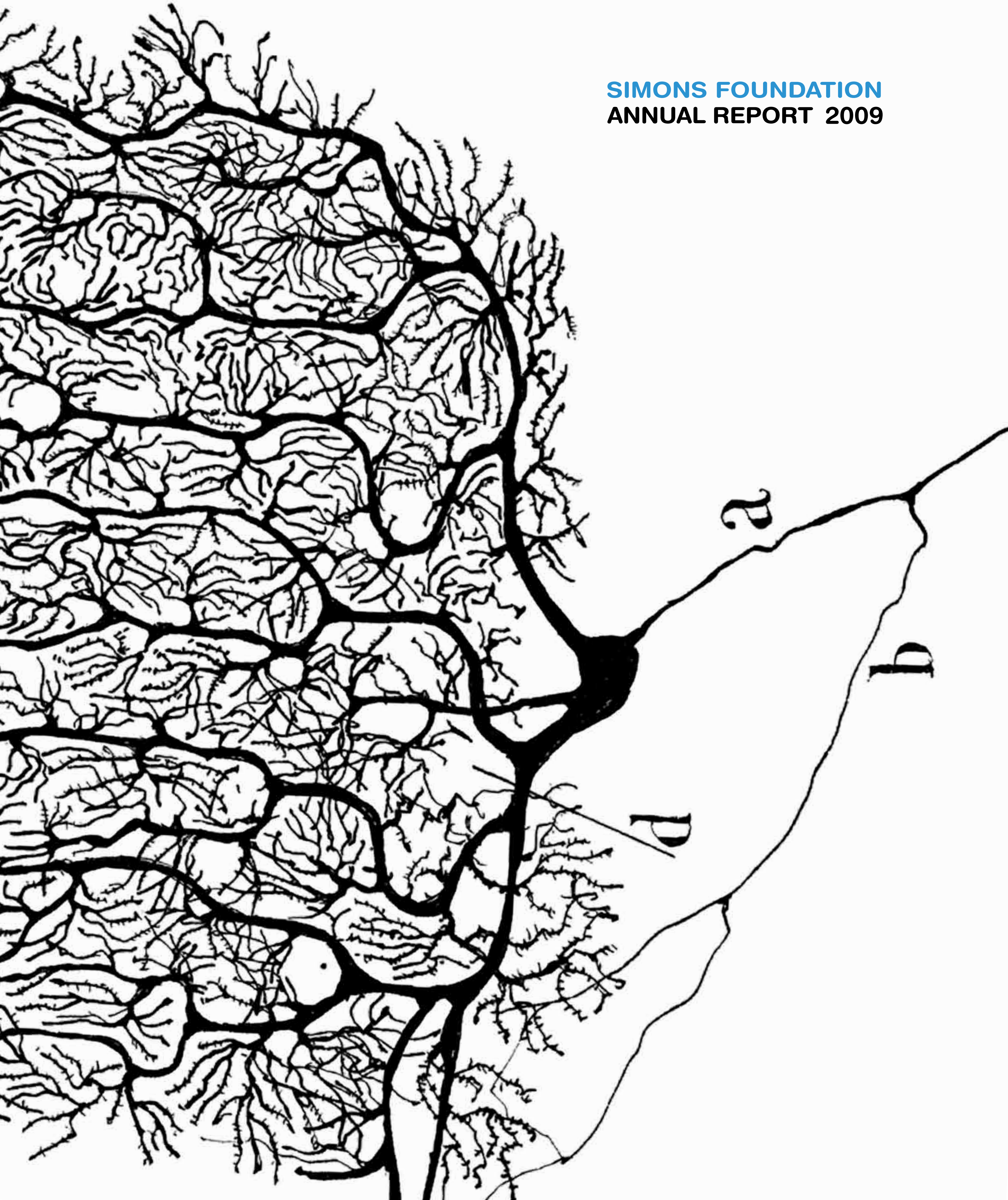
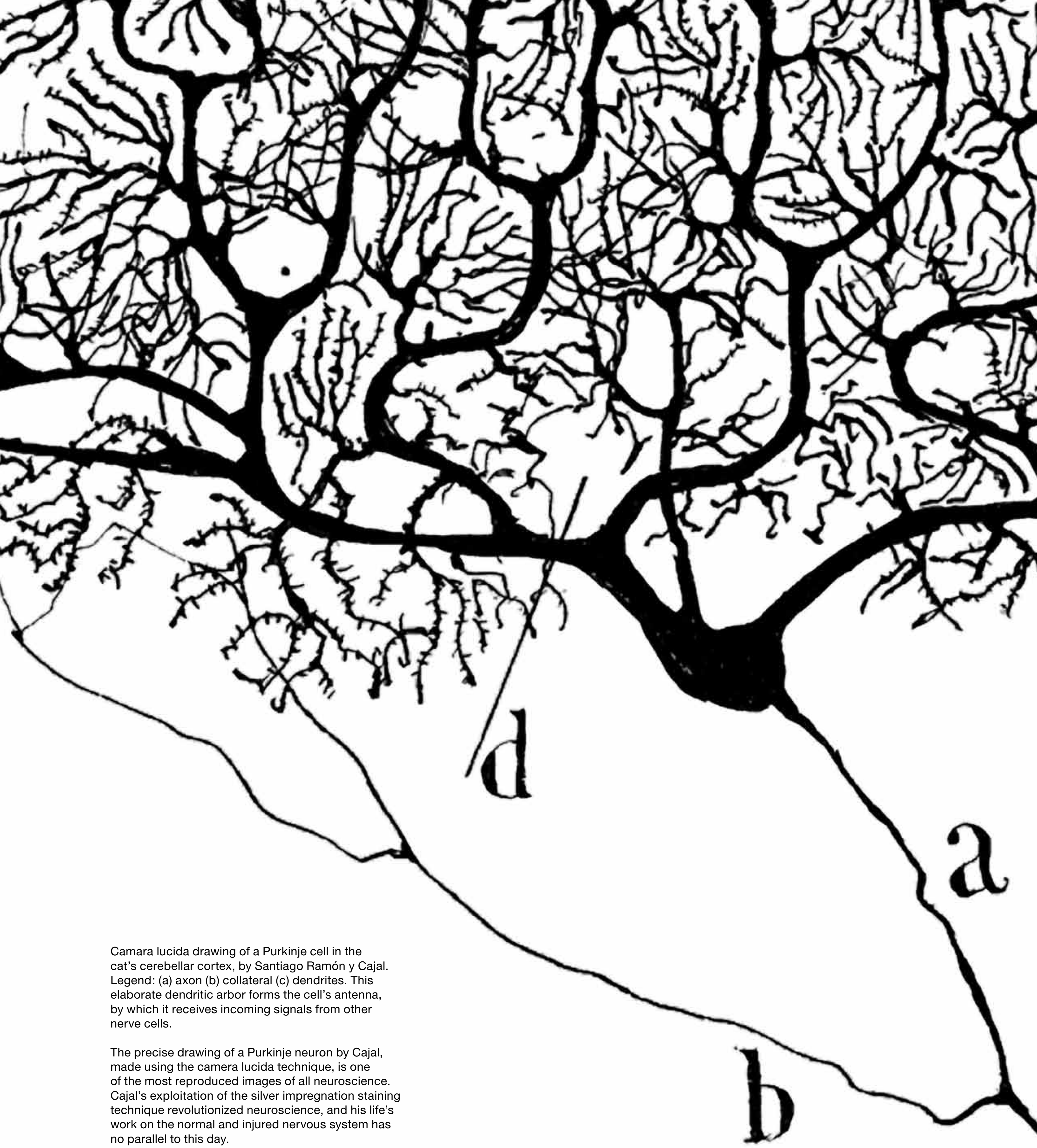
SIMONS FOUNDATION
ANNUAL REPORT 2009





Camara lucida drawing of a Purkinje cell in the cat's cerebellar cortex, by Santiago Ramón y Cajal. Legend: (a) axon (b) collateral (c) dendrites. This elaborate dendritic arbor forms the cell's antenna, by which it receives incoming signals from other nerve cells.

The precise drawing of a Purkinje neuron by Cajal, made using the camera lucida technique, is one of the most reproduced images of all neuroscience. Cajal's exploitation of the silver impregnation staining technique revolutionized neuroscience, and his life's work on the normal and injured nervous system has no parallel to this day.

The Simons Foundation extends its deepest gratitude to the granddaughter of Santiago Ramón y Cajal, Mª Angeles Ramón y Cajal, who holds the copyright to the Cajal imagery featured in this Annual Report. The Foundation also thanks Dr. Ricardo Murillo and Dr. Javier DeFelipe of the Cajal Institute in Madrid for their assistance.

Contents

Letter from the President

The mission of the Simons Foundation is to advance the frontiers of research in the basic sciences and mathematics.

FY 2009 was marked by three noteworthy events, each one of them underscoring the foundation's mission of supporting outstanding research in mathematics and basic science:

- An MIT conference in honor of our good friend and Jim's mentor, Isadore Singer.
- A groundbreaking ceremony for the Simons Center for Geometry and Physics.
- The first annual meeting of our Simons Foundation Autism Research Initiative (SFARI) researchers.

The Foundation's commitment to pure math has its roots, of course, in Jim's work as a mathematician. As an undergrad at MIT, Jim studied with several great mathematicians, among them Abel prizewinner Isadore Singer. From college mentor to lifelong friend, Is has played an important role in Jim's life, as well as those of hundreds of other students and colleagues. This past May, MIT and Harvard jointly hosted a conference to celebrate Is's 85th birthday. The Foundation was pleased to support this conference, which brought together many of the world's exceptional theoreticians, who pondered abstract questions by day and enjoyed a bit of revelry by night.

Coincidentally, in the same week as Is's birthday celebration, we held the groundbreaking ceremony for the Simons Center for Geometry and Physics (SCGP) at SUNY Stony Brook. Under a rented tent, in a parking lot adjacent to a stretch of dirt surrounding the Mathematics building, a small group of University personnel, academic researchers and Foundation staff members marked the occasion with speeches, architectural renderings, and champagne. The newly constructed center will bring mathematicians and physicists together to collaborate at the interface of the geometric side of mathematics and theoretical high-energy physics. Though the ceremony itself was simple and traditional, the aspirations represented by this venture are imaginative and far-reaching.

