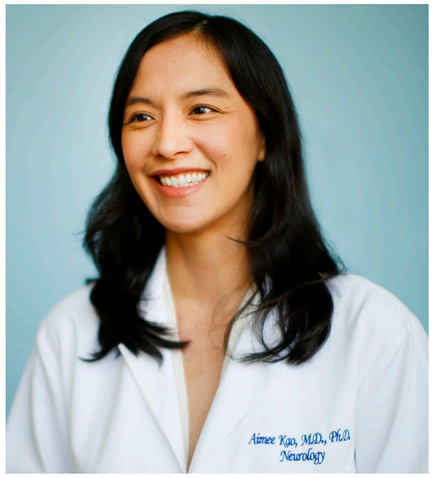
A The SRC gets such fantastic proposals. Many times I find myself shaking my head thinking 'How on earth did our project get chosen for an SIA?!' BRF is a prestigious funding organization and so naturally, very talented researchers apply. I really wish we had more money to be able support more of these projects. There are so many wonderful proposals we are not able to fund.

A new tool created by Dr. Krishnan gives scientists a window into neurodegenerative disorders, immune disorders, and even heart disease and IBD.

BRF Accelerates a Lab and Career

Dr. Aimee Kao generates human cell lines to model neurodegenerative disorders

Aimee Kao, M.D., Ph.D., was just getting her laboratory started in the Department of Neurology at the University of California, San Francisco (UCSF) when she was awarded a 2013 BRF Seed Grant. The Seed Grant helped fund an ambitious project to use induced pluripotent stem cells (iPSCs), which are adult human cells that have been genetically reprogrammed to mimic characteristics of embryonic stem cells, to study if faulty genes could be repaired to override mutations that cause an attack on neurons and brain function instead of protecting them.



"That was one of the first grants I got," said Kao, professor and leader of the UCSF Alzheimer Disease Research Center Neurodegenerative Disease Biomarker Core. It ultimately led to a collaboration with another researcher Jonathan Lin, M.D., Ph.D., associate professor in the Department of Pathology at the University of California-San Diego School of Medicine, and a 2018 publication in Human Molecular Genetics. The paper showed that mutations in the genes encoding a molecule called protein kinase RNA-like endoplasmic reticulum kinase (PERK) changed the way the protein responds to stress, increasing neuronal vulnerability which can cause neurodegeneration.

"We go through life every day managing a variety of environmental stressors like infection or bumps to the head," Dr. Kao said. "As life goes on, the effects of stress can accumulate as changes in our cells and bodies. You could see how the long-term ripple effects of these altered stress responses could ultimately lead to neurodegeneration by promoting cell death."

BRF's start-up Seed Grant investment of **$50,000** helped her grow her lab from having just one post-doctoral fellow and one research assistant to a team of ten. The data generated from the Seed Grant also gave her the confidence to apply for and win a string of five major grants, three from the National Institutes of Health, one from the Rainwater Charitable Foundation and another from the Chan Zuckerberg Initiative, totaling **over $6 million so far**.

Now, Kao's lab has shifted from a lab that predominantly studies neurodegeneration in the simple roundworm *C. elegans* to one that also devotes substantial effort to utilizing iPSCs and other cell models. **»**

"The BRF Seed Grant was crucial in establishing us as a lab that is leading the work on neuroregeneration research. Our success has been built on that foundation."

She also directs the UCSF Tau Consortium Human Fibroblast and Induced Pluripotent Stem Cell Bank that supplies other researchers studying neurodegenerative disease with human cell lines to model disease.

The lab still uses the roundworm *C. elegans* studies to generate hypotheses, do rapid genetic screens, or to observe biological processes in action. Then, they translate those insights into studies on human cells. They no longer focus on PERK, but they continue to study how cellular responses to stress contribute to neurodegeneration.

Like many in the field, Kao and her team have shifted their focus away from exclusively studying how mutations in single genes like Presenilin-1 or -2 causes an autosomal dominant Alzheimer's disease. She notes that such mutations account for a small percentage of neurodegenerative diseases. Instead, they are working to understand how "risk variants" that each confer a relatively small increased risk of disease can cumulatively alter neuronal physiology to lead to neurodegenerative diseases.

"Having one genetic risk factor doesn't increase your likelihood of getting a disease very much," Kao said. "But adding up these risk factors can help people come up with genetic risk scores. That could ultimately result in genetic biomarkers that help in stratifying people based on their overall risk of neurodegenerative disease." They are also working to understand the biological changes these genetic variations cause to lay the groundwork for the development of new types of treatments.

"Ultimately, we don't want to just stratify risk. We also want to help develop the cure," she said. "And BRF helped solidify my lab as a key player in this search."

SIA Update

BRF's 2020 Scientific Innovations Award winners investigate the basis of autism and schizophrenia

Sensory Deficits in Autism

Many people with autism have difficulties processing sensory information. Scientists don't yet understand what exactly happens in the brain to cause these deficits. Now, an ambitious study by the winner of BRF's 2020 Carl & Marilynn Thoma Foundation Scientific Innovations Award (SIA) aims to provide new insights on how autism-linked genetic mutations impair the sense of smell.

Sandeep Roberts Datta, M.D., Ph.D., associate professor in the Department of Neurobiology at Harvard University, and his team will genetically engineer mice with mutations linked to autism in humans. Then, they will use brain imaging to see how these mutations affect the brain circuits that process sensory information. Mice rely on their sense of smell to explore their environment and for social interactions. Specifically, they will zero in on how these mutations affect the sense of smell in mice, their brain activity, and their social interactions.

"The experiments are essential for understanding the deficits in social interaction in both mouse models of autism spectrum disorders and human patients."

Could an immune system-attack on the brain cause schizophrenia symptoms?

Schizophrenia affects about 20 million people worldwide, but the exact causes are not clear[1]. As a result, few treatments are available to help patients manage the delusions, hallucinations, and other symptoms of the disease. But research by one of BRF's 2020 SIA winners could shed light on one potential cause of schizophrenia symptoms and possibly lead to new treatment approaches.

Recently, scientists have discovered that encephalitis caused by the immune system attacking the brain can trigger schizophrenia-like symptoms.[2] This has led scientists to begin looking for signs of autoimmune disease in patients with schizophrenia. **Samuel J. Pleasure, M.D., Ph.D.,** professor of neurology at University of California, San Francisco, is one of them.

Dr. Pleasure and his team plan to use new techniques to look for molecules called autoantibodies that can cause the immune system to attack its own tissues. They will use these new tools to look for brain cell attacking autoantibodies in people with encephalitis who develop psychiatric symptoms, and in people with schizophrenia. They take it one step further and will also look for potential antibodies that attack viruses in these two groups to help determine if infection with a virus triggered the immune system attack.

The SIA grant will help them determine if a small subset of patients with schizophrenia have an infection or autoimmune condition causing their symptoms. If this is the case, it may enable new treatments for these patients that target the immune system attack or the viral infection that triggered it.

[1] World Health Organization. Fact Sheet on Schizophrenia. October 4, 2018.
[2] Dalmau J et al. Lancet Neurol. 2019;18(11):1045-1057.

BRAIN RESEARCH FOUNDATION
Innovate. Explore. Discover.

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$13,507,930 → **$350,035,890**

Our investment of **$13,507,930** in Seed Grants has generated **$350,035,890** in additional funding from larger institutions, such as the NIH.

For every $1 they receive from us, our grantees have gone on to secure almost $26 in future funding.

We are grateful to our Scientific Review Committee for helping us identify the most innovative and promising proposals and we thank them for their dedication to our mission.