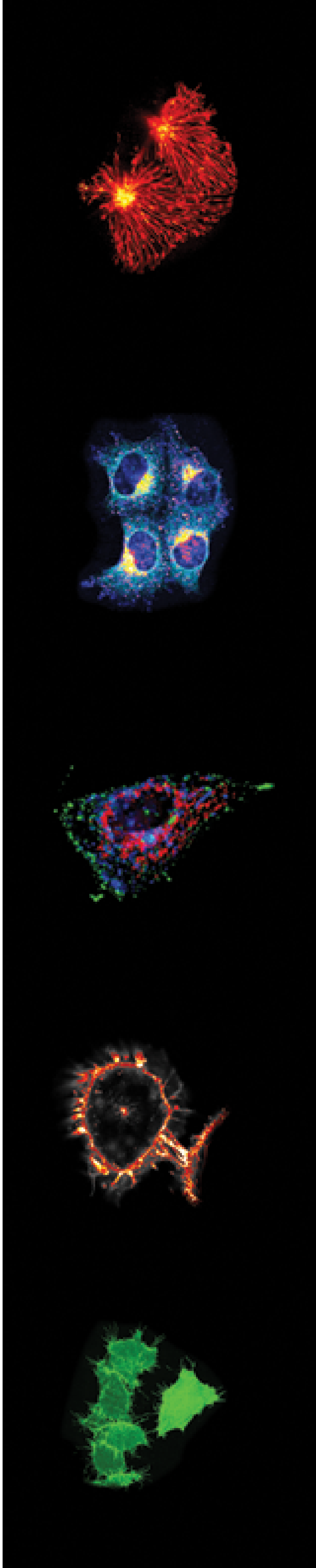
SIMONS FOUNDATION

# ANNUAL REPORT 2011



## APOPTOSIS IMAGES BY DR. ROLAND EILS

The pictures in this report illustrate the process of 'apoptosis,' programmed cell death, imaged through the technique of fluorescence microscopy. They come to us from the laboratory of Dr. Roland Eils of the University of Heidelberg and the German Cancer Research Centre.
Dr. Eils' work combines mathematical modeling with experiments in molecular cell biology to yield a detailed, quantitative understanding of basic cellular mechanisms. His knowledge in the fields of physics, mathematics and biology enables scientific results not likely attainable through a traditional approach. Such an integration of expertise comprises the relatively new field of systems biology, an illustration of this report's emphasis on cross-disciplinary activities.

The Simons Foundation is grateful to Dr. Eils for sharing these remarkable images with us.

SIMONS FOUNDATION

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

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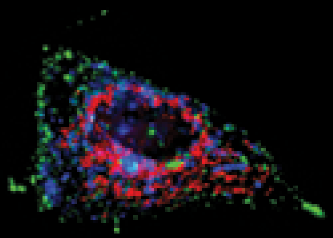

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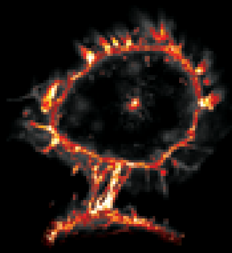
BUILDING DIGITAL RESOURCES





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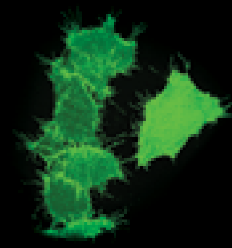
PROMOTING EXCHANGES





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FOUNDATION FACTS

# LETTER FROM THE PRESIDENT AND THE CHAIRMAN



Collaborative partnerships, networks and communities build upon each other and enable us to work together toward our common goals. Such interactions are the theme of our 2011 Annual Report.

Marilyn Hawrys Simons, Ph.D., and James H. Simons, Ph.D.

"Here I am: my brain is open," were the words Paul Erdős used when arriving at the home of a mathematical collaborator. Famous for his prolific research and itinerant lifestyle, Erdős was a consummate collaborator. So fruitful were his many research relationships that in his lifetime he wrote or coauthored over 1,475 academic papers, "many of them monumental, and all of them substantial," according to one biographer. Erdős is quoted elsewhere as wittily summing up his peripatetic lifestyle with the phrase, "another roof, another proof."

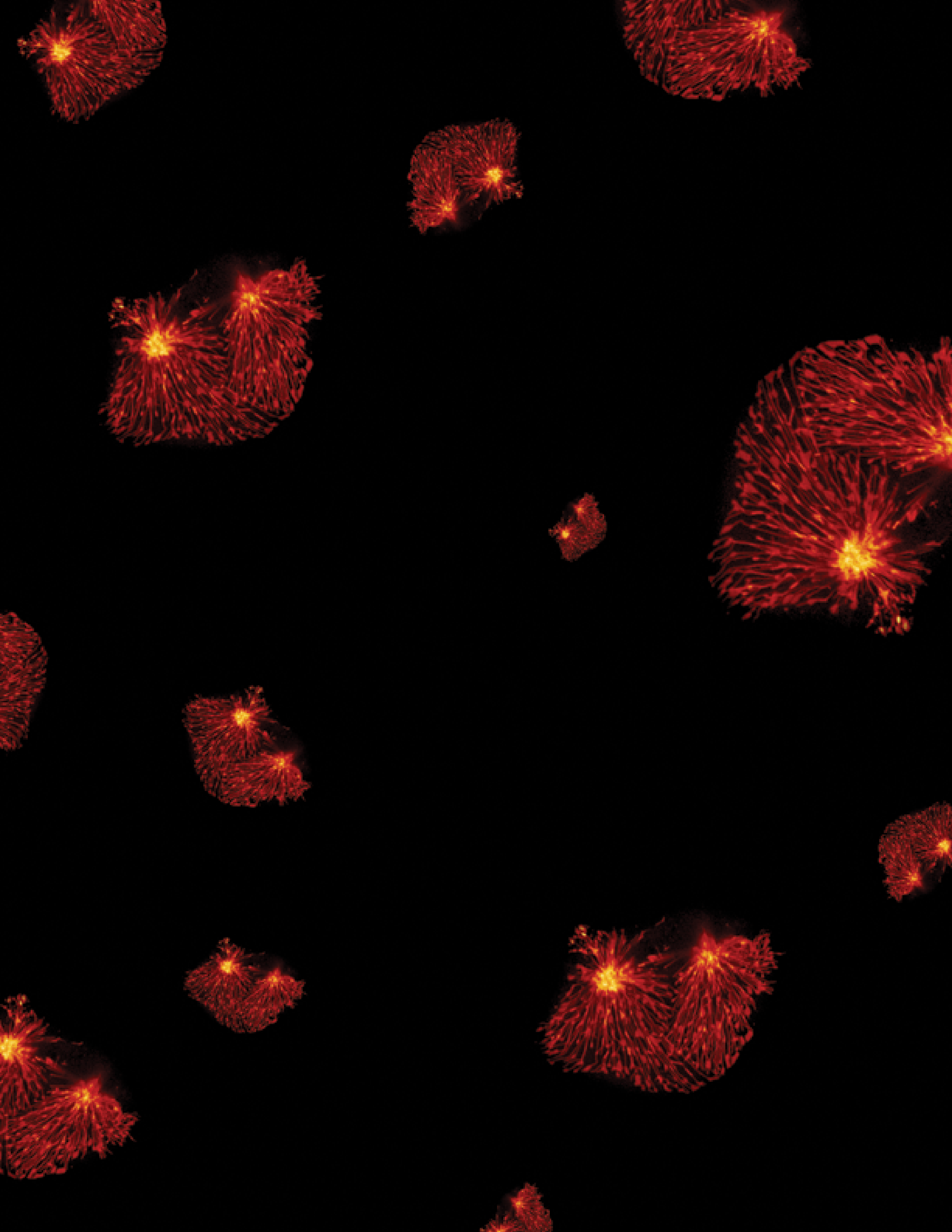
As Paul Erdős clearly illustrates, the synergy of collaboration is powerful. Its potential for stimulating research through partnerships within fields and even across them is significant. It is often the case that the whole is greater than the sum of its parts, even when those parts are widely diverse. At the Simons Foundation a core element of our strategy is to nurture this type of synergy through grant making that encourages interconnections.

The mission of the Simons Foundation is to support advanced research in mathematics and the basic sciences. To date, we have focused on the fields of mathematics, theoretical physics, computer science, quantitative biology and the biology of autism. In this report, you will read about those of our new initiatives that give researchers the opportunity to work together. Examples include a Collaboration Grants program in mathematics which allows researchers to meet face to face, sponsored workshops and symposia which bring scientists together around a particular question, and grants for interdepartmental studies which combine advances and insights from different fields. Beyond these direct support programs to individuals and institutions, the foundation also supports research networks by investing in resources for investigators. Infrastructure such as data collections, online tools and online archives help build dynamic research networks. Sharing information and communicating interactively, these communities disseminate knowledge and deepen understanding.

Additionally, the foundation supports learning communities such as Math for America's teaching corps, Stony Brook University's Simons Fellows, and the Museum of Mathematics' Math Encounters series. In these forums young people, teachers and seasoned researchers come together to share their knowledge and, most importantly, their curiosity and joy in pursuing mathematics and science.

Expanding this outreach further, we are delighted to contribute to outstanding efforts that provide the general public with access to high-quality educational programing. The doors to the Museum of Mathematics will soon open, and it will be the first museum of its kind in the United States. The World Science Festival, which brings laypeople together with eminent scientific scholars, continues to grow and foster the natural curiosity we all harbor for a more fundamental understanding of the world around us.

Collaborative partnerships, networks and communities build upon each other and enable us to work together toward our common goals. Paul Erdős understood the power of such interactions, and by traveling from place to place, he managed to work with 511 coauthors. Still, he must have felt constrained living at a time before the internet took hold. He recounted his mother saying to him, "Even you, Paul, can be in only one place at one time." Erdős continued his peregrinations throughout his lifetime, remaining inspired and optimistic about his next meetings. Pondering his mortality, Erdős reportedly mused, "Maybe, once I've left, I'll be able to be in many places at the same time. Maybe then I'll be able to collaborate with Archimedes and Euclid."