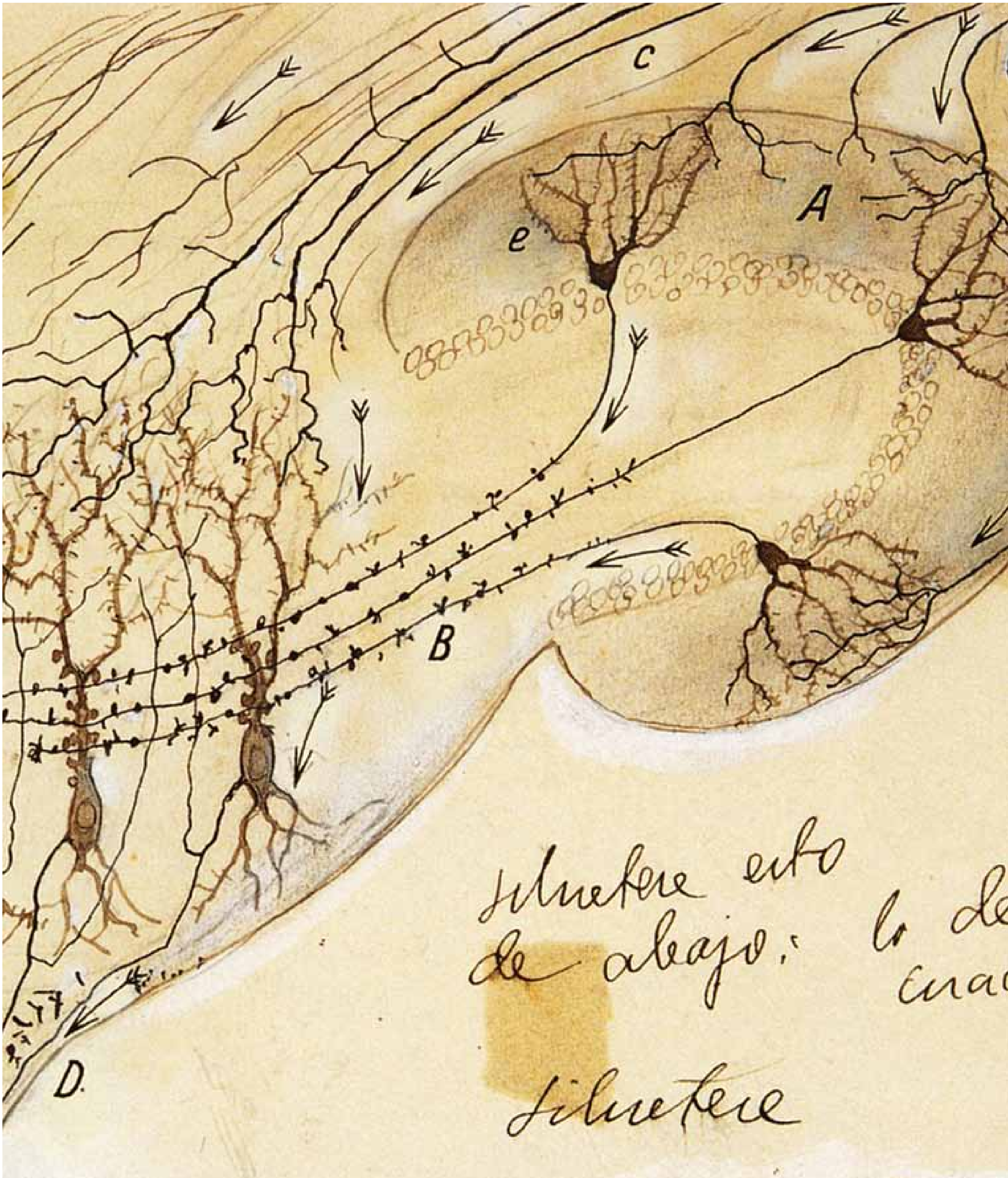
More than a thousand miles away, New Orleans was the venue for the Foundation's first annual meeting of SFARI Investigators. Hoping to do our part to provide a little post-Katrina stimulus, we invited over 100 scientists who received grants under our autism research initiative to meet in the French Quarter, March 31 - April 2. For two and a half days, these scientists shared their knowledge, questions, and insights about autism. Gene discovery, molecular mechanisms, neural circuits, cognition, and behavior were explored in depth, making the conference an inspiring highlight of the year.

We at the Simons Foundation are pleased to be able to contribute to advancing innovative research in pure math and science. Hopefully, these examples have conveyed the deep personal joy and excitement we experience in supporting the outstanding scholarship and creativity of so many remarkable researchers.

I hope you enjoy reading about the Simons Foundation's work over the past year in the pages that follow.

Sincerely,

Marilyn Simons
President
Simons Foundation


C
A
e
B
D.
de abajo:

Progress through Math and Science

Santiago Ramón y Cajal, 1933.
Diagram of the connections of the hippocampus.
From the collection of original drawings housed in the Cajal Museum (Cajal Institute, CSIC, Madrid).

Quantitative Biology

On the leafy campus outside Paris of the Institut des Hautes Études Scientifiques, there are no test tubes in sight, although researchers are working on new ways to treat heart failure.

Institute des Hautes Études Scientifiques Conference Center

On the leafy campus outside Paris of the Institut des Hautes Études Scientifiques (IHES), there are no test tubes in sight, although researchers are working on new ways to treat heart failure. The only sign that research is in progress are equations scrawled on blackboards. Instead of laboratory tests, IHES researchers are using mathematics to come up with better ways to model the geometry of the heart.

The research at IHES is an example of the growing field of quantitative biology, which deals with the relationships and interactions between various parts of a biological system. Also referred to as systems biology, the field bridges high-throughput data analysis, mathematics, and computational biology. Quantitative biology owes its existence to recent advances in areas such as genomics and imaging, which have generated vast amounts of information.

For the researchers at IHES, analyzing the huge trove of data on previous experiments on heart failure was their first priority. IHES researcher Robert Young developed software to evaluate experimental data on heart failure treatments and found inconsistencies, thus suggesting a new treatment protocol. Support of Young's work is part of the 12-year history of the Simons Foundation's contributions to IHES. Along with colleague Andrei Panfilov of the University of Utrecht, Young is using a mathematical technique called the Riemannian metric approach to model the geometry of the heart. Young and Panfilov hope their work could lead to improvements in cardiac resynchronization therapy, which relies on tiny electric shocks to correct an arrhythmia often found in patients with heart failure.

"The heart contracts because of electrical signals that go from cell to cell," Young said. "We are studying a way to measure distances in the heart. Distance can be defined as the time it takes a signal from one point to the other, and we are using the Riemannian metric to study these intervals."

At a biological level even more fundamental than the heart, members of the Mathematical Science Research Institute (MSRI) in Berkeley, CA, are using mathematics to understand organisms in terms of their full DNA sequences. With support from the Simons Foundation, MSRI held a workshop on mathematical genomics, where researchers discussed new approaches to genomic profiling; studies of human disease, particularly cancer and autism; genomic analysis; and model organisms. Lectures covered new technologies for sequencing, human polymorphisms that predispose to autism, the Cancer Genome Atlas, Markov processes and their application to understanding copy-number variation in malignant cells, and applications of combinatorics and pattern recognition to genetic problems.

If mathematics may help scientists understand the genome, researchers at The Rockefeller University in New York City are wielding the tools of physics to explore cellular mechanisms and other topics in biology. Rockefeller's Center for Studies in Physics and Biology, supported by the Simons Foundation, works to understand how physical laws govern the operation of the biochemical machinery and the processing of information inside cells. Researchers study both the basic physical properties of biological systems and the application of physical techniques to the modeling of neural, genetic and metabolic networks. Current research projects at the Center range from bioinformatics to molecular biophysics to neuroscience.

The diverse nature of systems biology draws researchers from many areas. The Simons Center for Systems Biology in the School of Natural Sciences at the Institute for Advanced Study in Princeton, New Jersey, seeks scientists with little or no formal training in biology who are able to apply novel ideas to key areas of biological research.

"When you have such a large body of information, you need new approaches to form a coherent hypothesis," said Arnold Levine, head of the Simons Center. "For example, we are investigating a heritable single-nucleotide polymorphism in a protein called MDM2, which may play a critical role in the formation and growth of cancers. We start with large data sets of information and then look for statistical associations using the tools of systems biology."

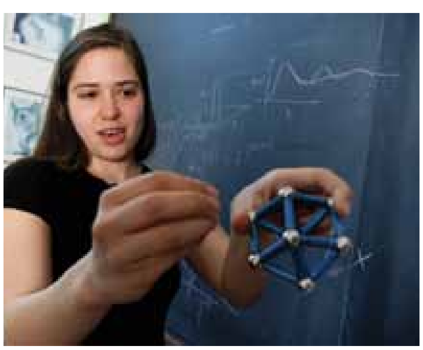
Simons Center scientists explore and mine large data sets of genomes of organisms, expression patterns of genes in normal and pathological conditions, the genetic diversity found in species, and clinical and molecular correlations. Current research includes a project to uncover genetic variations affecting cancer risks and responses to cancer treatment by using statistical methods and data from large-scale anti-tumor cancer drug screens.

With so many disciplines working together, the techniques of quantitative biology are expected to yield results in many fields. At Cold Spring Harbor Laboratory (CSHL), in Long Island, New York, the newly established Center for Quantitative Biology is expected to increase the power of research performed throughout the laboratory. The Center draws on experts in areas including applied mathematics, computer science, theoretical physics, and engineering. These experts interact closely with other CSHL researchers and will apply their approaches to research areas including genomic analysis, population genetics, neurobiology, evolutionary biology, and signal and image processing.

The CSHL Center has its roots in the work of Dr. Michael Wigler, whose lab at CSHL has developed mathematical and statistical methods for comparative genome analysis. These analyses have provided important new insights into cancer and complex human genetic diseases such as autism and schizophrenia.

"The Center is not only about making new tools to facilitate biological research," Wigler said. "It's also a means of drawing together under one roof some of the world's most gifted mathematical minds, who will apply their insights in powerful ways that will change how we think about data itself."

"Ultimately, the work of systems biologists may help answer profound questions," said Levine. "We want to know what is the neurological basis of consciousness," he added. "How does the brain function to store and retrieve memory? How do organisms survive and evolve with the immune system? I'm hopeful that by using the tools of systems biology, we will be able to address some of these very broad issues in the years ahead."



Dr. Natalie Arkus, Fellow
Center for Studies in Physics and Biology
The Rockefeller University

Participants in the Institute for Advanced Study biology seminar.

Math for America

Math for America has more than 300 Fellows and Master Teachers in several cities.

Math for America (MƒA) works to improve mathematics education in US public secondary schools and serve as a model in mathematics education. Founded in 2004, the program recruits, trains and retains outstanding mathematics teachers for the nation's public schools.

Currently, MƒA has more than 300 Fellows and Master Teachers in several cities, including New York City, Boston, Los Angeles, San Diego and Washington, DC. In the New York program, exceptional secondary school mathematics teachers already working in public schools are recruited into the four-year Master Teacher program. These teachers receive annual stipends and support for professional development and leadership opportunities. For mathematically knowledgeable and talented candidates who are new to teaching, MƒA offers a five-year Fellowship. After a demanding selection process, Fellows spend a year earning a master's degree in mathematics education with a partner college or university. Fellows then teach for four years in a public secondary school. The fellowship includes a full-tuition scholarship with generous stipends over five years to supplement their teacher's salary. The program includes mentoring, leadership opportunities and professional development services.

This year, MƒA added more than 100 new participants, the largest such increase in the organization's six-year history. Because MƒA's mission is not only to recruit great teachers but to retain them in teaching, it will pilot a new four-year MƒA Early Career Fellowship in New York. The new program provides stipends and professional support for teachers at a pivotal early point in their careers. MƒA now reaches teachers at every stage of their careers.

MƒA Fellows Frantz Nazaire and Julie Fetzner (right) interacting with students at "Mathematics and Bridges with the Salvadori Center," a professional development event hosted by MƒA.

