

# Science Philanthropy Successes

## Accelerating Progress in Autism Research: The Simons Foundation Autism Research Initiative (SFARI)

*A Case Study in How to Fund Basic Science Research on Human Health Issues*

The Simons Foundation Autism Research Initiative (SFARI) seeks to improve the scientific understanding and treatment of autism spectrum disorders by funding innovative research of the highest quality and relevance.

In 2002, Jim and Marilyn Simons, co-founders of the Simons Foundation, were approached by their friend's cousin, a researcher at Columbia University, about funding an autism research center there. This was followed by a presentation at Columbia's School of Medicine, then headed by Gerald Fischbach. Their ask was \$10 million. The Simons' interest was piqued, but another friend, a distinguished scientist also at Columbia, advised them to learn more about the autism funding landscape before diving in, and they determined to follow his advice.

## The Roundtable

In early 2003, the Simons asked Rodney Nichols, former head of the New York Academy of Sciences and a friend of Jim's, to organize a 'roundtable' of distinguished scientists, both in and outside of the field of autism, that they could attend. Nichols asked Paul Greengard, a Nobel Prize-winning neuroscientist at The Rockefeller University, to chair the meeting and help recruit the participants. An excellent group was assembled, including Thomas Insel, then head of the National Institute of Mental Health (NIMH).

*Thus, genetics would be a fertile area for research.*

At that daylong meeting, some answers were distilled. The Simons came away from the meeting with two realizations: 1) Given that concordance for autism was approximately 90 percent for identical twins and far less for fraternal twins and for regular siblings, the condition was highly genetic. In fact, the first gene, a mutation in which leads to autism, had just been discovered by the French scientist Thomas Bourgeron. Thus, genetics would be a fertile area for research. 2) With a few exceptions, autism was not yet attracting the attention of the strongest investigators, so drawing excellent researchers into the area should be a priority.

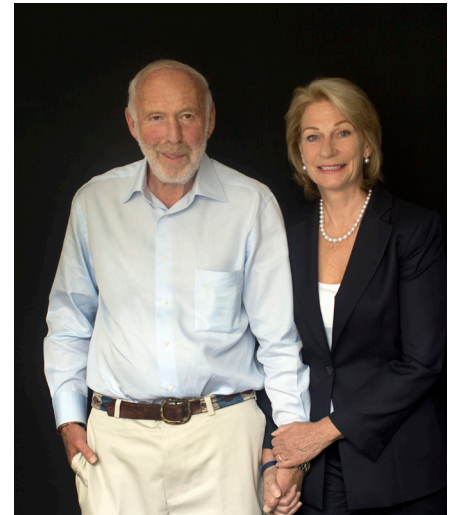
## Early Grants

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At Insel's suggestion, the Simons Foundation asked the Icelandic organization deCODE, renowned for finding genes, to submit a grant proposal. Greengard and his associate Nathaniel Heintz also proposed a grant. The Simons immediately funded the Greengard proposal without outside review, but when the deCODE proposal came in, Jim asked Michael Wigler, a friend and outstanding geneticist at Cold Spring Harbor Laboratory in New York, to review it. Surprisingly, Wigler exclaimed that autism was an area he himself wished to enter, and instead of reviewing the deCODE proposal asked to submit one himself. Jim was fine with this and asked someone else to review the deCODE proposal, which was funded.

Wigler's ensuing proposal was also funded and would turn out to be of great consequence to the SFARI program. Wigler studied copy number variations (CNVs), sites in the genome where there are too few or too many copies of a given gene or set of genes. CNVs are sometimes inherited and sometimes arise de novo in the affected offspring — i.e., the CNV is not present in the genome of either parent. He showed that people with autism have far more de novo CNVs than would be expected in neurotypical individuals. This was a striking result and suggested it would be productive to search for other types of de novo mutations in individuals on the autism spectrum — in families without a history of autism susceptibility (see Simons Simplex Collection below).

The Simons then visited the Massachusetts Institute of Technology, where Jim was on the board, and met a number of leading neuroscientists. This led to several more grants. They also visited the Yale Child Study Center and made a few grants there, most notably to Ami Klin for his early work on eye tracking in infants for the purpose of diagnosing autism early: work that he has pursued with meaningful success. A third grant was made to Christopher Walsh at Harvard Medical School jointly with the Nancy Lurie Marks Family Foundation. Walsh's work was excellent, and the Simons Foundation has continued to support him over the years.