# 07

## ENCOURAGING CONNECTIONS

*Topology of cell death*

Shown here, two HeLa cells, derived from cervical cancer, have been triggered for cell death by an extracellular soluble CD95 death ligand. As soon as the CD95 death receptor is stimulated, cells start the process of apoptosis. Typically cells die within a few hours depending on the strength of cell death induction. As the cells die, they become rounder, while still keeping membrane contacts on the substrate.

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# COLLABORATION GRANTS

simonsfoundation.org/mathematics-physical-sciences

“Being face to face, you discover mathematics you never would have via email or phone.”

Collaboration Grant recipients Purnaprajna Bangere and Margaret Readdy.

In the fall of 2010, 141 mathematicians from San Diego to Staten Island were awarded the foundation's first round of Collaboration Grants for Mathematicians. These grants boost the number of face-to-face collaborations among researchers. Such encounters are vital to a productive "mathematical marketplace."

Purnaprajna Bangere of the University of Kansas works with collaborators as far away as Spain and his native India. Purna, an algebraic geometer, compares himself to a zoologist, stalking diverse and exotic species known as varieties. Varieties are solution sets for systems of polynomial equations, and a great deal of work in algebraic geometry has focused on the classification and taxonomy of varieties in higher dimensions. What qualities might define a new classification? How populous is that species? Might we discover new species by positing other sets of topological invariants, the qualities that make varieties unique?

The current classification of varieties, Purna says, "is like the taxonomic division of vertebrates into categories like fish, reptiles and mammals, but still being able to distinguish mammals as different as whales and bats." This largely undifferentiated majority, called 'varieties of general type,' are of great interest — for example in string theory. Yet their structure and complexity have resisted the efforts of algebraic geometers to categorize or understand them properly.

With F.J. Gallego and Miguel González of the Universidad Complutense de Madrid, Purna has discovered new and esoteric species among surfaces of general type, and has mapped their population densities. The process has yielded fascinatingly counterintuitive results: even relatively primitive families of surfaces of general type exhibit nearly all the complexities of related but more advanced species. The collaborators also recently proved a theorem regarding geometric properties of the string-theory structure known as the Calabi–Yau threefold, solving a conjecture that stood for 14 years.

Combinatorialist Margaret Readdy of the University of Kentucky, whose work brings together algebra, geometry, topology and analysis, values the freedom the Collaboration Grant gives her to work with a wide range of colleagues, such as Richard Stanley at the Massachusetts Institute of Technology, Mark Goresky and Robert MacPherson at the Institute for Advanced Study, Louis Billera at Cornell University and Dennis Stanton at University of Minnesota.

One of Readdy's first papers (written with her husband, mathematician Richard Ehrenborg) analyzed ball-throwing sequences for a one-handed juggler, and she brings that same exuberance to her study of the face structure of polytopes. Triangles, squares and other two-dimensional polytopes are trivial; face structures of three-dimensional polytopes were fully characterized by Ernst Steinitz in 1900. But four-dimensional polytopes are "completely open," Readdy says. "We really don't know anything."

Solution spaces to real-world problems frequently take the form of polytopes. How do physicists understand particle interactions? How might an entrepreneur maximize profit for a given venture within a range of different market constraints? The topic often generates interesting angles on theoretical problems from other fields, as well.

"Being face to face, you discover mathematics you never would have via email or phone," Readdy says. At a recent talk she gave at Cornell, she recounts, "the room was packed with people from different areas of math, because they know I'll talk about something new and interdisciplinary. Travel and collaboration benefit many people on many levels."

09

# MATH + X GRANTS

simonsfoundation.org/
mathematics-
physical-sciences

> "The Simons grant will allow us to take inter-disciplinary collaboration to another level, using mathematical expertise in directly applicable ways."

Emmanuel Candès and François Baccelli will hold the first Math+X chairs.

Stanford University and the University of Texas at Austin became the first two recipients of the Simons Foundation's Math+X Grant. The program is designed to encourage novel collaborations between mathematics and other fields in science or engineering by creating new chairs at universities, joining mathematics departments with chosen partner departments.

Stanford's Simons Chair in Mathematics and Statistics was endowed this year, together with matching funds from the William and Flora Hewlett Foundation. The first holder is Emmanuel Candès, whose work with compressed sensing reinvented the mathematics of very large data sets. Compressed sensing allows reconstruction of accurate information from relatively sparse samples, with potential applications in fields ranging from astronomy to communications, to medicine and the military. Candès' discoveries earned him the National Science Foundation's Alan T. Waterman Award.

"We actually billed this as 'Math+X+Y+Z' in our proposal," says Steve Kerckhoff, mathematics chair at Stanford. "We already have joint math-and-statistics appointments, and several faculty are members of Stanford's interdisciplinary Institute for Computational and Mathematical Engineering. What we needed was a network of mathematically-oriented people in other departments: electrical engineering, computer science, theoretical and applied physics, even some biology and medicine. The Simons grant will allow us to take inter-disciplinary collaboration to another level, using mathematical expertise in directly applicable ways."

"A lot of interaction between mathematics and other fields these days is concerned with trying to utilize huge amounts of existing data, creating algorithms for signal processing, pattern recognition, sparse matrix representations, and stability of information," Kerckhoff says. "The hope here is to develop a group of people who know other fields well enough to affect the way data is presented from the outset, including the way instrumentation — chips, scanners, microscopes — is actually designed, so the resulting data may be utilized more quickly and effectively."

The University of Texas at Austin's proposal for a Simons Chair in Mathematics and Electrical and Computer Engineering focused on network science and information theory. Networks are fueling a wealth of basic research, as scientists seek governing principles common to a wide array of network applications, from communications to biology and the social sciences. "I think we're just at a nascent stage of understanding these networks," says mathematics department chair Alan Reid, "and that there are exciting theoretical and practical developments ahead."

Foundation support with matching funds from the University of Texas will support chair François Baccelli, a member of the French Academy of Sciences. Baccelli formed and led the research group on communication networks at the École Normale Supérieure (ENS) in Paris and later became director of computer science research. He is resident "network wizard" at the French National Institute for Research in Computer Science and Control (Institut National de Recherche en Informatique et en Automatique, INRIA). He heads TREC, a joint research team between INRIA and the ENS, investigating the modeling and control of communication networks.

"Baccelli is the right glue to hold the two sides together," says Reid, "a mathematician by training with a track record of research in electrical and computer engineering. As director of a research institute on network theory, he's had experience building up the kind of program we envision: leading a group that will be scientifically active and important; fostering new scientific discoveries, new and interesting mathematics, and maybe further connection to industry; and putting in place a structure for educating and training new generations of scientists."

# SIMONS CENTER FOR GEOMETRY AND PHYSICS

scgp.stonybrook.edu

“Collaboration between mathematicians and physicists is our raison d’être,” says John Morgan, the center’s director.

Kevin Williamson and Frances Chiaverini in BARKIN/SELISSEN PROJECT’s *Differential Cohomology: Dance of the Diagram*, performed in January 2011 at the Staller Center for the Arts for the SCGP workshop, “Differential Cohomology and Twisted K-Theory.” Photo by Christopher Duggan.

This year marked the first year of full programming at the Simons Center for Geometry and Physics at Stony Brook University. Inaugurated in November 2010, the center is a figurative — and literal — bridge between the university’s mathematics and physics departments.

The center was charged with a simple mission: to help mathematicians and physicists learn to speak each other’s languages.

“Collaboration between mathematicians and physicists is our raison d’être,” says John Morgan, the center’s director. “Over the past 40 years mathematics, inspired by thoughts coming out of physics, completely reinvigorated the interactions between algebraic topology, geometry and theoretical physics,” Morgan says. “Ideas from quantum field theory have frequently led to incredibly deep, powerful, but in many cases still inaccessible conjectures.”

The center’s approach was epitomized by its two programs this spring. Algebraic Topology with Applications to Physics concerns an area of mathematics, algebraic topology, that sheds light on a wide variety of geometric questions asked during the 1960s and early 1970s. “But then the interplay between algebraic topology and geometry sort of stopped, and it wasn’t clear how continuing developments in algebraic topology were related to geometry,” Morgan says. “So the two fields, once so close, were separated.” In recent years, however, physicists have realized that algebraic topology lies at the heart of a phenomenon in quantum field theory called mirror symmetry.

The other program, String Compactification, deals with string theory, whose fundamental premise is that space-time has not four dimensions but ten, the other six of which are wound up so tightly that we can’t detect them. The geometry and topology of these hidden dimensions “has a crucial impact on the physics of the dimensions you can see,” Morgan says.“There’s a beautiful interplay between what you can establish mathematically and what it would say about the physics.”

The center held 11 workshops in 2011, and an array of seminars, including a postdoc seminar that alternates between mathematics and physics speakers. The number of programs at the center will be ratcheted up to four per year; upcoming programs will deal with topics such as quantum computing, topological phases of matter, and random processes.

At any given time, the center hosts about 35 people, including permanent members, visitors and 12 three-year postdoctoral fellows. Visitors typically come for at least a month, so their ideas have time to percolate.

The center has even formed a postdoc exchange program with the Kavli Institute for Theoretical Physics in Santa Barbara, California, in which postdocs from each institution can visit the other institution for three weeks. The center has a more informal arrangement with the Beijing International Center for Mathematical Research, and is developing partnerships with other institutes.

While the center’s focus is mathematics and physics, it welcomes cross-pollination with other sciences and the arts. In 2011, it launched an ongoing mini-course on computational neuroscience and features concerts, play readings and art exhibits. It even commissioned a ballet, “Differential Cohomology,” inspired by a 2010 lecture Jim Simons gave at Stony Brook. Choreographed by Kyla Barkin and Aaron Selisson, the ballet had its premiere at the center in January 2011.

# LIFE SCIENCES AT STONY BROOK



The gift has given the hiring process an immediate boost, providing funds for an eventual 35 endowed professorships to attract star researchers to the university.