John Ewing

Q & A with the President
of Math for America

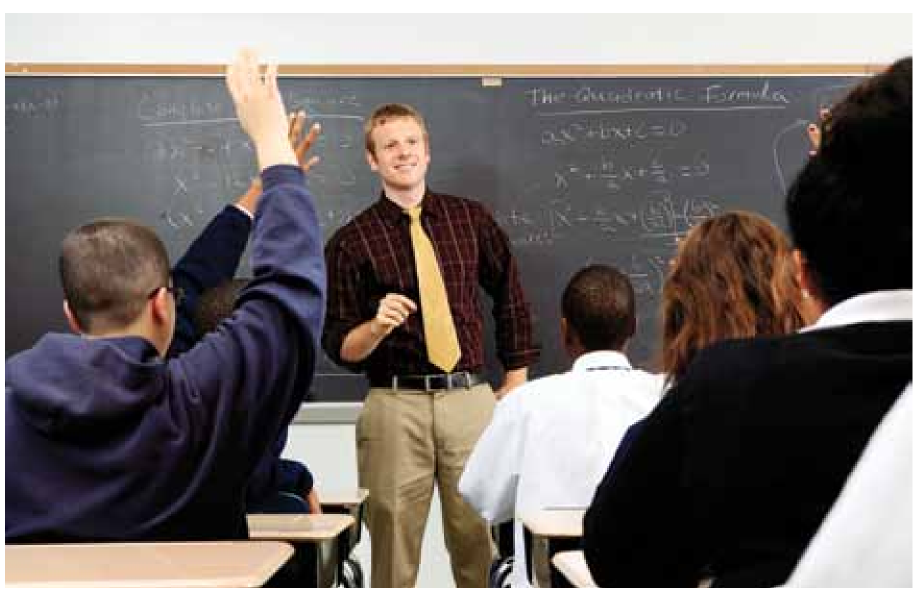
What makes a great math teacher?
You need to find people who are inspiring. Of course, mathematics teachers should know mathematics, and naturally they should know how to teach, but we are looking for much more than merely competent teachers – we want people who love mathematics and who will convey that love to their students. We are looking for the kind of teachers students remember for the rest of their lives. We are increasingly selective about the people we bring into the program, and we will become even more so in the next few years.

What is MƒA's ultimate goal?
The mission of MƒA is complex. We want great teachers because we want great students, but we don't want those students to be carbon copies of research mathematicians. While part of the goal is to launch students into careers as scientists or engineers who use mathematics, we also hope that those great students will go on to become lawyers or historians who know enough mathematics to function effectively in their professions. And as an organization, our goal is more than merely creating MƒA sites around the country. We want to show by example that by concentrating on the best teachers, we can change education in this country.

Our educational leaders have made an enormous effort to rehabilitate or remove the bottom 10 or 20 percent of teachers. But if we spend all our time on the worst teachers, and no time on the best, we will never dramatically improve education. MƒA is all about focusing on the top tier of teachers – to expand their numbers and to keep them in the classroom for generations of students.

How do you measure success?
We know we succeed when students succeed. Today, unfortunately, people often evaluate student achievement only by looking at annual test scores. They claim that test scores are objective, and this sounds like an attractive idea. But using only test scores to measure achievement is incredibly short-sighted. A test is a small sample of the many things a student learns, and it's incomplete. Great teachers prepare students to learn for a lifetime – they engage students, they inspire them, and they leave a legacy for learning that lasts far beyond a simple test at the end of the year. We have to find ways to measure that kind of great teaching, and then we can tell when we are successful.

MƒA Fellow Zach Korzyk teaching a math lesson to his students at Manhattan Village Academy.



Massachusetts Institute of Technology

With a long tradition of outstanding research, the Department of Mathematics occupies a core intellectual position at MIT.

With a long tradition of outstanding research, the Department of Mathematics occupies a core intellectual position at MIT. Among the illustrious former faculty are Norbert Wiener, known as the founder of cybernetics, and Claude Shannon, who helped develop information theory at Bell Telephone Laboratories. The many awards recently received by department faculty include the Abel Prize, two Veblen Prizes,the National Medal of Science, and two MacArthur Fellowships.

Mathematics was not always seen as a subject worthy of its own department at MIT. In the early years of the Institute, the teaching of mathematics courses was seen as a "service subject" for engineers. Finally, in 1933, mathematics was created as a separate department.

"As MIT became a major center for science and engineering research, the math department grew in stature," said Michael Sipser, who currently leads the department of about 50 faculty members and 110 graduate students. "There was a conscious decision to put resources into the math department, and extraordinary people were hired. These included Norman Levinson, winner of the Bôcher Prize, who in his later years made remarkable progress toward solving the famed Riemann Hypothesis, and Isadore Singer, co-author of the celebrated Atiyah-Singer Index Theorem, who recently won the Abel Prize."

In addition to its excellence in research, MIT trains some of the brightest undergraduates in the country. One measure of the mathematics department's success in this is in the number of its students that place in the top of the annual William Lowell Putnam Mathematical Competition. "Our terrific showing in the Putnam competition is a real demonstration of the great job the department is doing," said Sipser.

Simons Foundation founder Jim Simons studied and taught at MIT and has endowed three chairs in the math department. One of these is known as the Simons Chair, one is called the Norman Levinson Chair, and the third is temporarily known as the Simons chair but will be named the Isadore Singer Chair when Professor Singer retires. A faculty member named to one of these chairs holds the position for a decade. The chairs come with a discretionary fund to be used for travel or other research-related expenses.

"The ability to offer the stars in the department these chairs helps us attract and retain faculty," Sipser said. "It's all about the people. Math doesn't require a lot of resources for labs or equipment, but you do need resources to have terrific faculty."

Richard Melrose, Tomasz Mrowka and Richard Stanley are the current holders of the Simons-endowed chairs.

Richard Melrose

Simons Professor of Mathematics
MIT

A very small region of the surface of a sphere looks a lot like a very small region of a plane, and every point looks the same. Classical mathematical analysis deals mostly with spaces that are locally homogeneous and smooth, as in this example. One of the great 20th and 21st century frontiers is to extend our understanding to spaces that might look locally like the point at the end of an ice-cream cone, instead. This is the area in which Richard Melrose works.

Important examples of singular spaces come from smooth spaces with group actions; here the singularities appear as the sets where some part of the group acts trivially. Resolution in this setting allows topological invariants of the action, and of operators associated to it, to be investigated directly on a smooth space with corners, yielding for instance a direct definition of, ‘delocalized equivariant cohomology’ and the Chern character. Other examples include spaces that allow the direct realization of the long-time behavior of solutions to wave equations, including those in general relativity, and the moduli spaces of magnetic monopoles.

Melrose has been a Simons Professor of Mathematics since 2006. A graduate of Australian National University, he completed a Ph.D. at Cambridge University under the direction of F. Gerard Friedlander in 1974. Following a research fellowship at St. John’s College, Cambridge, he joined the MIT mathematics faculty in 1976.

Professor David Vogan called Melrose “the heart of the math department’s program in analysis.”

Professor Melrose received the Bôcher Prize of the American Mathematical Society in 1984, “...for his solution of several outstanding problems in diffraction theory and scattering theory and for developing the analytical tools needed for their resolution.”

Professor Melrose was elected Fellow of the American Academy of Arts and Sciences in 1986, and received a Guggenheim fellowship in 1992. For MIT, Professor Melrose served as Chair of the Graduate Student Committee, 1996-99, and Chair of the Pure Mathematics Committee, 1999-02.

Tomasz Mrowka

Simons Professor of Mathematics
MIT

MIT Professor Mrowka's research centers on the interaction between low-dimensional topology and high-energy physics. "It turns out that the equations used to study high-energy physics can be used to solve a lot of different problems," said Mrowka. "For example, the equations physicists use to investigate quarks also have applications to knot theory, which in turn provides insight into DNA, which has knot-like properties."

Low-dimensional topology is concerned with understanding potential mathematical models for space and space-time—that is, mathematical objects that look three-dimensional (like ordinary space) or four-dimensional (like space-time). The two-dimensional case is rather easy to visualize. The surface of a ball, a doughnut, or a coffee cup are examples. A potter with a strange sense of humor could make a coffee cup with many handles. The surfaces of these exotic cups would (essentially) exhaust all possible two-dimensional examples. In higher dimensions, the possibilities are much more varied. It turns out that for dimensions 5 and higher, the understanding of all possibilities can be largely reduced to difficult problems in algebra and homotopy theory. The case of dimension 3 was recently clarified by the 2004 work of Perelman that showed Hamilton's Ricci flow decomposes three-dimensional manifolds into geometric pieces as conjectured by Thurston. The case of dimension 4 remains mysterious. Currently the main tools for understanding the four-dimensional case builds on work initiated in 1984 by Simon Donaldson. He discovered that the behavior of solutions to equations of high-energy physics like Yang-Mills equations can be used as a tool to distinguish different space-times. Using this tool in 1990, Mrowka and Robert Gompf of the University of Texas discovered a new class of four-dimensional spaces of a kind completely unimagined before.

"The differential equations we used for this problem were introduced by the physicists," said Mrowka. "It was quite shocking that differential equations have anything to say about low-dimensional topology."

Mrowka was drawn to the study of low-dimensional topology because "so much mathematics comes together in this field, such as differential equations, algebraic geometry, and symplectic geometry. You get to learn just about everything, and I've always found that very compelling. I like the idea of being a mathematician, not just a specialist."

In 2007, the American Mathematical Society awarded Tomasz Mrowka and Peter Kronheimer the Veblen Prize in Geometry, "for their joint contributions to both three- and four-dimensional topology through the development of deep analytical techniques and applications."

Richard Stanley

Norman Levinson
Professor of Applied Mathematics
MIT

Like chess, combinatorics is the study of patterns. Combinatorics is a branch of mathematics that is concerned with discrete objects and patterns with little internal structure, but it can also involve other types of math where there is a great deal of structure. Combinatorial objects can often be encoded within much more complicated and abstract structures. These connections lead to new unifying principles in combinatorics and to new results in the related areas of mathematics.

Stanley's interest in combinatorics had its start in applications. Originally, he was interested in algebra and number theory, but while still in college at the California Institute of Technology, he worked as a research scientist at NASA's Jet Propulsion Laboratory (JPL). It was the heyday of the space program, and Stanley helped develop the error-correcting codes that spacecraft sent back to earth.