Jim and Marilyn Simons

*Image Credit: Bea de Gea*

## The Think Tank

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A year and a half after the roundtable, the Simons needed to learn even more about the science of autism. Marilyn and her friend Laura Slatkin, who ran the New York Center for Autism (now called the NYC Autism Charter School), arranged a two-day meeting of distinguished scientists, including some autism researchers, but primarily comprising neuroscientists. Fischbach agreed to select the participants and chair the meeting. Roughly 30 scientists attended, and several other autism groups plus the NIMH sent representatives and in some cases provided financial support. Many of the scientists gave talks, and all attendees participated in spirited discussions. Jim and Marilyn had indeed learned more of the science, but felt they did not yet know how to properly run a grantmaking program.

## The Creation of SFARI

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It was becoming clear to Jim and Marilyn that their autism research program needed an experienced leader: an outstanding scientist who understood the grantmaking process and had good taste in whom to support. Jim formed a search committee for this position. Paul Nurse, then-president of Rockefeller University, agreed to serve, as did Harold Varmus, former head of the National Institutes of Health. Wanting a third search committee member, Jim thought of Fischbach, who had just stepped down from his leadership role at Columbia. Jim met Fischbach over lunch to discuss the search committee and to urge him to join. However, during the discussion, Fischbach waxed increasingly enthusiastic about the foundation's autism program, and Jim finally asked him if he was interested in the position himself. He said yes. When Jim presented this option to Nurse and Varmus they affirmed that Fischbach would be great for the role.

Fischbach joined the foundation in 2006. He was quickly joined by other scientific staff: Marta Benedetti, scientific manager for the Michael J. Fox Foundation for Parkinson's Research and consultant for the Multiple Myeloma Research Foundation; neuroscientist John Spiro, a senior editor at Nature; and geneticist Alan Packer, an editor at Nature Genetics. He also brought in Marion Greenup, a first-class administrator whom he knew at Columbia, to head grants administration.

*The SFARI team helped raise the quality of talent in the field of autism.*

As a first order of business, Fischbach and his new team developed the infrastructure for effective grantmaking, adding a needed level of structure and scientific judgment. They helped initiate a process for open applications and insisted on two criteria for evaluating grant proposals: 1) relevance to autism and 2) excellence of the scientist and the proposed science. Also at this time, Fischbach began to develop an advisory board to oversee the SFARI program and a review committee for evaluating grants.

Although the autism program was now on solid ground operationally, Jim continued in his direct involvement in SFARI's work. Marilyn, as president of the foundation, interacted daily with SFARI administrative staff, but Jim, a scientist himself, was closely integrated into the scientific decisions and worked closely with Fischbach. Although SFARI is now a large and well-developed program, Jim and, more recently, Marilyn still track SFARI funding decisions and progress at regular meetings with the scientific staff.

Importantly, the SFARI team helped raise the quality of talent in the field of autism. "Our goal was to move the entire field of research forward, and in particular develop a better understanding of the genetics and downstream molecular mechanisms," Marilyn says. SFARI invested significant time calling and meeting with the best scientists working in brain science and encouraged them to apply for grants. Because of Fischbach's reputation and background in neuroscience, scientists knew they would be judged fairly in their proposals. And as the proposals' scientific rigor went up "several notches," according to Fischbach, so did awareness of the Simons Foundation.

"Throughout the process, Jim and Marilyn were tremendous supporters and inspirational," Fischbach says. "And Jim was so instrumental to our startup and early years. His instincts and taste are right on the money. Jim came to our science meetings, offered opinions and became a colleague. The Simons don't just give money and disappear."

## The Simons Simplex Collection

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Early in Fischbach's tenure it became clear that, to make progress, SFARI would need to develop a large cohort of individuals with autism and their families; all family members would be genotyped and the individuals with autism thoroughly phenotyped as well. Wigler suggested that the cohort consist of families having exactly one child with autism and at least one typical sibling. He believed that was the best way to find de novo mutations. The team agreed and decided to aim for a cohort of 3,000 families. Much work went into the planning to create and maintain this cohort and its biological samples: Exactly what measurements would be used in the phenotyping? Where would blood samples be stored, what fraction would be used to create DNA, and where would it be extracted? Who would be eligible to receive samples? Where would collection centers be located, and what criteria should be used in establishing such centers? It took about 18 months to settle all these issues, and the Simons Simplex Collection (SSC) was launched in 2008.