James Simons and Marilyn Simons, Stony Brook, New York, 2011.

In 1968, Stony Brook University handed Jim Simons a golden opportunity: chairmanship of its mathematics department, together with a mandate to build up the department by hiring stellar new faculty members. Today, the Simons Foundation is extending a similar opportunity to the university's current department chairs, in the form of a $50 million matching challenge grant to fund endowed professorships and graduate fellowships across academic disciplines.

Stony Brook University president Samuel L. Stanley Jr., M.D., announced the gift on December 14, 2012, alongside a personal gift of $100 million to the university from Jim and Marilyn Simons. Combined, these form the largest gift in the history of Stony Brook University, and represent "a transformational moment" in the institution's history, says Stanley.

"Marilyn and I owe a great deal to Stony Brook," says Jim Simons, chairman of the board of the Simons Foundation.

Stony Brook University was launched only 54 years ago to create a flagship university for the State University of New York system. Since then, it has developed into a world-class research university. At the same time, its faculty-student ratio lags behind those of its 60 peer institutions in the prestigious Association of American Universities. It is estimated that Stony Brook would have to hire more than 200 new faculty members to bridge this gap.

While achieving this goal will take time, the Simons Foundation gift has given the process an immediate boost, providing funds for an eventual 35 endowed professorships to attract star researchers to the university. The gift also provides for 40 graduate fellowships.

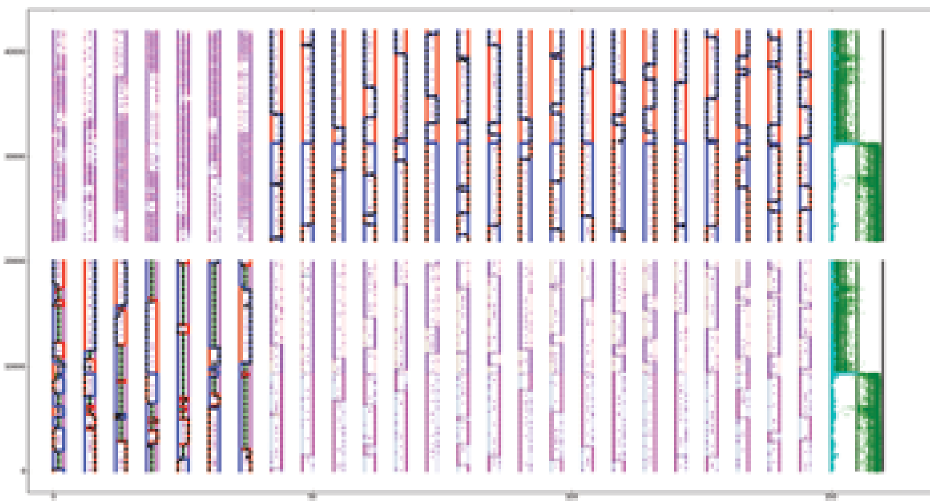
The first $25 million of the gift has been committed outright, and the remainder is to be paid in installments as Stony Brook achieves various fundraising milestones to meet the matching challenge. Dr. Stanley has kicked off fundraising efforts by committing to a six-figure donation from him and his wife, Dr. Ellen Li, to provide scholarships for economically disadvantaged students.

The Simons Foundation grant "is inspiring many in the Stony Brook community to join together in fulfilling our potential to be among the greatest public research universities in the country, a place where unparalleled heights in research, education and discovery are reached," Dr. Stanley says.

# SUPPORT FOR SYSTEMS BIOLOGY

simonsfoundation.org/
life-sciences

The exponential upsurge in available data permits a new model — and level — of inquiry, shifting biology from a primarily descriptive science to a more analytical one.



Simulation of the output of a computational algorithm to distinguish the maternal and paternal contributions to an individual's genome, by researchers at the Simons Center for Quantitative Biology at Cold Spring Harbor Laboratory.

A dozen or so years ago, for a change of pace, Jim Simons invited his friend, biologist Michael Wigler, to give a lecture about big unsolved problems in biology to the mathematicians and statisticians at Renaissance Technologies, the hedge fund management company Simons founded in 1982. Yet as Wigler spoke on topics from genome sequence analysis to cellular signaling, Simons realized that these subjects weren't in fact such a departure from the kinds of problems tackled daily at Renaissance Technologies.

"I remember thinking, 'If the guys in this building dropped everything and worked on these problems, they'd make great progress,'" Simons recounts. The questions Wigler was trying to answer "just called out for" the kinds of methods that were the natural currency at Renaissance, he says.

Simons' epiphany, along with similar ones by other scientists around that time, heralded the dawn of a new field of biology known as quantitative biology, or systems biology, depending on whom you ask. As researchers have begun to explore what quantitative methods have to offer biology, Simons is keeping alive his early vision of the field's promise: over the past seven years, the Simons Foundation has invested heavily in quantitative biology research, creating two centers devoted to its study and fostering ambitious collaborations between top research institutions in biology and mathematics.

Biology has had a quantitative side for many decades. But in the last 10 to 15 years, quantitative methods have begun migrating to center stage as advances in areas such as imaging and high-throughput genetic sequencing have produced a deluge of data, of an order of magnitude previously unheard of by biologists.

"There's so much data coming in now that we don't even have the ability to store it," says Arnold Levine, director of the Simons Center for Systems Biology at the Institute for Advanced Study in Princeton. "Analyzing the kind of data we've been getting in the last decade requires a very different way of doing science than in the previous 40 years, when you might discover one gene at a time, or one protein."

The exponential upsurge in available data permits a new model — and level — of inquiry, shifting biology from a primarily descriptive science to a more analytical one. Just as condensed matter physicists figured out in the 19th century how to segue from an understanding of the individual interactions of water molecules to a description of the large-scale flow of water, systems biologists face the challenge of translating massive amounts of data at the level of molecules or genes into an understanding of complex behavior on the scale of cells, individuals or even populations.

"We can now describe at the molecular level, for example, how two neurons in the brain interact through a synapse, but that's still several layers below the layer of thinking, memory and love," says Stanislas Leibler, a professor at the Institute for Advanced Study. "The ultimate goal of systems biology is to find a language for these kinds of collective phenomena."

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The foundation's support of systems biology research began formally in 2005 with the creation of the Simons Center for Systems Biology at the Institute for Advanced Study (IAS), legendary for its strength in mathematics and physics. Levine had joined the faculty of IAS a few years earlier as its first-ever experimental biologist, with a mandate from IAS and the Simons Foundation to create a systems biology center. Before Levine's arrival, IAS mathematicians had considered some theoretical biology questions, but without an experimental biologist to guide them, "they didn't get much traction," Simons says.

Arriving at IAS, Levine found a cadre of mathematicians, physicists and computer scientists eager to sink their teeth into substantial biological problems. Together the center's researchers have since tackled a wide range of topics, from the genetics of the HIV and H1N1 viruses to the metabolic pathways of the Masai, an ethnic group in Kenya and Tanzania. And while IAS is a very small place — its entire permanent faculty typically numbers 25–30 people — a constant influx of visitors and long-term members has enabled the systems biology center to extend its reach far beyond the institute's walls. "We've trained maybe 30 people here over the last decade who are now at universities and biotech companies across the country," Levine says.

In 2008, the Simons Foundation expanded its quantitative biology commitments to include the establishment of a partnership between IAS and The Rockefeller University in New York City, and the creation of the Simons Center for Quantitative Biology at Cold Spring Harbor Laboratory, in Cold Spring Harbor, New York.

IAS and Rockefeller offer complementary strengths: IAS has an almost unparalleled history in mathematics and theoretical physics, while Rockefeller, the country's first institution devoted entirely to biomedical research, places its focus squarely on experimental biology. The two institutions now share joint visiting professors and graduate and postdoctoral fellows, Thursday morning coffee sessions, and an annual symposium whose stated goal is to evoke "undisciplined conversation."

Leibler, who holds joint appointments at Rockefeller and IAS, appreciates the opportunity to slow down and take the long view when at IAS.

"Maybe because it doesn't have labs, the institute is one of the rare places where you can step back a bit and think about where biology is going in the long term," he says.