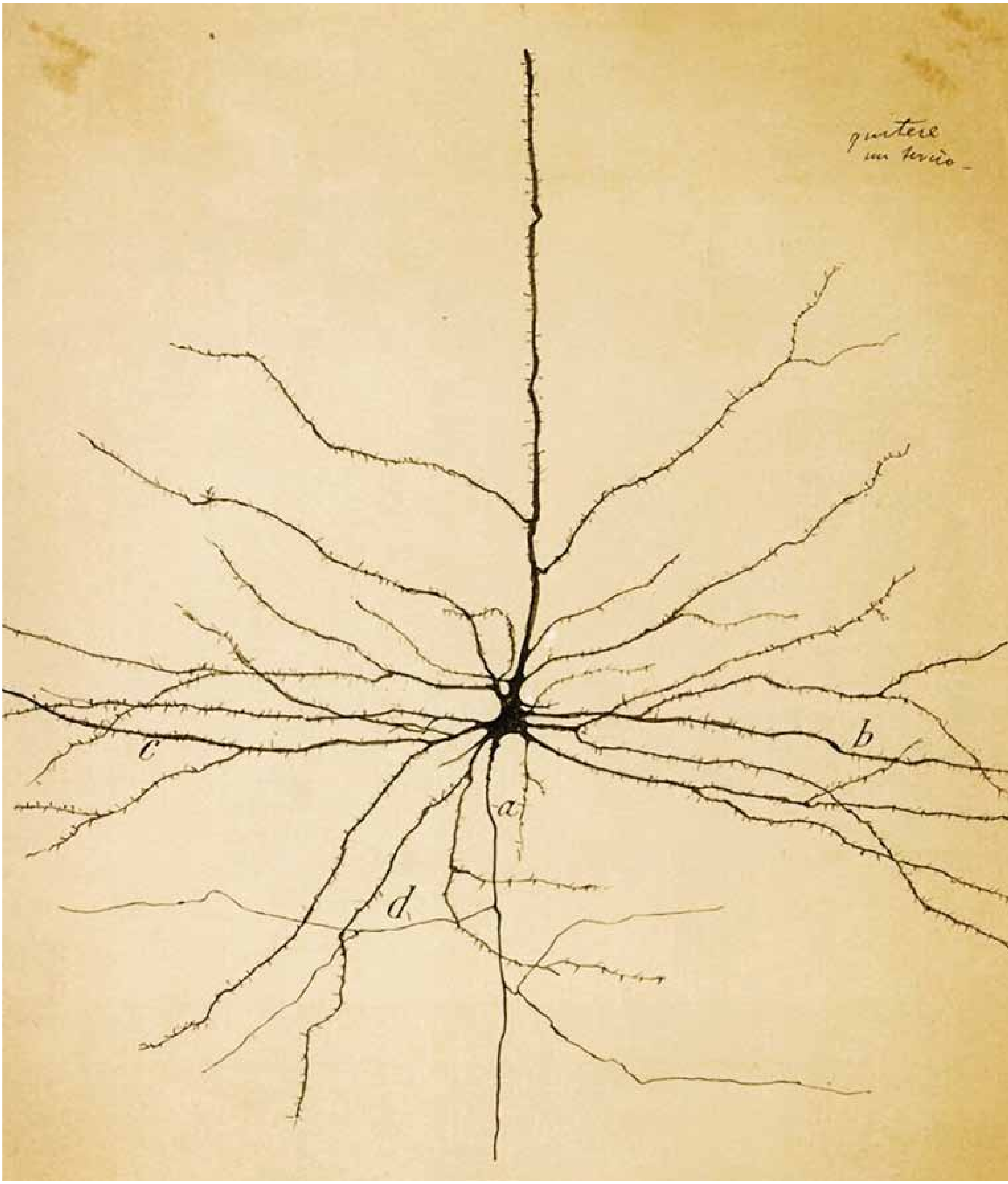
"The work at JPL concerned very combinatorial problems," recalled Stanley, "but I never thought of combinatorics as a serious subject to work in."

Stanley's original plan was to study algebra and number theory, but his work at JPL and subsequent discussions with Gian-Carlo Rota convinced him of the depth and beauty of combinatorics. He went on to receive a B.S. in mathematics from the California Institute of Technology in 1966 and a Ph.D. in mathematics from Harvard University in 1971, under the direction of Gian-Carlo Rota at MIT.

He joined the MIT faculty in 1973 and has had 51 Ph.D. students. He has held the Norman Levinson Professorship of Applied Mathematics since 2001.

Stanley's work in combinatorics has garnered many awards, among them the Leroy P. Steele Prize for mathematical exposition for his books *"Enumerative Combinatorics,"* volumes 1 and 2. He is a member of the American Academy of Arts and Sciences and the National Academy of Sciences.

"My particular interest is in finding connections between combinatorics and other branches of mathematics," Stanley said. "I am trying to develop unifying principles between these subjects."


c
b
a
d

SFARI:

Simons Foundation Autism Research Initiative

Santiago Ramón y Cajal, 1899.
Drawing showing a Golgi silver-impregnated, pyramidal-shaped neuron. The figure legend states: “Deep giant pyramidal neuron of the motor region of a man of thirty years. a, axon; b, c, dendrites that were followed for more than one millimeter; d, [axonal] collaterals.” From the collection of original drawings housed in the Cajal Museum (Cajal Institute, CSIC, Madrid).

Gerald D. Fischbach

Scientific Director

The Simons Simplex Collection ended its third year in 2009, with more than 1,700 families evaluated at 12 university clinics around the country and in Canada.

The Simons Simplex Collection (SSC) ended its third year in 2009, with more than 1,700 families evaluated at 12 university clinics around the country and in Canada. We expect to reach our current goal of 3,000 families early in the first quarter of 2011. The quality of the data and the reproducibility between sites remains extremely high. I believe that the SSC is extraordinary in its richness of clinical detail, rigor in collecting and recording data, and uniformity across sites.

In the coming weeks, we will discuss various extensions of the SSC beyond the original goal of searching for *de novo* mutations in simplex families. For example, we may want to study more severely disabled children or multiplex families, or focus more intensely on female subjects.

A new effort, the Simons Structural Variation Project (SSVP), is under way. We will work with clinical labs around the country to identify individuals with certain recurrent genetic lesions, for example the 16p11.2 deletion. We will study these individuals in depth clinically and genetically and with various imaging protocols. Isolated reports have appeared looking for phenotypic similarities of given lesions, but a large-scale study is needed. I expect that the SSC and the SSVP will remain resources for the autism research community for years to come.

In addition to the search for genetic risk factors, our grants program continues at an extremely high level. The 2009 RFA added 23 new grants to our roster, and we now fund 91 investigators. Details about each project can be found at https://sfari.org/investigators.

We find it convenient to divide our research into three categories: gene discovery; molecular mechanisms; and neural circuits, cognition and behavior. Of course, there are overlaps between these areas, and we hope that there will be more interdisciplinary collaboration between investigators working across categories.

To boost such partnerships, we held our first annual meeting in New Orleans in 2009. The meeting was a remarkable success and one of the most exciting meetings that I have ever attended. Members of the SFARI community presented new data and reviewed complex areas of inquiry, and several new collaborations were initiated.

The New Orleans meeting also was valuable in highlighting the many new approaches now under way. Collaborations are further enhanced by a series of small workshops held at the Foundation throughout the year.

Advances in our understanding of autism require the effort and talent of a broad community. Judging from progress over the past five years, I am convinced that we are on the verge of significant breakthroughs in molecular analysis of known autism risk factors, and in the discovery of new ones. SFARI will maintain its focus on the impact of such factors on the brain and how this information will lead to improved therapies.

GD Fischbach

Gerald D. Fischbach
Scientific Director

John Allman

SFARI Investigator

The characteristic features of autism may be obvious on the outside, but scientists are only beginning to uncover structural changes inside the brain.

The characteristic features of autism may be obvious on the outside, but scientists are only beginning to uncover structural changes inside the brain.

Two of those researchers are John Allman and Barbara Wold, who are performing comprehensive analyses of genes expressed in post-mortem brains from individuals with autism. They are using a direct sequencing technology, called RNA-Seq, developed by Wold and her collaborators to quantify gene expression.

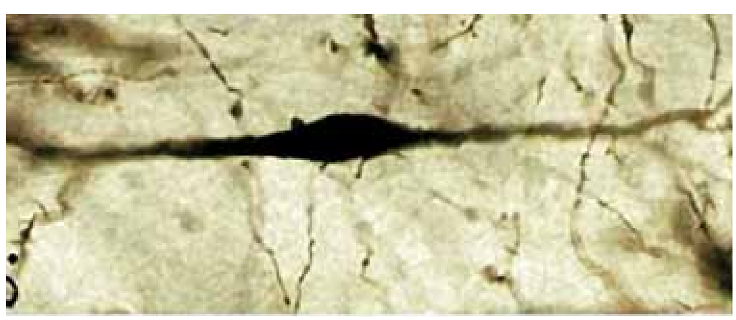
“In effect, what we’re doing is taking a very high-resolution snapshot of the disease at a frozen moment in time and space,” Allman says. Wold and Allman are both professors of biology at the California Institute of Technology. A few years ago, Wold heard Allman talk about his work on Von Economo neurons — the large, sparingly structured cells linked to social and emotional behaviors seen in diseases such as fronto-temporal dementia.

“I found the emerging story of these cells fascinating,” Wold recalls. Von Economo neurons are located in two brain areas, the fronto-insular and anterior cingulate cortices. Functional imaging and microscopic studies have shown that these areas, and the Von Economo neurons in particular, are involved in autism.

The researchers have thus far characterized the fronto-insular cortex in seven autistic brains and eight controls, from individuals ranging in age from age 4 to 22 years.They are beginning their analysis of gene expression in laser micro-dissected Von Economo neurons and other cells.

“Finding the processes that are different may point to a number of the important causes of autism,” Wold says, “and help us to know what’s common and what’s idiosyncratic.”

VENs stained with the Golgi method



Evan Eichler

SFARI Investigator

To understand the genetic mutations involved in autism, Evan Eichler has an odd proposal: Look elsewhere.

To understand the genetic mutations involved in autism, Evan Eichler has an odd proposal: Look elsewhere.

"We can't afford to be elitist about the disease that we study," says Eichler, a professor of genome sciences at the University of Washington. "These mutations are cutting across diseases."

In early 2009, Eichler's team published a study showing that a deletion in a particular section of chromosome 15 is a risk factor for epilepsy. The very same deletion had already been associated with autism, schizophrenia and mental retardation.

Eichler proposes to track these rare mutations as they occur in different physical manifestations, arguing that other factors, such as an individual's genetic background or environment, can influence the ultimate outcome.

Throughout his career, Eichler has taken a genome-centered view, looking for clues in DNA sequences to understand evolution and human disease.

In 2002, Eichler mapped the location of repeated sequences, called segmental duplications, in the human genome. He found that segmental duplications, once considered rare, make up more than five percent of the human genome, and occur on all chromosomes. From this, he predicted hotspots that could be prone to genetic accidents leading to disease.

In 2006, he and his team screened these hotspots in people with mental retardation, and found enough mutations to explain approximately three to five percent of cases. "We hit pay dirt there," he says.

Hoping to bring similar dividends to autism research, he is scanning 1,000 hotspots in DNA samples from the Simons Simplex Collection (SSC).

Deletions and duplications of segments of DNA have previously been linked to autism, but they are rare, and scientists frequently have not been able to find the same mutation in more than one individual, making it difficult to understand a given mutation's role in causing the disorder.

Focusing on hotspots missed by other studies in a narrowly defined population like the SSC may boost the chances of finding repeat instances of rare mutations, Eichler says. So will looking farther afield at broader phenotypes. He plans to take a 'genotype-first' approach to see if mutations found in the SSC also occur in people with a loosely defined version of autism.

"The diseases are all interrelated," he says. "And the mutations are actually leading the way."

Hazel Sive

SFARI Investigator

Transparent zebrafish probably aren't the first animals that come to mind as a system that could be used to study autism.

Transparent zebrafish probably aren't the first animals that come to mind as a system that could be used to study autism. These small creatures clearly lack the complex behavioral repertoire of humans, which is abnormal in patients with autism.

Nevertheless, the fish share many genes with people, and an arsenal of genetic technologies is now available to manipulate those genes. The result: an ideal system to probe genetic functions implicated in autism.

Traditional models rely on animals mimicking aspects of autism. Hazel Sive, a member of the Whitehead Institute for Biomedical Research, plans to use zebrafish as a tool to examine the function of autism-related genes during brain development. "That is, we don't require that the fish mimic the behavioral changes seen in autism, only that they have a gene similar to that mutated in the human condition. Then we have a handle to study activity of the gene," Sive says. "This is a very different way of using animals to study mental health disorders."