*Today, more than 200 projects and researchers use SSC resources each year, and SSC data have been used in a multitude of published papers. To date, there are nearly 450 projects that have used SSC data.*

The resulting database and biological samples were made freely accessible to all qualified researchers, freeing them from the time-intensive and expensive process of finding their own genetic specimens or participants. Today, more than 200 projects and researchers use SSC resources each year, and SSC data have been used in a multitude of published papers. To date, there are nearly 450 projects that have used SSC data.

“When we began the SSC, scientists had only one gene identified as related to autism,” Fischbach says. “The hope was that the SSC would lead us first to the genes, then, ultimately, to a better

understanding of the biology. Today, through the work done using the SSC and other smaller collections, there are about 100 genes that we can say with a high degree of certainty play a role in the condition.” And thanks to these early insights into the genetics of autism, efforts to understand the downstream biology are now vigorously underway.

## Measuring Outcomes

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As the program evolved, the SFARI team also developed ways to monitor and support the research they fund. The SFARI science team keeps track of a grant's progress and then gives feedback to the scientists. “For a particular project, a member of the science team reads the written progress report, judges it as meritorious or not, presents that to the rest of the science team and gets a report from the grant office on how the money was spent or not spent,” Fischbach says. “Did they do what they said they'd do? Did they hire the people they said they'd hire? Did they buy the equipment they said they'd buy?”

SFARI increased the size of grants when necessary, but Fischbach says the foundation was also aware of the danger of giving people too much money. “We initially gave people up to \$500,000 a year,” he says, but “eventually, the biggest grant was about \$250,000 because we found that recipients often couldn't wisely use the \$500,000.” Today, SFARI awards still hover in that range, but now that the field has some years under its belt, SFARI also grants up to \$325,000 per year for three years for “compelling, high-impact research on an experimental hypothesis for which preliminary data have already been gathered.”

*There is value even in 'failed' research, which allows scientists to then turn to other ideas.*

One important measure of success is whether SFARI scientists publish results in respected journals — and that is often the case — but Fischbach points out that success is never guaranteed. “It’s a disappointment when projects don’t pan out. For example, if the results are not as predicted or if research does not create significant new knowledge,” he says. “But there is value even in ‘failed’ research, which allows scientists to then turn to other ideas. And it’s important that we give people enough freedom to explore.”

Another way to monitor program efficacy is by creating a scientific advisory board. Formation of external boards as a programmatic checkpoint provides additional reassurance to applicants and to government groups that foundation money is being spent responsibly in pursuit of its stated mission. The SFARI board, created in 2007, meets twice a year and is comprised of top scientists — but not current grantees — in various disciplines related to autism. Such boards are convened to give unbiased advice and opinions about programmatic direction and decisions. SFARI’s advisory board comprises researchers in neuroscience, genetics, cell biology, developmental biology, molecular biophysics, autism, psychiatry and pharmaceutical development. It provides counsel regarding SFARI’s four major funding areas: gene discovery, molecular mechanisms, cognitive science and translational efforts to accelerate therapeutic discovery.

## Keeping the Momentum Going

Since 2009, SFARI has held annual meetings for its grantees, inviting scientists to present their recent work. The meetings last a day and a half, providing ample time for important mingling and discussion. These meetings have become increasingly exciting as the field has progressed.

The foundation also continues to seek advice from the community through periodic small workshops, Fischbach says. “For example, we’ll say, ‘We’re considering funding stem cell research. We’d like you to come to the foundation with these five other people and present your ideas on what the pros and cons are of doing so.’ We consider their ideas and decide whether to act or not. It’s amazing how willing people are to come and contribute their ideas and help.”

From the beginning, SFARI established resources beyond the SSC to assist the investigators studying autism. Soon after the launch of its website, SFARI.org, the SFARI team determined that the platform would not just be a programmatic site with information on how to apply for funding but also a hub where scientists could go to read about the latest developments in autism research. The recruitment of journalist Apoorva Mandavilli launched the news arm of SFARI.org, which turned out to be so successful that it later branched off to become the independent news site, Spectrum. Spectrumnews.org is now the ‘go-to’ website for autism research news. And it should be noted that, although funded by the foundation, the publication is editorially independent of SFARI, with its own advisory board.