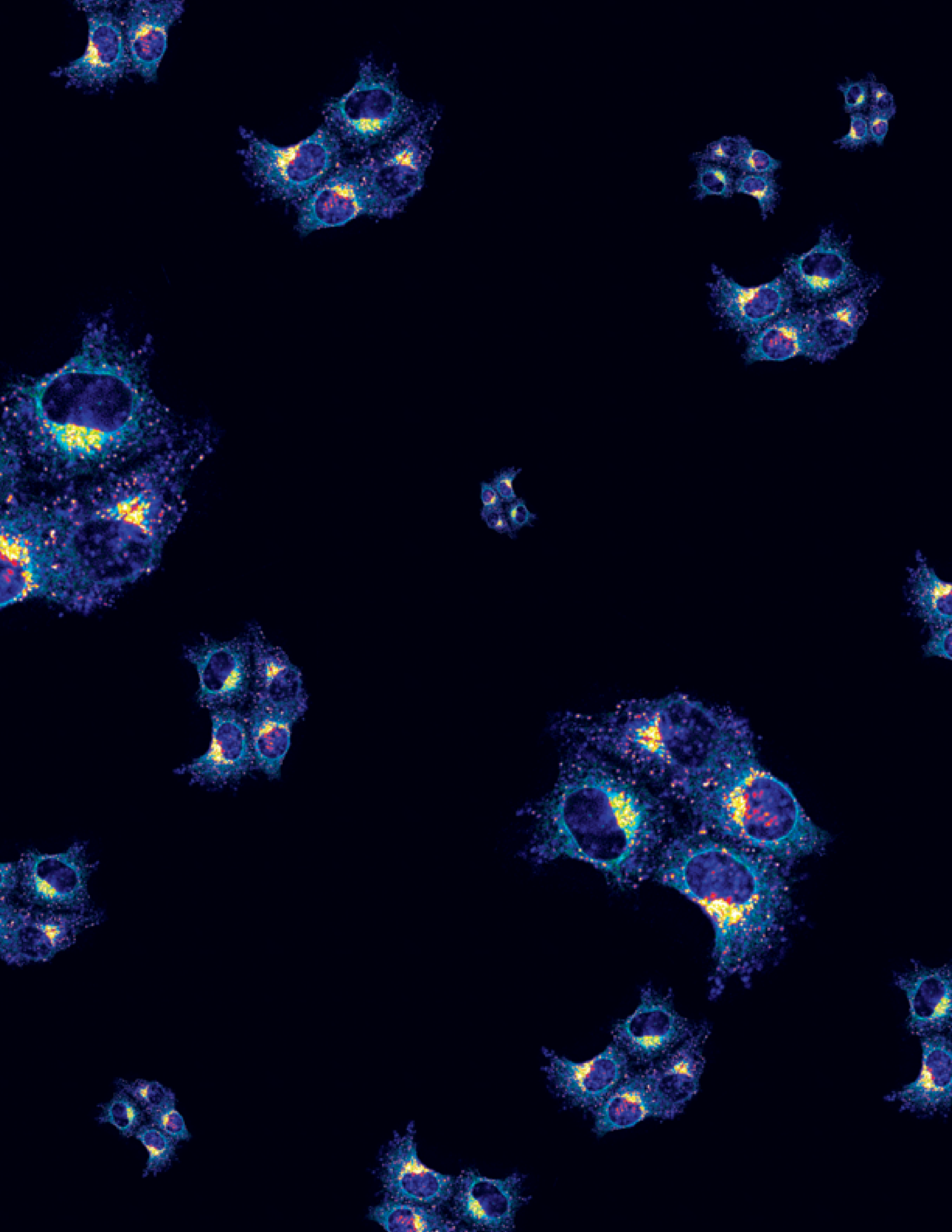
***

Cold Spring Harbor Laboratory, meanwhile, was already an established strength in quantitative biology when the Simons Foundation created the center there: several faculty members, including Wigler, were actively pursuing quantitative biology research. But the center's creation has assisted that laboratory in growing into an even greater quantitative biology powerhouse. The center has nine faculty members as of March 2012, and plans to grow to 12 to 13 faculty, and to about 50 total individuals, including postdocs and other researchers. The goal is to build up a dynamic group trained not only in genetics and neuroscience, but also mathematics and physics.

One recent focus at the center has been the use of machine-learning techniques to search for genomic markers that could indicate a particular cancer patient's prognosis, and which treatments would be most effective. In recent work, for example, the researchers have been looking for markers that suggest which breast cancer patients are most likely to benefit from particular treatments. "These approaches will have a profound medical impact," Wigler says.

While these particular studies have clear practical implications, researchers at the two Simons centers are not under particular pressure to produce work with immediate practical application. After all, observes Simons, when IAS was created in 1930, its founders didn't tell Einstein which equations to solve. Likewise, he says, the Simons Foundation doesn't have a specific goal in mind in supporting the two quantitative biology centers.

"We are happy to see efforts at the most basic level," Simons says."It's not that we don't expect applications, but we just don't know what they will be yet."



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## ENABLING RESEARCH NETWORKS

*Spatial organization of death receptors*

Imaged here are HeLa cells; the dotted patterns show the fluorescently tagged ligand for the receptor CD95, the molecule CD95L, which triggers apoptosis in target cells. While the CD95 receptor is present in most cells of our body, the CD95 ligand is expressed only in specialized cells and kept trapped inside these cells until they are required to kill target cells.

# SIMONS SIMPLEX COLLECTION

sfari.org/sfari-initiatives/
simons-simplex-collection


On 21 October 2011, more than 100 investigators and clinicians who worked together on the Simons Simplex Collection gathered in New York City to celebrate this achievement in autism research. Between 2006 and 2011, teams working out of 13 university clinics across North America painstakingly amassed a wealth of high-quality genetic and phenotypic data, including biospecimens, from nearly 2,700 'simplex' families.

## SIMONS SIMPLEX COLLECTION

In 2011, SFARI finished recruiting families to participate in its Simons Simplex Collection (SSC), a major resource for researchers investigating the causes of autism and those developing educational and clinical interventions for individuals on the autism spectrum.

The foundation has now shifted from recruitment of these families to supporting their continued participation in future research studies.

Five years in the making, the now-complete collection stores biospecimens and genetic and phenotypic data from 2,644 'simplex' families. Simplex families have only one child with autism and unaffected parents. The collection is by far the world's largest repository of data from simplex families.

The Simons Foundation is grateful to the families who generously provided their data and time for the collection, as well as to the clinical staff and the research teams at the 13 sites that collected the data.

# SSC@IAN

iancommunity.org/cs/
simons_simplex_community/


## SSC@IAN

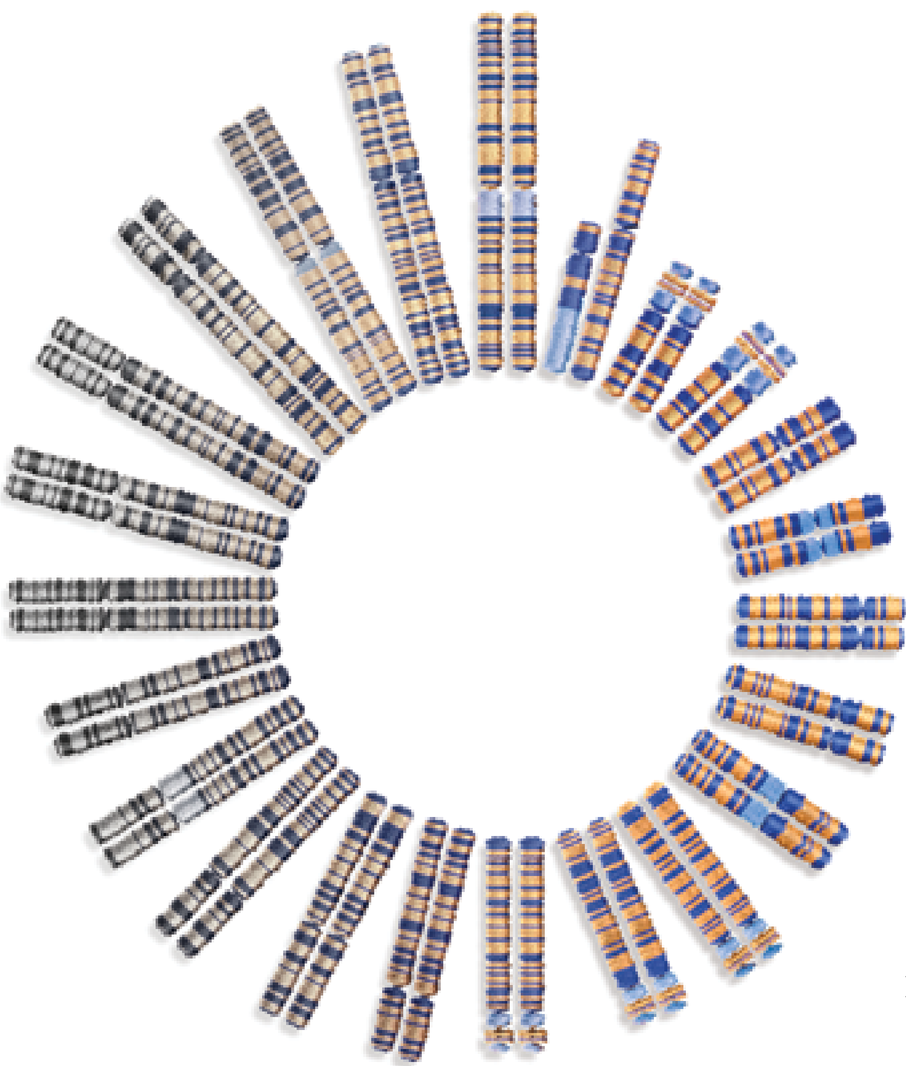
The Simons Foundation and the SSC's test sites are now working to maintain contact with families to help ensure their participation in future research studies.

A collaboration with the Interactive Autism Network (IAN) was established to support an online registry of the SSC's families. Each family member has also been assigned a Global Unique Identifier (GUID), which allows researchers to enroll the participant in future studies without any risk of duplication or overlap.

For more information on the SSC@IAN, please visit iancommunity.org/cs/simons_simplex_community/.

**STATISTICS:**

# *Simons Simplex Collection Use to Date*



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Researchers Using SSC Resources

155

Projects Using SSC Resources

200

Requests for Phenotypic Data

42

Requests for Genetic Data

8

Requests to Recontact SSC Families for New Research Projects

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# SIMONS VARIATION IN INDIVIDUALS PROJECT

sfari.org/sfari-initiatives/simons-vip

Autism researchers started wondering: what insights might emerge from studying a collection of individuals whose cases of autism all had the same genetic cause?

Simons VIP participant, age 4, is excited to see 'pictures of her brain' from a structural MRI scan at the University of Washington, one of three testing sites for the project.

A thorny problem greets researchers studying people with autism: the genetics of autism are so heterogeneous that each individual in a research study is likely to have a different genetic cause of his or her disorder. This diversity can make it hard to pry out useful information about, for example, whether a given treatment is effective.

"Autism is not a single disease," says Wendy Chung of Columbia University. "You might have a drug that would be effective for kids with a particular genetic form of autism, but if you tried to do a clinical trial, statistically you would never recognize the subset that responds to the treatment."

About three years ago, autism researchers started wondering: what insights might emerge from studying a collection of individuals whose cases of autism all had the same genetic cause?

Out of this question was born the Simons Variation in Individuals Project (Simons VIP), a multi-site collaboration that began in September 2010, led by Simons Foundation Autism Research Initiative deputy scientific director John Spiro together with Chung and funded by the Simons Foundation. The project's first goal is to collect clinical and biological data from children with a deletion or duplication of the 16p11.2 segment of the genome, which has been associated with autism and other various neuropsychiatric disorders. Among individuals with autism, 16p11.2 deletions or duplications are relatively common, appearing in about one percent of individuals with autism.