Scientists have also identified a number of genetic regions in the past few years that are linked to autism. They are trying to pinpoint which of the genes within these larger genomic chunks may trigger the disorder.

One notable region on human chromosome 16, first linked to autism by Mark Daly's group, contains about 25 genes. Sive's team knocked out 14 of the genes in zebrafish and subsequently discovered that almost all of them appear to play a vital role in the developing brain. In some cases, loss of gene function caused the brain to be misshapen and small. In others, nerve cells grew in atypical directions and patterns.

"[It] is very surprising to see so many devastating brain abnormalities in the fish associated with this small set of genes," Sive says.

The next step, Sive notes, is to remedy the mutations — for example, by supplementing a protein missing in those with the disorder. Her team also hopes to test a number of small molecules that may someday translate into therapeutics able to make the fish better. "That's the really risky part," she says, "but the payoff is potentially enormous."

Kevin Pelphrey

SFARI Investigator

“We might be able to target interventions to the individual child’s genome, instead of using a one-size-fits-all model.”

With its characteristic feature of social withdrawal, autism is an alluring subject of study for Kevin Pelphrey, who is fascinated by how the mind learns to understand and interact with other people.

People with autism can have a wide range of social and emotional skills. “Some kids with autism are terrible at reading other people’s psychological dispositions, or have continued outbursts long past the age at which meltdowns are normal, while other children present fewer challenges in these areas,” Pelphrey says.

For the past year, he has been trying to find out how these differences take root in the brain, and how the signals of the autistic mind may be affected by genetic variation.

Pelphrey, Harris Associate Professor of Child Psychiatry and Director of the Child Neuroscience Laboratory at the Yale Child Study Center, has so far scanned the brains of 24 young children with autism as they engage in social or emotional tasks, such as playing games that are rigged to lose, or watching movies of other people.

He studies children as young as 4, who typically can’t stay calm inside the noisy, tunnel-like magnetic resonance imager. So, he first lets the children get used to a mock scanner that looks like a colorful rocket ship or train. This training has raised retention rates in his research from about 25 to approximately 80 percent.

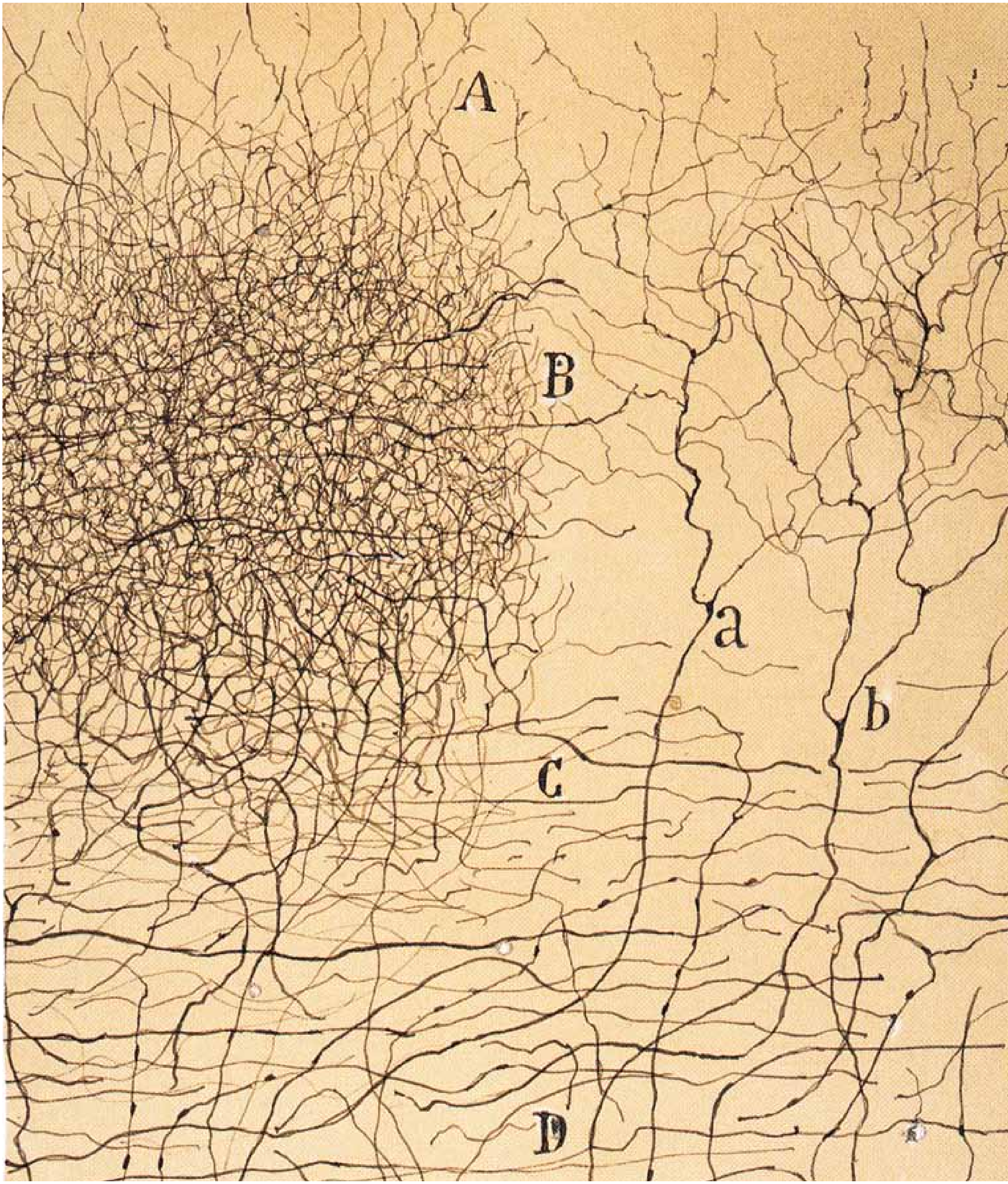
Pelphrey plans to test about 70 children, most of whom are participants in the Simons Simplex Collection, a gene bank of families with autism. Because the children are all genetically screened, Pelphrey can look for meaningful connections between particular gene variants and brain activity.

For instance, in one set of experiments, he is looking for genetic ties with the ability to perceive others’ intentions.

The two genes Pelphrey is focusing on are one piece of the serotonin transporter, called 5-HTTLPR — which is required for the development of the social regions in the brain and has long been associated with autism — and COMT, which is also involved in regulating emotions but has not yet been linked to autism.

Pelphrey has found that compared with control groups, the brains of children with autism respond differently to the social tasks depending on the variant of 5-HTTLPR they carry.

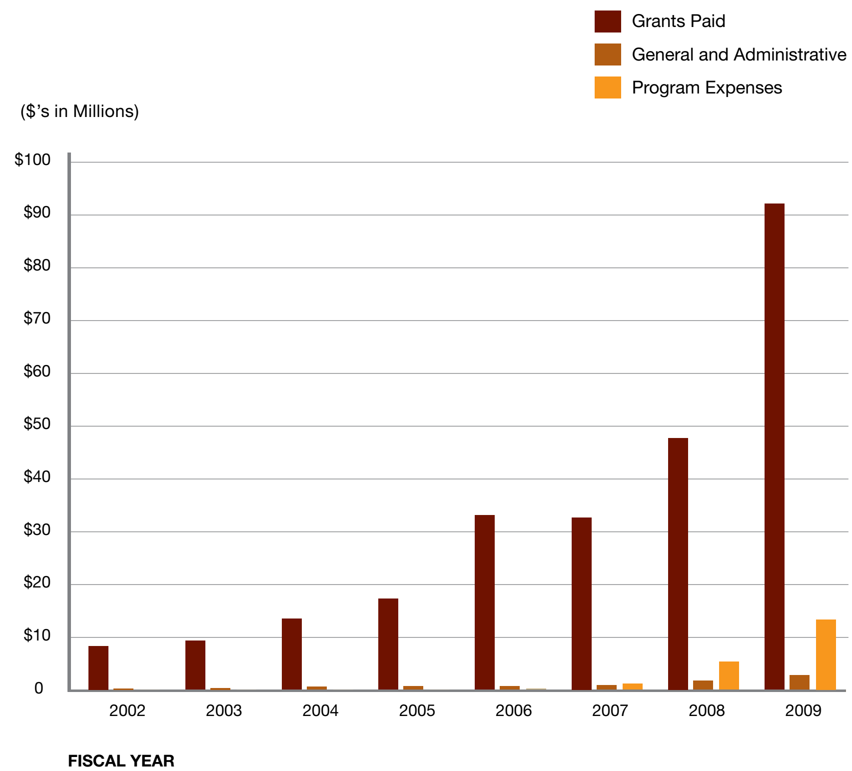
If variations in the gene do prove to be important, it could have a big impact on treatment for the disorder, Pelphrey says. “We might be able to target interventions to the individual child’s genome, instead of using a one-size-fits-all model.”


A
B
a
b
C
D

Financials

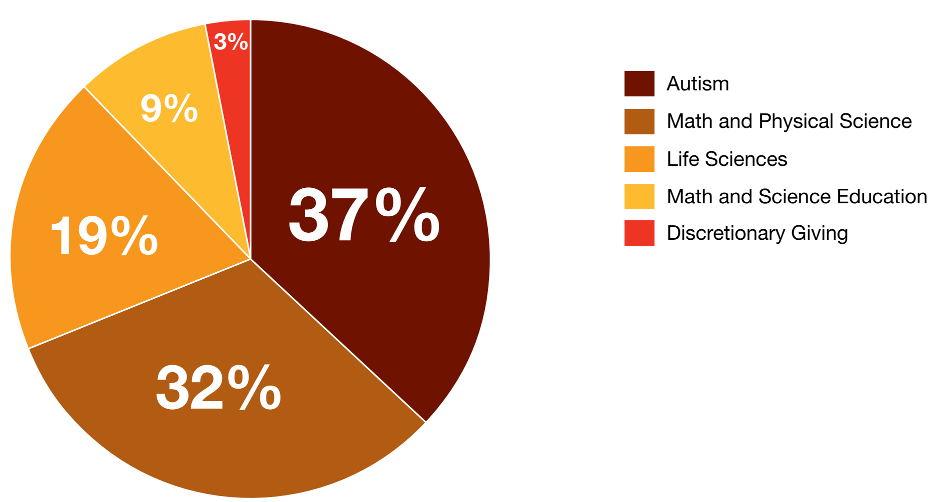
Santiago Ramón y Cajal, 1899.
Sensory plexus of the human cerebral cortex.
From the collection of original drawings housed in the Cajal Museum (Cajal Institute, CSIC, Madrid).