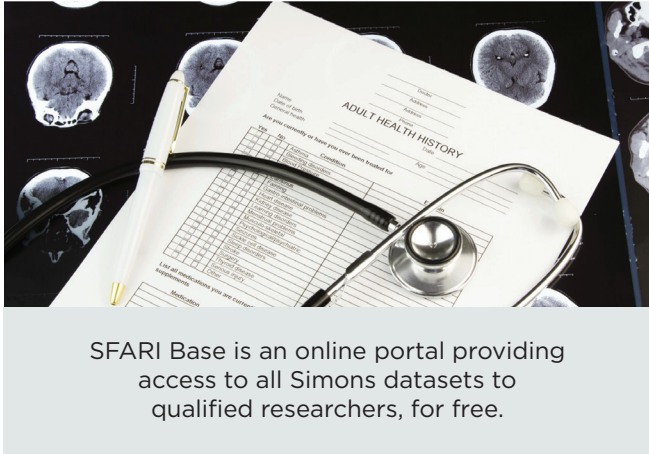


SFARI’s 13th science meeting in April, 2018 brought together over 150 SFARI investigators, collaborators, with foundation staff.

*Image Credit: Simons Foundation*

Other web-based resources SFARI created to help scientists are SFARI Gene, SFARI Base and programs for making available animal models of autism for experimentation. SFARI Gene is an online database that lists all genes that have been implicated in the literature as related to autism, provides links to all research papers on those genes and ranks the strength of evidence supporting that gene as an autism gene. SFARI Base is an online portal providing access — initially just to the SSC data, but now to all Simons datasets — to qualified researchers, free of charge.

SFARI Base



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In 2013, Fischbach stepped down from SFARI to launch a large foundation-funded neuroscience research collaboration, the Simons Collaboration on the Global Brain. Jim organized a search committee, headed by renowned neurobiologist Cori Bargmann, to identify Fischbach's successor. The choice was Louis Reichardt, then director of the graduate neuroscience program at the University of California, San Francisco and one of the founding editors of *Neuron*. Arriving in mid-2013, Reichardt's first objective was to build on the solid base already laid by Fischbach and the team.

Reichardt and the SFARI team launched a new strategic plan, identifying several areas where federal and philanthropic funding were inadequate to facilitate rapid progress, and set about to tactically address them.

The SPARK (Simons Partnership for Autism Research and Knowledge) program, driven by the insight of SFARI's director of clinical research, geneticist Wendy Chung, is a prime example of what emerged from the plan. SPARK's goal is to recruit 50,000 people with autism — and their families — to not only give genetic samples and phenotypic information, but to remain accessible for future studies, including for any upcoming drug trials. Autism is so heterogeneous a condition that no single drug could possibly be effective for all individuals, but could be effective for different slices of the autistic population. The SPARK collection will be big enough that such slices can have meaningful numbers of participants. When complete, SPARK will be the largest autism cohort ever created, and its data are freely available to qualified researchers.

A second example of tactical planning, aimed at expanding the autism research community, is the Bridge to Independence program. This award provides \$495,000 over three years in lab funding to talented young researchers who wish to work on autism. Armed with such a grant, the recipients are more likely to secure tenure-track positions at good universities, thus increasing the number of strong people in the autism field.

Other plans are underway to drive progress, including working to identify autism biomarkers, stem cell studies, and planning for trials in Canada and Europe of a drug that may help a particular subset of autistic people.

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SFARI is thriving under Reichardt's leadership; today it funds more than 250 investigators in the United States and abroad and spends \$75 million per year on grants and program costs.

## A Model for Progress

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In Fischbach's eyes, it was a combination of factors that made SFARI into the multifaceted program it has become. The field of autism research was ready for a boost of quality and good science, and SFARI was launched at the right time, he says. SFARI developed an expert staff, available and accessible to scientists as a source of information and guidance, and these capable people reinforced the foundation's credibility as a leading strategic funder in the field.

*“When we began the SSC, scientists had only one gene identified as related to autism...Today there are about 100 genes that we can say with a high degree of certainty play a role in the condition.”*

*- Gerald D. Fischbach, Distinguished Scientist and Fellow, Simons Foundation*

“It was a combination of leadership, good scientific judgment and getting the science right,” he says. “And I say this over and over again: You cannot overstate the importance of Jim and Marilyn Simons' leadership. Their visible passion for the science inspired the team to deliver the best.”

SFARI ultimately became their model program as the Simons began to professionalize their giving for their other investments in math and basic science. The foundation hired top scientists as directors for each of its grantmaking areas, with Jim overseeing these programs and Marilyn continuing to oversee the business and administrative activities of the foundation.

“The decisions made for the SFARI program in the early 2000s were the ones that really shaped the whole Simons Foundation,” Marilyn says.



For additional reading, visit [sfari.org](http://sfari.org).

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