Families participating in the study begin by interfacing with genetic counselors at Emory University in Atlanta, and then flying to one of three clinical sites — Baylor College of Medicine in Houston, the University of Washington in Seattle or Children's Hospital Boston — where the entire family undergoes a battery of psychological and medical tests, along with the collection of biospecimens and a structural MRI. Some families continue on for functional brain imaging (fMRI or MEG) studies at the University of California, San Francisco, or at Children's Hospital of Philadelphia. So far, the sites have tested about 100 carriers of 16p11.2 mutations and their families, and the project is on track to complete its goal of testing 200 carriers by approximately the end of 2012.

Coordinating such a large project, which involves nearly 100 clinicians, psychologists, statisticians and other professionals, has required communication at every level, says Jennifer Tjernagel of the Simons Foundation, the study's project manager. The six sites have frequent email and phone discussions to identify common issues and provide smooth transitions for the families as they move through the phases of the project. Meanwhile, the Simons Foundation acts as 'central command,' laying out detailed protocols to ensure consistency.

"We're paying exquisite attention to how the data is collected," says Spiro.

In studies of rare disorders, recruitment is often a roadblock. The Simons VIP has sidestepped this obstacle by harnessing the power of online networking: it has created an online community, Simons VIP Connect, for families of 16p11.2 carriers. While families can join the site without joining the study, many families have come to the study through the online community.

Families in the study have benefited from information about their individual children that the study's tests generate. The families have also returned the favor by educating researchers about unexpected issues.

"Building the family community has really informed the researchers about the issues these families struggle with," Tjernagel says. "Sometimes they were things that initially hadn't been on our radar to look into closely."

# SFARI: RECENT ADVANCES



Evidence is mounting that autism has hundreds of different genetic causes. Yet the biological pathways these genes contribute to are likely to be much fewer in number.

SFARI Investigators at the SFARI annual meeting in Washington, D.C.

SFARI Investigators carry out a wide range of research studies, from identifying new autism candidate genes and examining mouse models of autism to comparing how autism diagnoses are made in different clinics. Once a year, these researchers come together to share new findings and ideas, and form new collaborations. In these pages, the Simons Foundation is pleased to present some highlights of the past year's research by SFARI Investigators.

## SPONTANEOUS MUTATIONS

A pair of studies published 9 June, 2011 in *Neuron* offer definitive evidence that rare, spontaneous mutations underlie many cases of autism[1,2].

The two independent studies — led respectively by SFARI Investigators Matthew State of Yale University and Michael Wigler of Cold Spring Harbor Laboratory in New York — examined genetic data from more than 1,000 families belonging to the Simons Simplex Collection, a database of clinical and genetic information from families that have one child with autism and unaffected parents and siblings.

The teams found that children with autism were four times more likely than their unaffected siblings to have spontaneous, non-inherited mutations called copy number variations (CNVs), in which a portion of DNA is duplicated or deleted. The CNVs in the children with autism tended to be longer and contained more genes than those of their siblings.

The researchers uncovered about 75 CNVs that may be implicated in autism. While most of these mutations appeared in just one child with autism, 11 children had mutations in a region called 16p11.2, highlighting the region's importance in autism.

Intriguingly, four children had extra copies of a region called 7q11.23, which, when missing, causes Williams syndrome, characterized by a hypersocial disposition. The region could be a Rosetta Stone for studying social brain circuitry, State says.

## PROPOSED ANGELMAN THERAPY

A cancer drug called topotecan shows promise as a treatment for Angelman syndrome, a disorder related to autism, researchers reported 21 December, 2011 in *Nature*[3]. In work supported by the Simons Foundation, the researchers found that topotecan turns on a silent copy of the Angelman syndrome gene UBE3A, which regulates the rate at which certain brain proteins get broken down.

UBE3A is an example of an 'imprinted' gene: Only the version inherited from the mother is normally functional. When that maternal copy is missing or broken, the result is Angelman syndrome, characterized by seizures and difficulties with language and sensory processing.

The researchers, led by SFARI Investigator Benjamin Philpot of the University of North Carolina, Chapel Hill, examined mice whose maternal copy of

UBE3A had been deleted, and bathed the mice's neurons in a series of more than 2,000 compounds. Low concentrations of topotecan activated the paternal copy of UBE3A, they found.

## MAPPING THE INTERACTOME

Evidence is mounting that autism has hundreds of different genetic causes. Yet the biological pathways these genes contribute to are likely to be much fewer in number. A new map of portions of the autism 'interactome' — the network of proteins involved in the disorder — has taken a key step toward identifying these pathways by uncovering hundreds of new interactions among proteins encoded by autism genes, researchers reported 8 June, 2011 in *Science Translational Medicine*[4].

The researchers, headed by SFARI Investigator Huda Zoghbi of Baylor College of Medicine in Houston, started by examining proteins linked to autism-related genetic syndromes such as fragile X and Rett syndromes. Next, the team 'fished' for proteins that interact with these proteins, mapping out a network of 539 proteins.

The network turned up connections among seemingly unrelated genes. For example, the researchers found that the genes behind two different autism syndromes — Phelan-McDermid syndrome and tuberous sclerosis — interact with at least 21 shared protein partners involved in the functioning of synapses, the junctions between neurons.

Understanding the pathways in which autism-related proteins interact may ultimately offer a more efficient path toward developing treatments than focusing on one genetic disorder at a time, Zoghbi says.

## MOUSE MODEL

A new mouse model of autism has turned the spotlight on a brain region that has not previously received a lot of attention from autism researchers: the striatum, which is involved in planning, movement and rewards. Mice carrying a deletion in the autism candidate gene SHANK3 lack several synaptic proteins and have unusually long, thorny neuronal branches in the striatum, reported a research team headed by SFARI Investigator Guoping Feng of the Massachusetts Institute of Technology. The findings were published 28 April, 2011 in *Nature*[5].

The mice are severely impaired, displaying autism-like symptoms, such as problems with social interactions and obsessive grooming. People with mutations in SHANK3 typically have Phelan-McDermid syndrome, which causes severe intellectual disability and language delays, among other symptoms.

The study compared two different types of mutants with disruptions in different parts of the SHANK3 gene. The mutants with the more damaging of the two disruptions were more severely affected. People with autism likewise carry different kinds of mutations in SHANK3; the new study may help to shed light on why their symptoms vary.

And the study suggests that researchers should consider the possible role of the striatum in autism. Many studies have focused on the hippocampus, a region involved in learning. Some imaging studies, however, have found that children with autism have unusually low activity in the striatum, which, like the hippocampus, is involved in much of the brain's higher processing.

## DIAGNOSES, RE-EVALUATED

The particular autism spectrum disorder with which a child is diagnosed may depend in large degree on the clinician making the diagnosis, a new study suggests. Published online 7 November, 2011 in the *Archives of General Psychiatry*, the study details huge inconsistencies across different clinics in the criteria for diagnosing classic autism, Asperger syndrome, and pervasive developmental disorder-not otherwise specified (PDD-NOS)[6].

The research team, headed by SFARI Investigator Catherine Lord, director of the Institute for Brain Development at New York-Presbyterian Hospital, examined diagnoses at 12 medical centers that had participated in data-gathering for the Simons Simplex Collection. Even though the sites all used the same 'gold standard' diagnostic tests, the different sites varied widely in their diagnoses.

For example, two sites diagnosed less than 40 percent of the children with classic autism, while another site gave that diagnosis to every child. And one site diagnosed all children with an intelligence quotient score above 115 with either Asperger syndrome or PDD-NOS, while another site put the cutoff score at 70.

Rather than assigning one of the three labels to a child, Lord says, it might be more useful for clinicians simply to describe the various dimensions of the particular child's disorder.

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1: Sanders S.J. *et al. Neuron* **70**, 863-885 (2011)

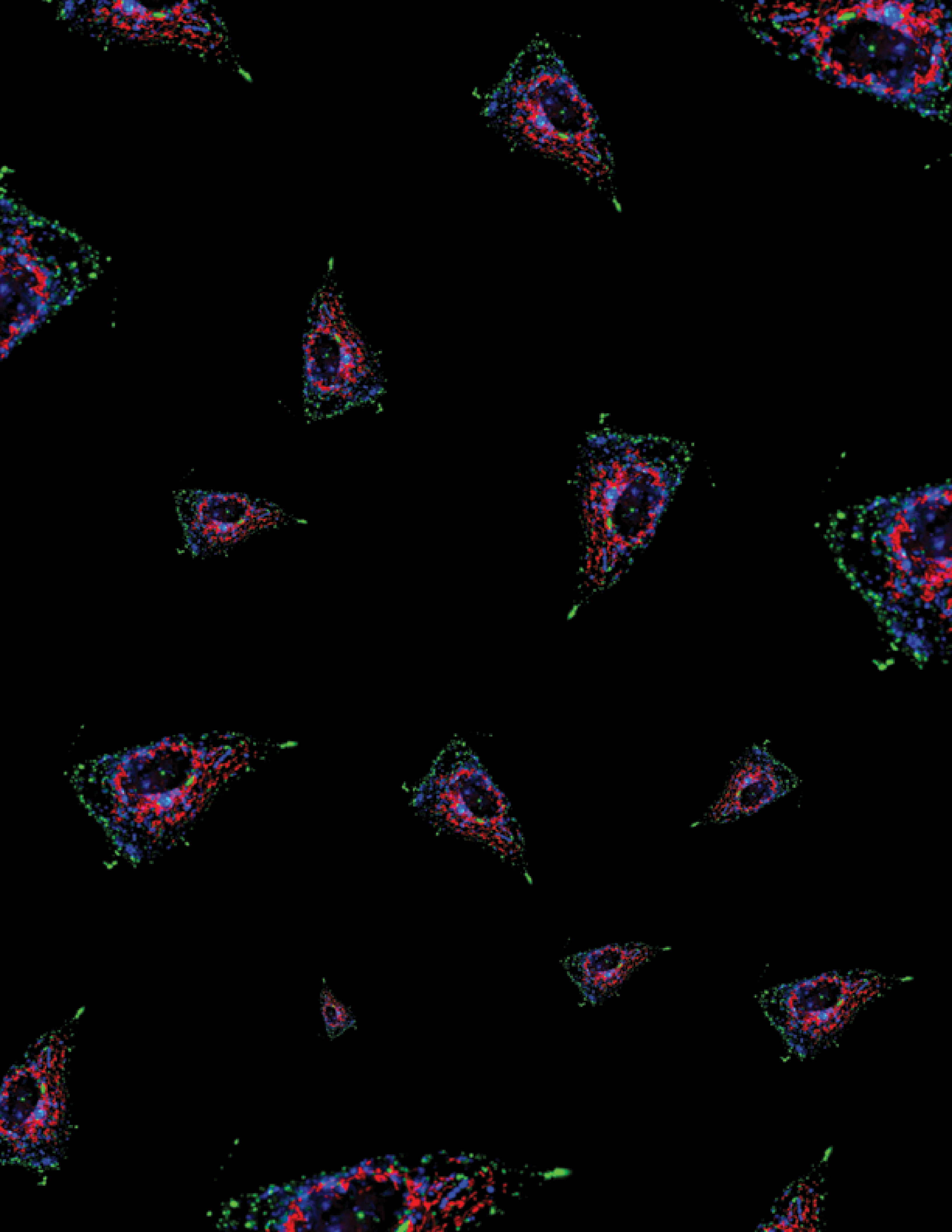
2: Levy D. *et al. Neuron* **70**, 886-897 (2011)