Proportions of Expenses



Grant Payments by Category

Fiscal Year 2009



Balance Sheet

ASSETS	June 30, 2009	June 30, 2008
Cash and Cash Equivalents	$ 165,283,151	$ 27,861,666
Investment Portfolio	1,215,842,647	1,064,269,117
Property and Equipment, Net	24,741,715	16,094,323
Prepaid Excise Taxes	72,429	182,146
Other	110,550	93,749
Total	**1,406,050,492**	**1,108,501,001**

LIABILITIES	June 30, 2009	June 30, 2008
Grants Payable	228,668,378	129,546,444
Deferred Excise Tax Liability	10,189,983	8,659,983
Other	0	0
Total	**238,858,361**	**138,206,427**

NET ASSETS		
UNRESTRICTED NET ASSETS	**$1,167,192,131**	**$970,294,574**

Income Statement

REVENUE	June 30, 2009	June 30, 2008
Contributions	$ 305,217,105	$180,480,577
Investment Income	101,650,404	290,467,232
Total	**406,867,509**	**470,947,809**

EXPENSES	June 30, 2009	June 30, 2008
Grants Paid	92,024,914	47,660,532
Change in Grants Payable	99,121,934	52,855,809
General and Administrative	2,717,557	1,649,880
Program	13,280,162	5,287,127
Depreciation and Amortization	315,684	222,199
Federal Excise Taxes	2,509,717	2,908,800
Total	**209,969,968**	**110,584,347**

NET INCOME	**$196,897,541**	**$360,363,462**

Trustees

Marilyn H. Simons, Ph.D.
President

Marilyn Hawrys Simons, Ph.D., has worked primarily in the nonprofit sector as a volunteer for the past 20 years, focusing on education. She has served as president of the Simons Foundation since 1994. Ms. Simons is currently president of the board of LearningSpring School, a school for children diagnosed with autism spectrum disorders, and is a member of the board of trustees of the East Harlem Tutorial Program. Ms. Simons is also a trustee of the Cold Spring Harbor Laboratory. She received a B.A. and a Ph.D. in economics from the State University of New York at Stony Brook.

Mark Silber, J.D., M.B.A.
Vice President

Mark Silber, J.D., M.B.A., is vice president and general counsel at Renaissance Technologies, where he has held responsibility for finance, administration and compliance since joining the firm in 1983. Prior to joining Renaissance, he was a Certified Public Accountant with the accounting firm of Seidman & Seidman, now BDO Seidman. Mr. Silber holds a bachelor's degree from Brooklyn College, a J.D. and L.L.M. in tax law from the New York University School of Law, and an M.B.A. in finance from the New York University Graduate School of Business Administration.

James H. Simons, Ph.D.
Secretary and Treasurer

James H. Simons, Ph.D., is secretary and treasurer of the Simons Foundation. Dr. Simons is Board Chair and founder of Renaissance Technologies. Prior to his financial career, Dr. Simons served as chairman of the Mathematics Department at the State University of New York at Stony Brook, taught mathematics at Massachusetts Institute of Technology and Harvard University, and was a cryptanalyst at the Institute of Defense Analyses in Princeton, N.J. Dr. Simons' scientific work was in the area of geometry and topology, and his most influential work involved the discovery and application of certain measurements, now called Chern-Simons invariants, that have had wide use, particularly in theoretical physics. Dr. Simons holds a B.S. from the Massachusetts Institute of Technology and a Ph.D. from the University of California, Berkeley, and won the American Mathematical Society's Veblen Prize for his work in geometry in 1975. He is a trustee of the Stony Brook Foundation, Rockefeller University, Massachusetts Institute of Technology, Brookhaven National Laboratory, the Mathematical Sciences Research Institute, the Institute for Advanced Study, the American Academy of Arts and Sciences, and the American Philosophical Society.

Simons Foundation Staff

www.simonsfoundation.org

Maria Adler, M.B.A.
Vice President, Finance

Marta Benedetti, Ph.D.
Associate Director for Research

Sascha Brodsky, M.S., M.I.A.
Director of Communications

Meghan Criswell
Administrative Assistant

David Eisenbud, Ph.D.
Vice President for Mathematics

Gerald D. Fischbach, M.D.
Scientific Director

Chris Fleisch, B.S.
Technology Manager

Andrea Gallego, B.A.
Executive Assistant

Adrienne Greenberg, B.S.
Business Manager

Anastasia Greenebaum, J.D., M.I.D.
Special Projects Manager

Marion Greenup, M.P.H., M.Ed.
Vice President, Administration

Fang Han B.B.A. C.P.A.
Accounting Manager

Stephen Johnson, Ph.D.
Informatics Director

Apoorva Mandavilli, M.S., M.A.
Executive Editor

Amy Millette, B.A.
Manager of Conferences and Events

Dave Mosher, B.S., B.A.
Web Editor

Alan Packer, Ph.D.
Associate Director for Research

Lauren Rath, B.A.
Grants Associate

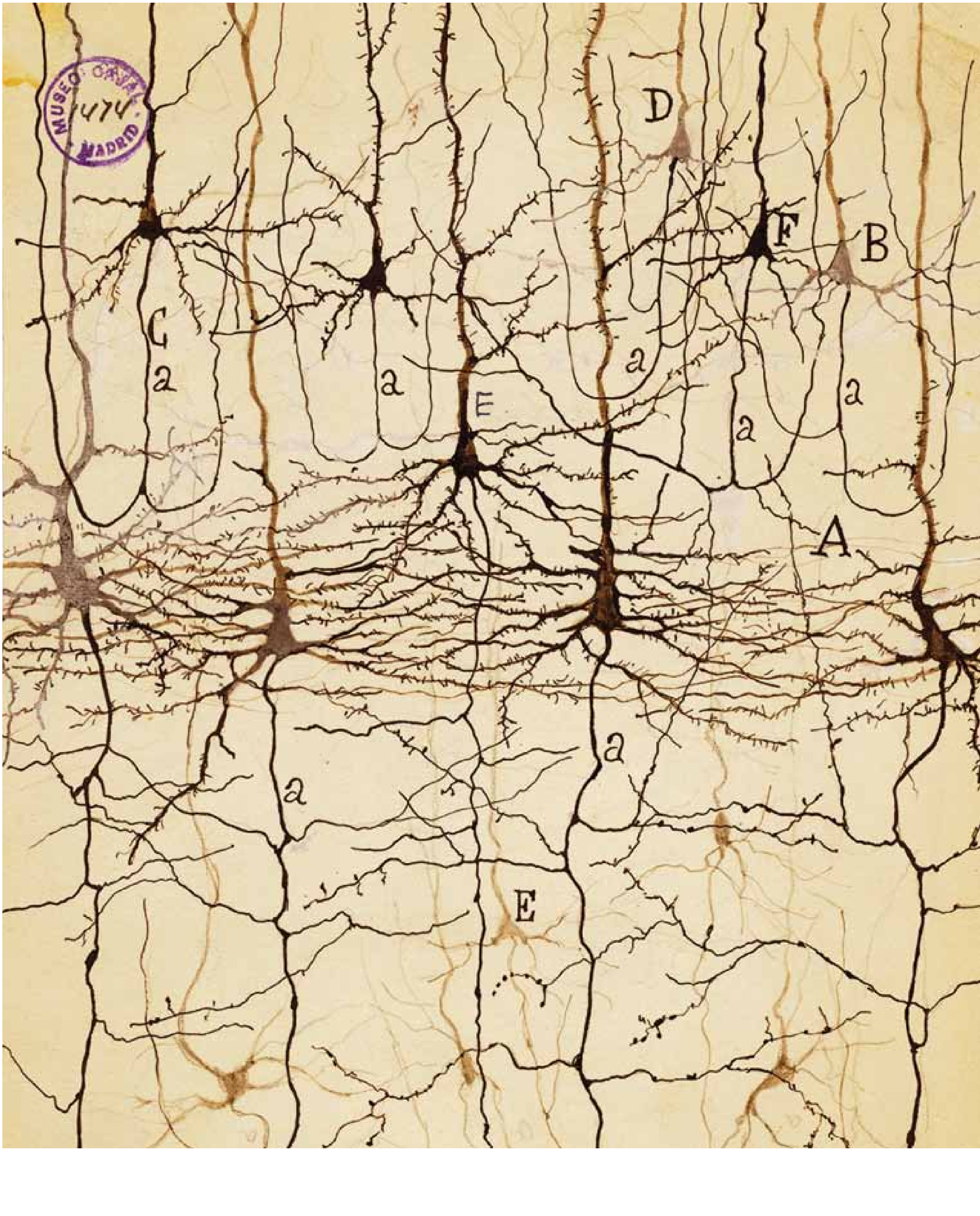
Marilyn Simons, Ph.D.
President

James H. Simons, Ph.D.
Secretary and Treasurer

John Spiro, Ph.D.
Senior Associate Director for Research

Sherrie Vasallo, M.B.E.
SFARI Project Manager

Patricia Weisenfeld, M.P.A.
Director of Family Giving


MUSEO CAJAL
1474
MADRID
D
F
B
C
a
a
a
a
a
E
A
a
a
E

Grants

Santiago Ramón y Cajal, 1921.
Drawing of Golgi silver-impregnated neurons in a section cut through the pyramidal cell layer of the cat's visual cortex.
From the collection of original drawings housed in the Cajal Museum (Cajal Institute, CSIC, Madrid).

Grants

The Simons Foundation supports outstanding individual researchers and institutions seeking funding for advanced work in the basic sciences and mathematics, with a focus on innovative scientific projects where our involvement will play an essential role. In the course of this support, the foundation is interested in partnering with other entities, or providing matching support where appropriate.

Historically, the Simons Foundation has accepted only solicited grant proposals. All grant decisions are made by the trustees of the foundation and the foundation staff. The foundation does not make awards to individuals, except through their institutions.

Grants to Institutions

MATH AND PHYSICAL SCIENCE

American University of Beirut
Beirut, Lebanon

Friends of the Institut des Hautes Études Scientifiques
New York, New York

Harvard University
Cambridge, Massachusetts

Massachusetts Institute of Technology
Cambridge, Massachusetts

Mathematical Sciences Research Institute
Berkeley, California

Stony Brook University
Stony Brook, New York

University of California, Berkeley
Berkeley, California

MATH AND SCIENCE EDUCATION

Science Festival Foundation
New York, New York

Math for America
New York, New York

LIFE SCIENCES

Beth Israel Deaconess Medical Center
Boston, Massachusetts

Cold Spring Harbor Laboratory
Cold Spring Harbor, New York

Institute for Advanced Study
Princeton, New Jersey

Memorial Sloan-Kettering Cancer Center
New York, New York

Rockefeller University
New York, New York

AUTISM

Baylor College of Medicine
Houston, Texas

Beth Israel Deaconess
Medical Center
Boston, Massachusetts

California Institute
of Technology
Pasadena, California

Children's Hospital Boston
Boston, Massachusetts

Children's Hospital Philadelphia
Philadelphia, Pennsylvania

Cold Spring Harbor Laboratory
Cold Spring Harbor, New York

Columbia University
New York, New York

Weill Medical College of
Cornell University
New York, New York

Duke University
Durham, North Carolina

Emory University
Atlanta, Georgia

Georgetown University
Washington, District of Columbia

Harvard Medical School
Boston, Massachusetts

Johns Hopkins University
Baltimore, Maryland

Massachusetts General Hospital
Boston, Massachusetts

Massachusetts Institute
of Technology
Cambridge, Massachusetts

McGill University
Montreal, Canada

Mount Sinai School
of Medicine
New York, New York

New York University
School of Medicine
New York, New York

Princeton University
Princeton, New Jersey

Research Foundation for
Mental Hygiene, Inc., at New York
State Psychiatric Institute
New York, New York

Rockefeller University
New York, New York

Rutgers, The State
University of New Jersey
New Brunswick, New Jersey

Salk Institute for
Biological Studies
La Jolla, California

Stanford University
Menlo Park, California

University of California,
Los Angeles
Los Angeles, California

University of California,
San Diego
San Diego, California

University of California,
San Francisco
San Francisco, California

University of Illinois at Chicago
Chicago, Illinois

University of Massachusetts
Medical School
Worcester, Massachusetts

University of Michigan
Ann Arbor, Michigan

University of Missouri
Columbia, Missouri

University of North Carolina
at Chapel Hill
Chapel Hill, North Carolina

University of Oxford
Oxford, England

University of Pennsylvania
Philadelphia, Pennsylvania

University of Texas
Southwestern Medical Center
Dallas, Texas

University of Washington
Seattle, Washington

Vanderbilt University
Nashville, Tennessee

Washington University
in St. Louis
St. Louis, Missouri

Whitehead Institute for
Biomedical Research
Cambridge, Massachusetts

Yale University
New Haven, Connecticut

SFARI Scientific Advisory Board

Dennis W. Choi, M.D., Ph.D.
Emory University

Wendy Chung, M.D., Ph.D.
Columbia University

Thomas M. Jessell, Ph.D.
Columbia University

Nancy Kanwisher, Ph.D.
Massachusetts Institute of Technology

Richard P. Lifton, M.D., Ph.D.
Yale University

Catherine E. Lord, Ph.D.
University of Michigan Autism and Communication Disorders Center

J. Anthony Movshon, Ph.D.
New York University

Martin Raff, M.D.
University College London

Simons Investigators

Ralph Adolphs
California Institute of Technology

John M. Allman
California Institute of Technology

Dan Arking
Johns Hopkins University School of Medicine

Mark Bear
Massachusetts Institute of Technology

Arthur Beaudet
Baylor College of Medicine

Raphael Bernier
University of Washington

Randy Buckner
Harvard University

Joseph Buxbaum
Mount Sinai School of Medicine

Brian Chait
The Rockefeller University

Aravinda Chakravarti
Johns Hopkins University School of Medicine

Andrew Chess
Massachusetts General Hospital

John Constantino
Washington University in St. Louis

Edwin Cook, Jr.
University of Illinois at Chicago

Eric Courchesne
University of California, San Diego

Christopher Cowan
University of Texas Southwestern Medical Center

Mark Daly
Massachusetts General Hospital

Ted M. Dawson
Johns Hopkins University School of Medicine

Robert Desimone
Massachusetts General Hospital

Curtis Deutsch
University of Massachusetts Medical School

Ricardo Dolmetsch
Stanford University

Michael D. Ehlers
Duke University

Evan Eichler
University of Washington

Noemie Elhadad
Columbia University

Guoping Feng
Duke University

Gordon J. Fishell
New York University School of Medicine

Simon Fisher
University of Oxford

Eric Fombonne
McGill University

John Gabrieli
Massachusetts Institute of Technology

Nicholas Gaiano
Johns Hopkins University School of Medicine

Daniel Geschwind
University of California, Los Angeles

Jay Gingrich
Research Foundation for Mental Hygiene, Inc. at New York State Psychiatric Institute

Joseph Gogos
Columbia University

Ann Graybiel
Massachusetts Institute of Technology

Paul Greengard
The Rockefeller University

James F. Gusella
Massachusetts General Hospital

Nathaniel Heintz
The Rockefeller University

Barbara Hempstead
Weill Medical College of Cornell University

Z. Josh Huang
Cold Spring Harbor Laboratory

Kimberly Huber
University of Texas
Southwestern Medical Center

Eric R. Kandel
Columbia University

Young Shin Kim
Yale University

Ami Klin
Yale University

Richard Krauzlis
Salk Institute for Biological Studies

Abba Krieger
University of Pennsylvania

Louis Kunkel
Children's Hospital Boston

David Ledbetter
Emory University

Arnold J. Levine
Institute for Advanced Study

Pat Levitt
University of Southern California

J. Troy Littleton
Massachusetts Institute
of Technology

Dan Littman
New York University
School of Medicine

Catherine E. Lord
University of Michigan

Christa Lese Martin
Emory University

Steven McKnight
University of Texas
Southwestern Medical Center

Judith Miles
University of Missouri

Alea Mills
Cold Spring Harbor Laboratory

Anthony Monaco
University of Oxford

Charles Nelson
Children's Hospital Boston

Sasha Nelson
Brandeis University

Daniel Notterman
Princeton University

Pavel Osten
Cold Spring Harbor Laboratory

Opal Ousley
Emory University

Luis Parada
University of Texas
Southwestern Medical Center

Karen Parker
Stanford University

Paul Patterson
California Institute of Technology

Kevin Pelphrey
Yale University

Steven Petersen
Washington University in St. Louis

Bradley Peterson
Columbia University

Joseph Piven
University of North Carolina
at Chapel Hill

Vijaya Ramesh
Massachusetts General Hospital

Louis Reichardt
University of California,
San Francisco

Bernardo Sabatini
Harvard Medical School

Joshua Sanes
Harvard University

Rebecca Saxe
Massachusetts Institute
of Technology

Robert Schultz
The Children's Hospital
of Philadelphia

Morgan Sheng
Massachusetts Institute
of Technology

Maggie Shiffrar
Rutgers, The State University
of New Jersey

Pawan Sinha
Massachusetts Institute
of Technology

Hazel Sive
Whitehead Institute for
Biomedical Research

Jesse Snedeker
Harvard University

Matthew State
Yale University

Thomas Südhof
Stanford University

David Sulzer
Columbia University

Mriganka Sur
Massachusetts Institute
of Technology

Jim Sutcliffe
Vanderbilt University

Susumu Tonegawa
Massachusetts Institute
of Technology

Li-Huei Tsai
Massachusetts Institute
of Technology

Richard Tsien
Stanford University

Michael Ullman
Georgetown University

Flora Vaccarino
Yale University

Christopher Walsh
Beth Israel Deaconess
Medical Center

Stephen Warren
Emory University

Zachary Warren
Vanderbilt University

Lauren Weiss
University of California,
San Francisco

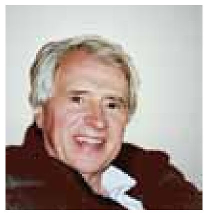
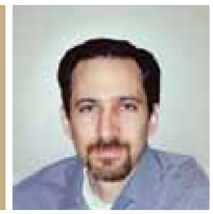
Michael Wigler
Cold Spring Harbor Laboratory

Larry Zipursky
University of California,
Los Angeles

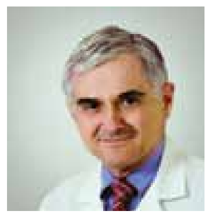
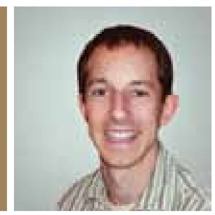
Huda Zoghbi
Baylor College of Medicine

2009 Simons Investigators

The Simons Foundation Autism Research Initiative funds investigators who are working to enhance our understanding of autism. At the present time, we fund research in three areas: gene discovery, molecular mechanisms, and cognition and behavior. We hope this community of scientists will work together to blur the distinctions and technical hurdles that keep these approaches too far apart.


Ralph Adolphs

John Allman

Dan Arking

Mark Bear

Arthur Beaudet

Raphael Bernier


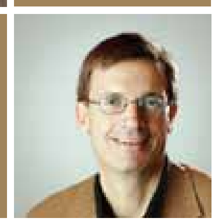

Randy Buckner

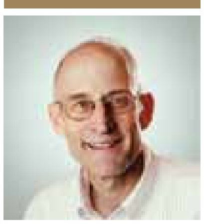
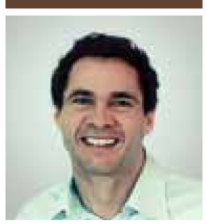
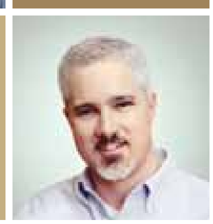
Joseph Buxbaum

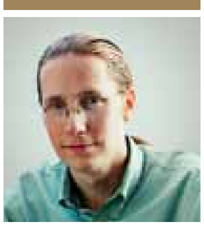
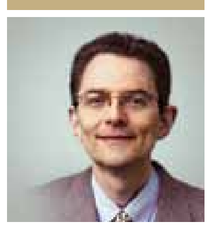
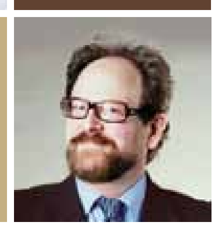
Brian Chait

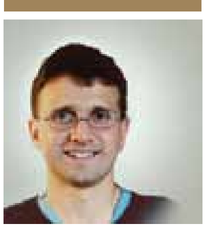
Aravinda Chakravarti

Andrew Chess

John Constantino



Edwin Cook Jr.