3: Huang H.S. et al. *Nature* **481**, 185-189 (2011)

4: Sakai Y. *et al. Sci. Transl. Med.* **3**, 86ra49 (2011)

5: Peça J. *et al. Nature* **472**, 437-442 (2011)

6: Lord C. *et al. Arch. Gen. Psychiatry* **69**, 306-313 (2012)



# 23

## BUILDING DIGITAL RESOURCES

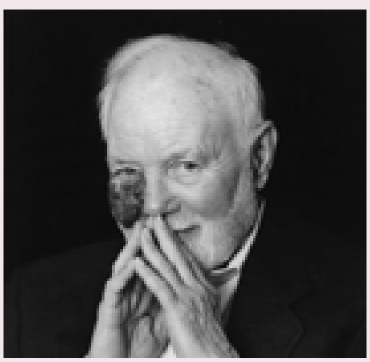
*Power plants and transport containers*

In this breast cancer cell, fluorescence microscopy reveals three important cellular structures: mitochondria (red), early endosomes (green), and late endosomes/lysosomes (blue). Mitochondria are membrane-enclosed organelles that have a diameter of a few hundred nanometers, and lengths of up to several microns. Mitochondria are considered the cellular power plants since they produce most of the ATP that is used as a source of chemical energy, but they are also involved in a number of other essential cellular processes, such as cell death and the control of cell cycle and growth. Endosomes are membrane-bound compartments that underlie intracellular membrane trafficking. Early endosomes regulate receptor sensing of extracellular cues. Late endosomes are sites of intracellular degradation (i.e., lysosomes) and essential components of signal transduction and metabolic pathways.

# SCIENCE LIVES

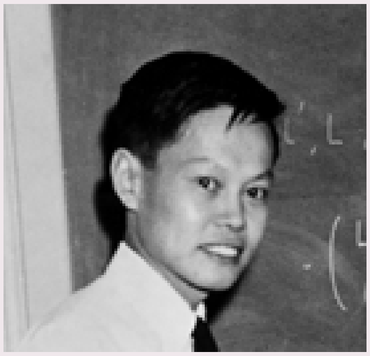
simonsfoundation.org/mathematics-physical-sciences

This year, the Simons Foundation launched its Science Lives project, a series of extended interviews with some of the giants of twentieth century mathematics and science. This collection, organized in collaboration with Hugo Rossi of the University of Utah, is meant to provide scientists, historians and students the opportunity to see and hear these great men and women discuss their lives and their thinking both about their science and about our world.



ISADORE SINGER ON COLLABORATING WITH D. B. RAY *circa* 1970:

"The Ray-Singer collaboration came about because his office was next to mine, and I walked in one day, and he was computing … ratios and determinants, and I said, 'Well that's a very fancy computation; you're trying to get it by such and such methods. It seems to me if this torsion is independent of the metric, one ought to be able to prove that on general grounds and not by computational methods.' D. B. Ray was a brilliant mathematician, really brilliant. I enjoyed his company very much, and that started our collaboration. We ended up showing that you could describe this topological invariant in terms of analysis in determinants … that was rather revolutionary to try and do. And I must say that some very prominent mathematicians of an older generation who had tried to get some geometric insight into that came and congratulated us on doing it by such novel methods. Do I feel that it is inspiration that I'm talking about here? Yes, I'm always exploring; that's quite right. 'I'm always exploring' is a good metaphor. I think of this vast forest, and I think if I could only just start a path in such and such a direction…. And I'm quite happy when it turns out that that path turns in to a highway that's really remarkable, but that's fast…."



CHEN-NING YANG ON THE CHINESE AND AMERICAN EDUCATION SYSTEMS:

"In China I would say the majority of the parents say that the Chinese educational system is no good. Because they say, 'Look, my kids have no free time; look at the American kids: the American kids have all kinds of free time to do this and do that, and our system would create people who only know books and know nothing else.' But in America you have also this 'Tiger Mother' book, which evidently touched a nerve with American parents. So apparently there are two camps: one said that [author Amy Chua] is absolutely right, the other said that she's to be denounced (laughs)! I think what's happening is that there are two different philosophies of education, and in my opinion neither is perfect....

Actually, I believe what is going on is the following: I think the Chinese system is better for students let's say from [the 60th to the 90th percentile]. Why? Because you drill the students, [and] they are bright enough to learn. So after they graduate from school, they can do exercises, and they come to America and become the best students. Why? When I was teaching freshmen here in Stony Brook, most of the students cannot manipulate trigonometric functions. But when I taught freshmen in Tsinghua, that was not the problem; they had all been trained.... That is the reason why in all these international tests the American students perform near the bottom. But for somebody who is [in the 90th percentile or over], it's obvious that the American system is better. Why? Because the ... American system allows them to have more imagination, bolder ideas, and also with the American venture capital system, many of them could prosper. So you have safe jobs; you have all these people who create a wealth for the whole world. So it depends on the student which philosophy is better."

FRIEDRICH HIRZEBRUCH (1927–2012) ON LIVING IN GERMANY IN WORLD WAR II:

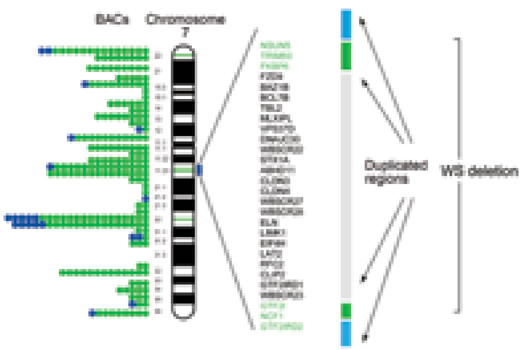
"I was living with my family in the city of Hamm, it was far north in the Ruhr district, and I went to a local *gymnasium* as we say — secondary school — where my father was even the director, teaching mathematics. But on March 22, 1943, I was fifteen, and I was drafted to the *Luftwaffenhelfer*, which means the anti-aircraft artillery helpers. And we were in a fire position of the local anti-aircraft and aircraft guns, of course. The teachers came to us [there], and we had German and history and mathematics and physics and Latin. We all joked that the enemy languages, English and French, were cut out. The whole school had one room for itself with beds, and there we did military training in the morning and school instruction in the afternoon.... Sometimes [there were] alarms in the night, but not many dangerous things happened, except once a [small bomb hit our] fire position, and I went to the hospital, but my friends had only had slight injuries....

Finally we were released of this service in the late fall of '43. We then waited for the drafting order to the *Arbeitsdienst* as it is called, 'working service,' digging trenches, doing all kinds of things; but in fact it was a pre-military education, and my drafting order was expected. Then, on December 5, the great, great attack on Hamm, my city, happened and the city was very much destroyed, including our house. My family was [already safe] in their refuge in a small town in the Sauerland called the Montagne area, and I was there too. [However, the day after the strike] my younger brother was still running around the destroyed house, and the mailman came and brought [my] draft order and my brother said, 'Well this family went away, they are completely bombed out, and I don't know their address.' So the mailman took the draft order away with him and wrote that he could not deliver it. *Ja*, this was the genius of my brother, I think, fourteen years old or so."

# SFARI GENE 2.0

gene.sfari.org

> "This distillation of all candidate genes to 30 'top suspects' should facilitate cross-fertilization between autism genetics and other approaches to understanding the disorder."




The above ideogram illustrates the region of chromosome 7q11.23 that when duplicated has been shown to confer increased risk for autism. This region is also commonly deleted in Williams syndrome, a rare genetic disorder typically characterized by a hypersocial personality. Image courtesy of Julie Korenberg, Ph.D., M.D., and Li Dai, Ph.D., of the University of Utah.

As high-throughput genetic scans identify hundreds, or even thousands, of possible autism genes, an ambitious effort spearheaded by the Simons Foundation is helping researchers bring some order to this flood of data.

In partnership with MindSpec, Inc., a nonprofit autism research organization, the Simons Foundation has developed SFARI Gene, a website and freely available database that provides detailed information on more than 300 autism candidate genes.

Launched in 2008 and aggressively expanded in 2011, SFARI Gene offers researchers annotated information on autism-relevant mouse models, protein interactions, and copy number variations (regions of DNA that are duplicated or deleted).