Eric Courchesne

Christopher Cowan

Mark Daly

Ted M. Dawson

Curtis Deutsch



Ricardo Dolmetsch

Michael D. Ehlers

Evan Eichler

Noemie Elhadad

Guoping Feng

GordonJ. Fishell

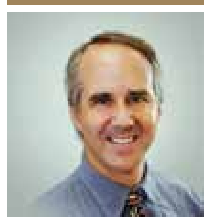
Simon Fisher

Eric Fombonne

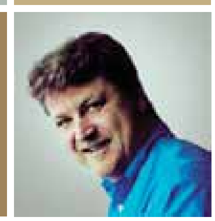
John Gabrieli

Nicholas Gaiano

Daniel Geschwind



Jay Gingrich



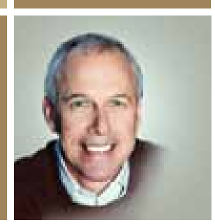
Joseph Gogos

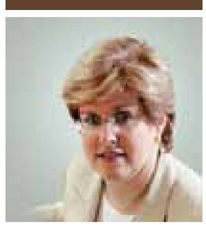
Ann Graybiel

Paul Greengard

James F. Gusella

Nathaniel Heintz

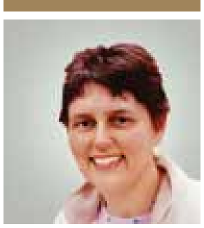




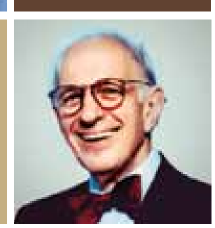
Barbara Hempstead

Z. Josh Huang

Kimberly Huber



Eric R Kandel



Young Shin Kim

Ami Klin

Richard Krauzlis



Abba Krieger

Louis Kunkel

David Ledbetter

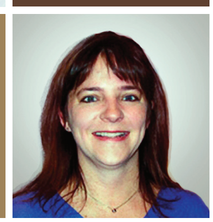
Arnold J. Levine

Pat Levitt

J. Troy Littleton

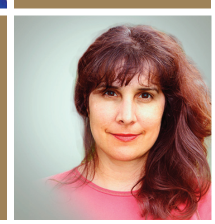


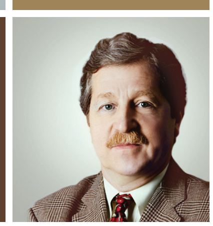
Dan Littman

Catherine E. Lord

Christa Lese Martin

Steven McKnight

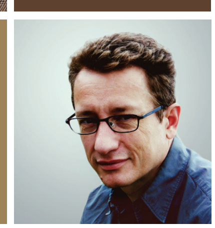
Judith Miles

Alea Mills



Anthony Monaco

Charles Nelson

Sasha Nelson

Daniel Notterman

Pavel Osten


Opal Ousley

Luis Parada

Paul Patterson

Kevin Pelphrey

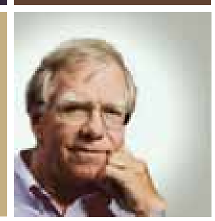
Steven Petersen

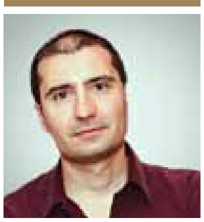
Bradley Peterson

Joseph Piven

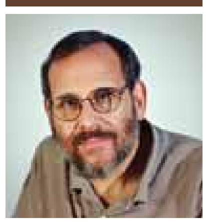
Vijaya Ramesh

Louis Reichardt

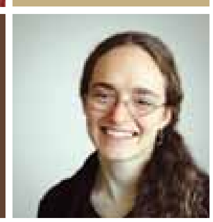




Bernardo Sabatini



Joshua Sanes

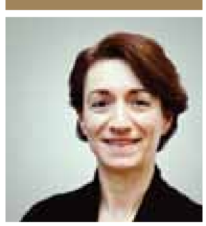


Rebecca Saxe

Morgan Sheng

Maggie Shiffrar

Pawan Sinha



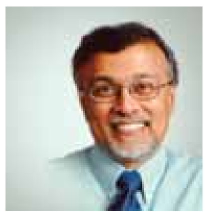
Hazel Sive

Jesse Snedeker

Matthew State

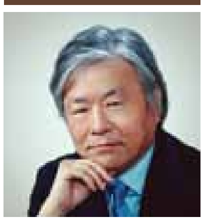
Thomas Südhof

David Sulzer



Mriganka Sur

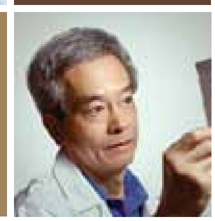
Jim Sutcliffe



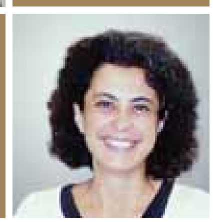
Susumu Tonegawaa

Li-Huei Tsai

Richard Tsien

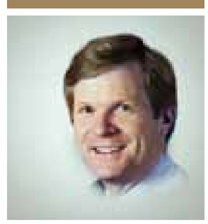


Michael Ullman

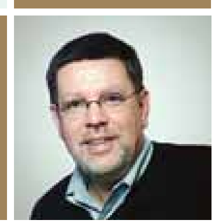


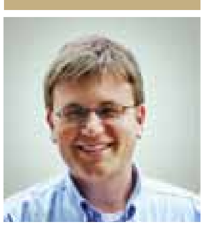
Flora Vaccarino

Christopher Walsh

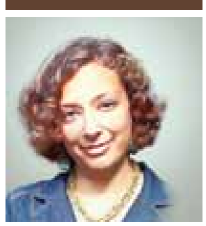


Stephen Warren

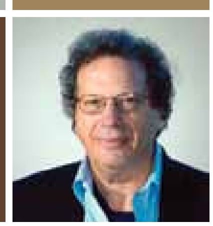




Zachary Warren

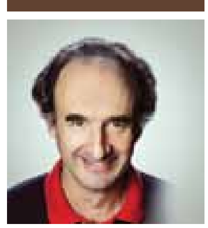


Lauren Weiss

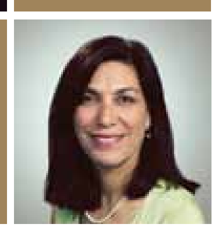


Michael Wigler

Larry Zipursky

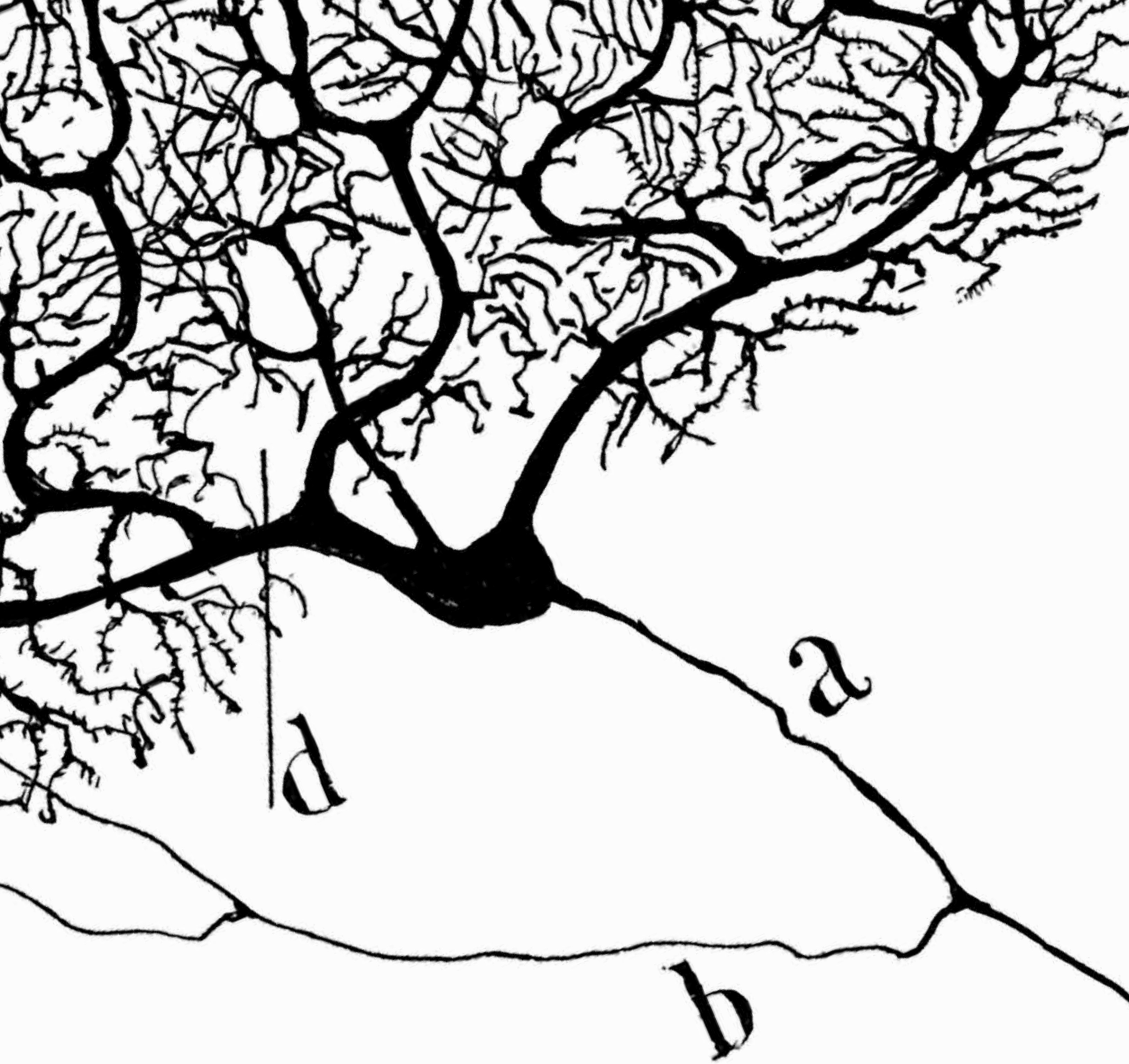


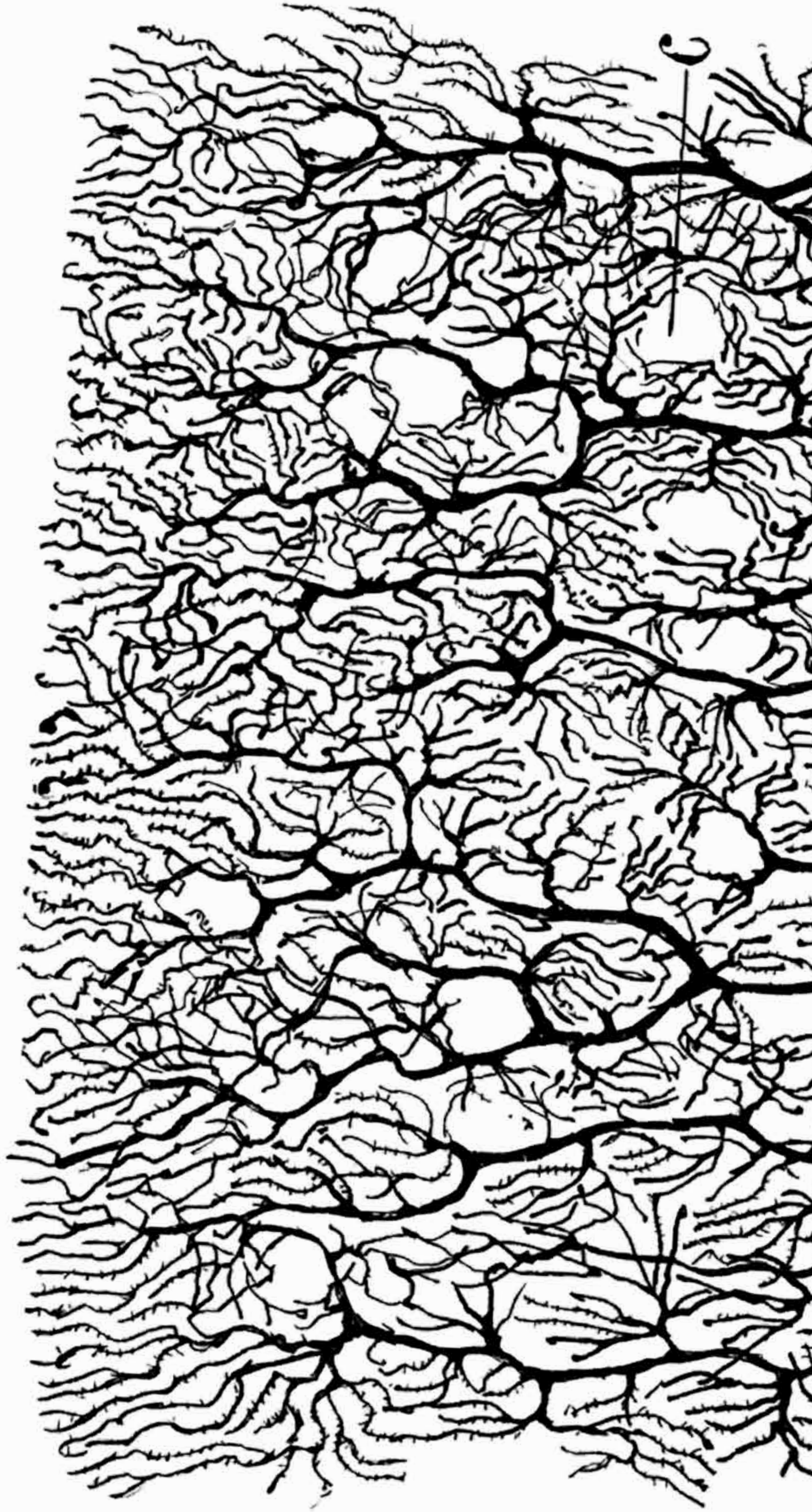
Huda Zoghbi



For more information on the Simons Foundation and SFARI, please visit our websites:

www.simonsfoundation.org
www.sfari.org


a
d
b



SIMONS FOUNDATION

160 Fifth Avenue
New York, NY 10010
Tel. 646 654 0066

www.simonsfoundation.org

SFARI

www.sfari.org