And, most recently, this resource now offers a 'score' for each candidate gene, indicating the strength of the evidence of its role in autism. This module was developed in collaboration with six independent geneticists from institutions across the country. Importantly, these researchers also created scoring rules to ensure consistent application in every case.

"As the number of genes and publications has increased, we realized that it would not be enough just to curate the data," says Sharmila Banerjee-Basu, director of MindSpec. "So we developed a collaborative initiative to help offer a perspective on which genes have the strongest evidence."

"I think the scoring process was pretty successful at identifying maybe 30 genes that have good evidence," says Dan Campbell of the University of Southern California, one of the six panelists.

"This distillation of all candidate genes to 30 'top suspects' should facilitate cross-fertilization between autism genetics and other approaches to understanding the disorder," Campbell says.

"If you want to generate a hypothesis about, say, the role of gene-environment interactions in autism, you have to identify a particular gene and a particular environmental factor to study," he says. "If you don't know which genes are worth looking at, it's hard to state a hypothesis."

At a recent meeting on gene-environment interactions, environmental autism researchers who were not experts in genetics told Campbell how delighted they were finally to have a short list of genes to focus on.

Another happy by-product of the scoring process is that the six researchers, all at the early stages of their careers, formed valuable connections with one another as they discussed scoring criteria over the phone and at workshops.

"The project was a great springboard for getting together junior investigators with similar goals but different backgrounds," Campbell says. "Several of them I had not met before, but now if I have a question, I'll shoot them an email. It has been very productive and will bring about more collaborations."

One of the project's main goals for the coming year is to figure out ways to integrate feedback from users themselves into the scoring process.

"We want to expand the collaboration to as broad a range of people working in autism as possible," says Alan Packer, associate director of research at the Simons Foundation.

# SFARI.ORG

sfari.org

## SFARI.org's redesign includes expanded expert commentary on a range of topics, as well as an interactive forum and wiki.

SFARI.org team clockwise from left: Emily Singer, Peggy Kaplin, Jessica Wright, Apoorva Mandavilli (executive editor and director) and Lydia Jung.

SFARI.org, the central resource of the Simons Foundation's autism research initiative, relaunched in September 2011 with a sleek new design and features to boost SFARI's mission of advancing autism research. The goal of the upgrade was to increase collaboration within the SFARI research community, a diverse group of geneticists, neurobiologists, molecular biologists and other researchers whose work is relevant to autism.

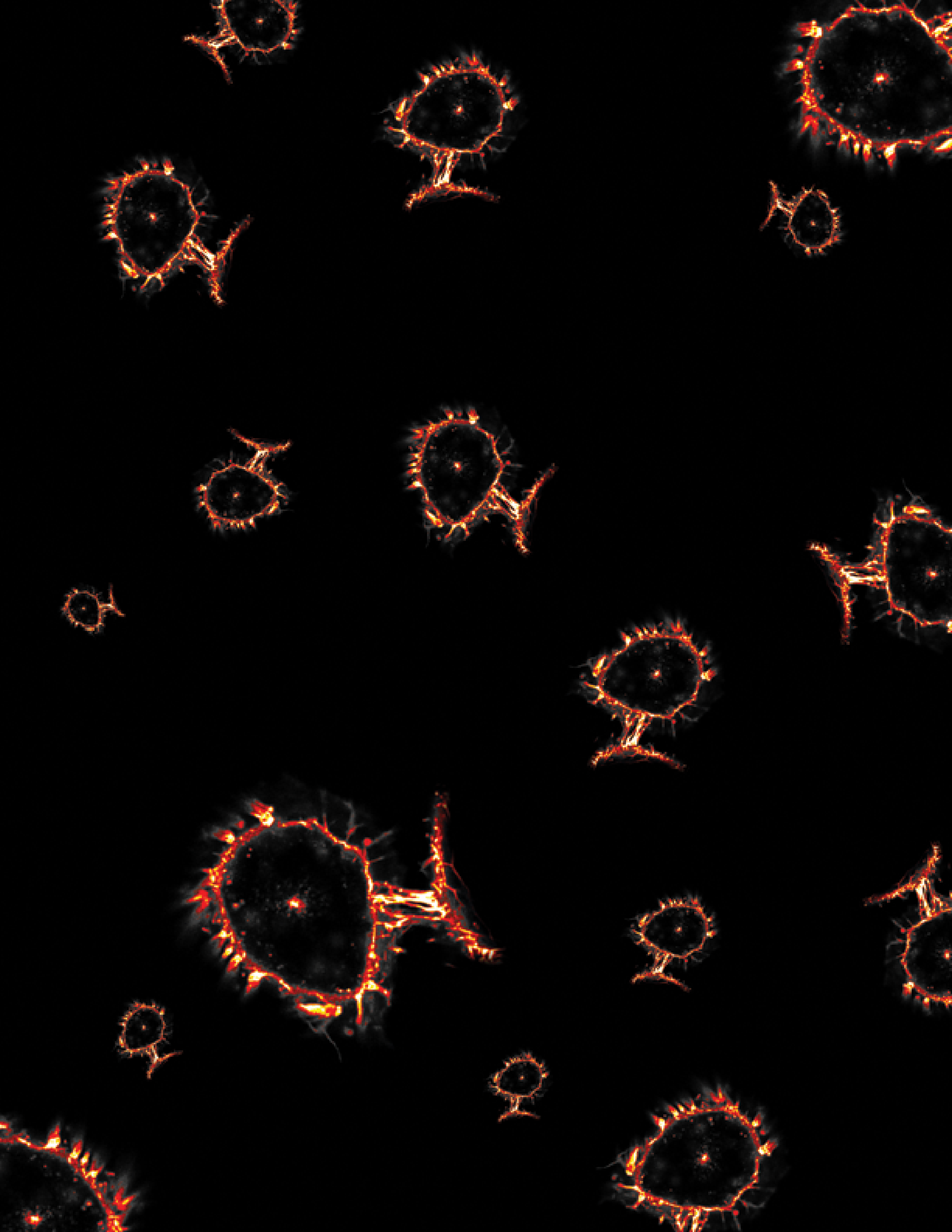
In addition to providing a cleaner look and a brisk functionality, the redesign includes an expanded News & Opinion section that provides expert commentary on a range of topics, including molecular research, clinical studies, genetics and cognition. The new design also features SFARI Wiki, an encyclopedia of autism terms and topics, written and edited by scientists. The site remains a portal to important resources for researchers, such as SFARI Gene (sfari.org/resources/sfari-gene), which itself recently relaunched, and SFARI Base (sfari.org/resources/sfari-base).

A central component of the relaunch was the creation of SFARI Forum, a password-protected discussion space where researchers can exchange ideas and engage in dialog directly with one another, debating current theories and seeding new ones along the way. The foundation hopes that SFARI Forum will allow researchers to readily and quickly communicate across institutions and disciplines, advancing autism research in the process. And dialogue has already begun.

"SFARI.org is helping to foster a more collaborative environment by allowing immediate feedback on emerging autism research," says Helen Tager-Flusberg, president of the International Society for Autism Research.

"The feedback on the new website has been uniformly positive," says Gerald Fischbach, scientific director at the Simons Foundation. "Of most significance, the new site allows for more immediate dialog and feedback with informed opinions about how this work fits into the spectrum of autism research. This facilitates discussion among scientists and ultimately new collaborative efforts."

The relaunch of SFARI.org was more than a year in the making, as its designers sought ways to give the autism research community more of a voice on the site while maintaining the accuracy and quality of the information available there. The future will include development of SFARI Forum into an active discussion space for autism researchers, a place for high-level conversations on diagnostic tools, neurological research and other topics.



# 29

## PROMOTING EXCHANGES

*Heterogeneous distribution of death receptors*

CD95 receptors fused to fluorescent proteins are typically homogeneously distributed over the plasma membrane. Here, HeLa cells expressing such receptors are imaged through fluorescence microscopy by focusing on the substrate on which the cells adhere. The heterogeneities that can be seen may correspond to the complex topology of the membrane, but they may also be attributed to local accumulations of receptors in domains such as focal adhesion sites.

# MATHEMATICAL SCIENCES RESEARCH INSTITUTE

msri.org

"MSRI creates a very, very fertile environment, with high-level research and discussions happening all the time," Naor says. "This amazing interaction just speeds up the research of everybody."

MSRI unveiled this statue of S.S. Chern at a centennial celebration of Chern's life.

The Simons Foundation was pleased to continue its long-term relationship with the Mathematical Sciences Research Institute (MSRI) in 2011, supporting not only the Eisenbud Professorship and Simons Visiting Professorships there, but a centennial celebration in honor of MSRI's founding director, Shiing-Shen Chern, held in October and November.

Perched high atop the Berkeley Hills on the far eastern edge of the UC Berkeley campus, the Mathematical Sciences Research Institute enjoys a majestic view of San Francisco Bay. Stanford professor Persi Diaconis once described it as "the absolute crown jewel" of mathematics institutes. The institute serves many communities of mathematics enthusiasts, from top-flight research mathematicians, to post-docs and graduate students, to high school students and their teachers.

Central to the institute's activities are semester-length programs that gather mathematicians from all over the world to focus on cutting-edge fields of study. 2011 saw three such gatherings, with spring programs in arithmetic statistics and in free boundary problems, and a fall program devoted to a "jumbo semester" in quantitative geometry.

"It's not really a field, quantitative geometry," says Assaf Naor of the Courant Institute, architect of the program on the topic. "It's a way of thinking." Geometry was classically a qualitative pursuit. "But modern questions are inherently quantitative," Naor maintains. "Everything is geometry: social structures, the stars in the sky, the internet, proteins." Important new insights can be gained from depicting giant data sets or the internet as geometric structures, but the geometry required is more concerned with reasonable approximations than with idealized relationships. Discussions and workshops brought in a wealth of different perspectives: harmonic analysis, dynamical systems and ergodic theory, probability, group theory, and connections to computer science.

"MSRI creates a very, very fertile environment, with high-level research and discussions happening all the time," Naor says. "This amazing interaction just speeds up the research of everybody." Some of the semester's main results will appear in a special issue of the *Proceedings of the National Academy of Sciences*. "The field of quantitative geometry has that feel of something that has reached a kind of critical momentum," says MSRI director Robert Bryant. "It will now, with any luck, develop very rapidly." That forward movement, Bryant believes, will draw from both present and future research talent. "The participation of leading researchers in the field is critical for the success of these programs, and the Simons and Eisenbud Professorships make it possible for us to bring in those senior people," he says. "Also, the foundation's challenge grant to MSRI has made available money to support a growing number of post-docs."

The Simons Foundation also helped mark an important historical milestone for MSRI. "Fall 2011 was the 100th anniversary of the birth of our founding director, Shiing-Shen Chern, who was a seminal figure in modern differential geometry," says Bryant. "The Simons Foundation supported this centennial celebration, which enabled us to bring in world experts in differential geometry, as well as bright young people from around the world, to come and give talks. The talks were all recorded, they're up on the website, and they've been very popular.

"In addition, the Simons Foundation also funded a film about Chern's work and legacy, *Taking the Long View: The Life of Shiing-Shen Chern*," Bryant continues. "Chern had an enormous effect, and the film captures what one person can do who has wisdom and experience and drive. The foundation also commissioned a wonderful new statue of Chern for the entrance to Chern Hall here, which we unveiled during the centennial conference."

# SIMONS SCIENCE SERIES

simonsfoundation.org/mathematics-physical-sciences

Audience members ask a lot of questions, sometimes bringing in the perspectives of their own fields.

In February 2011 Sanjeev Arora delivered his talk, "When and How Can We Compute Approximately Optimal Solutions to Intractable Computational Problems?"

In 2010, the Simons Foundation began inviting about a hundred scientists from the New York area to a monthly interdisciplinary colloquium. "The idea was to bring scientific interaction to the foundation itself, and to enable interaction in a different sphere than was going on already," says David Eisenbud, the foundation's director for Mathematics and the Physical Sciences. "We hit on the idea of gathering a special, small group to come to our offices eight times during the academic year for talks that mostly would not be in their own field."

This project, called the Simons Science Series, brings together top researchers in various areas to create new connections that will advance thinking on cutting-edge problems in mathematics, computer science and basic science.

The 2010–2011 Science Series featured talks on theoretical computer science and neuroscience. Speakers like Jon Kleinberg of Cornell, whose work on networks and search algorithms earned him a MacArthur "genius grant," spoke about the computational approaches to analyzing the vast data sets now available, which offer new perspectives on everything from the interrelationships of large populations to the behavior of a single individual. Avi Wigderson of the Institute for Advanced Study (IAS), Michael Kearns of the University of Pennsylvania, and Sanjeev Arora of Princeton also delivered talks on varied topics in computer science.

Neuroscience colloquiums included talks like John Donoghue's presentation on neurorestoration, a frontier field that requires the combined efforts of neuroscientists, computer scientists, mathematicians, clinicians and engineers. Donoghue, director of the Institute for Brain Science and a professor of neuroscience and engineering at Brown, discussed recent progress in brain-computer interface, which allows severely paralyzed patients to control a range of devices through tiny sensors implanted in their brain circuitry. Previous neuroscience talks were given by David Heeger of New York University, Stanislas Leibler of Rockefeller University, Aviv Regev of the Broad Institute, and Partha Mitra from Harvard University and Cold Spring Harbor Laboratory.

The 2011–2012 Science Series focuses on theoretical physics and the biological sciences. Arnie Levine of the Institute for Advanced Study led off the series with a discussion on the tension between fidelity in genetic transmission and an error frequency that generates enough diversity to permit selection and changes in the species. Levine presented evidence linking mutations and polymorphisms in three human genes: P53, the discovery for which Levine is best known, along with P63 and P73; all are part of a mechanism that kills cells where stress can cause too high an error frequency in DNA replication, which leads to autism, some early onset cancers, and developmental abnormalities. Levine was followed by Larry Abbott of Columbia University, who spoke on mathematical and computational studies of neural network models.

Theoretical physicist Charles Marcus of Harvard University ended the year's series with a talk about experimental progress toward controlling quantum mechanical coherence and entanglement, and their possible future use for information processing.

Audience members ask a lot of questions, sometimes bringing in the perspectives of their own fields. "Lecturers are often quite surprised," Eisenbud reports, "because in the usual scientific colloquium, audiences are often pretty quiet. A number of speakers have told me what a pleasure it was to speak to an audience with that kind of interest and breadth. And there's a lot of talk at the reception afterwards. It seems to be a very successful format."

# SIMONS SUMMER RESEARCH PROGRAM

stonybrook.edu/simons

"I treat them like graduate students instead of high school students, and they surprise me all the time," Berhane Ghebrehiwet says.

Nithin Tumma, 17, accepts the Intel Science Talent Search top award of $100,000 from Intel president and CEO Paul Otellini. Photo courtesy of Intel.

When Michigan high school student Nithin Tumma applied last year to the Simons Summer Research Program, which pairs students with Stony Brook University scientists for eight weeks of research, he doubted his chances of getting a spot in the competitive program.

But Tumma did get in, and a year later the research he performed as a Simons Fellow propelled him to a first-place finish at the 2012 Intel Science Talent Search, considered by many to be the premier national high school science competition.

The Simons Summer Research Program, supported by the Simons Foundation and individual faculty grants, is nearing its third decade on the Stony Brook campus.

"Over the years, the program has influenced so many young talents," says Berhane Ghebrehiwet, a professor of medicine at Stony Brook who has mentored program students, including Tumma, for 20 years.

Originally designed to support 10 local high school students per year, the program has grown to 35 students each year, many from out of state. This year, the program received 257 applications.

Some of the students in the program have done scientific research before and have a clear idea of the directions they want to pursue. Tumma, for example, already knew that he wanted to do research in computational biology.

"I asked Dr. Ghebrehiwet if it would be okay to ask some of my own questions, and he said that would be great," Tumma recalls. "He supported me in coming up with the right questions and designing my experiments."

Tumma used computational analysis to study the crystal structure of a protein called GC1QR. He identified the site at which an HIV protein called GP41 binds to GC1QR in certain immune cells, prompting the cells to produce a chemical 'death signal' that makes the immune system attack itself. Knowing this binding site could ultimately lead to new HIV therapies, Ghebrehiwet says. Tumma also studied GC1QR in connection with cancer, showing that cancer cells in vitro that are treated with antibodies to GC1QR stop proliferating.

Other students in the program are new to research. "Some of the students feel lost at first," Ghebrehiwet says. "But that's what we're here for, to guide them in the right path." Mentoring the students requires significant time and energy, observes Karen Kernan, the program's director. "It is this effort by the research scientists," she says, "that keeps the program so vibrant."

In addition to Tumma, 4 other 2011 Simons Fellows were also among the 40 finalists in the 2012 Intel Science Talent Search. This strong showing was not atypical: the program routinely produces semi-finalists and finalists at the Intel competition, as well as at the prestigious Siemens Competition in Math, Science & Technology.

Ghebrehiwet says the secret to mentoring these talented students is to have high expectations. "The more you raise the bar, the more they can surprise you," he says. "I treat them like graduate students instead of high school students, and they surprise me all the time."

# MATH FOR AMERICA

mathforamerica.org

"The U.S. urgently needs to foster outstanding mathematics instruction in every school throughout the country," says John Ewing, president of M*f*A.

M*f*A Master Teacher Tim Evans with students.

For many decades, the United States has led the world in mathematics and science. American mathematicians and scientists solved longstanding problems, made breakthroughs in pure and applied areas, and established leading academic centers of excellence across the nation.

Maintaining that excellence requires having an excellent K–12 education system in order to train the next generation of researchers, and that requires having high-quality K–12 math and science teachers — teachers who know and love the subjects they teach.

Math for America (M*f*A) was founded to ensure this excellence. Now in its eighth year, M*f*A's mission is to build a corps of outstanding beginning and experienced mathematics and science teachers at the secondary level — teachers who can communicate their subject to all students, who can be creative in the classroom, and who can inspire the next generation of researchers.

Through selective recruitment of prospective mathematics teachers, called M*f*A New Teacher Fellows, and through strategic support of excellent 'Master Teachers' already in U.S. school systems, M*f*A brings talented new teachers into the profession and connects them to the master craftsmen of teaching, establishing a supportive community of math and science educators.

"The U.S. urgently needs to foster outstanding mathematics instruction in every school throughout the country," says John Ewing, president of M*f*A. "Math for America believes that the best way to build excellence is to start with excellence — and the first step is to recognize and support the great teachers we already have in the classroom. That strong base of teachers exists, and their excellence is contagious."

By offering these groups of talented educators generous stipends and membership in a dynamic professional community, M*f*A creates a lively community of professionals. M*f*A sponsors a broad array of colloquia for its members, many facilitated by the Master Teachers themselves. Regional meetings conducted on a regular basis offer mini-courses in which educators at various stages of their careers talk mathematics, discuss pedagogy and generally exchange ideas.

The program also encourages its teachers to pursue further accreditation in the form of National Board Certification and to attend other seminars in their field.

To date, M*f*A has admitted nearly 600 teachers across the country and plans to expand its flagship New York Program to a cadre of 1,000 outstanding teachers, which in 2013 will include science as well as mathematics. In building this program, M*f*A not only serves as a model for a future national program, possibly bringing tens of thousands of outstanding mathematics and science teachers together, but also conveys prestige on the teaching profession, making it more attractive to talented young people.

# MATH ENCOUNTERS

momath.org/math-encounters/

“We wanted to create a program that would expose people to these ‘aha’ moments about math, even if they aren’t mathematicians.”

Math Encounters speaker Erik Demaine.

When internationally renowned mathematician Erik Demaine introduced the concept of a hyperbolic paraboloid to a packed house in the Baruch College Conference Center last March, it's hard to say how many in the audience had ever heard of such a thing. But after helping Demaine recreate one of these saddle-shaped mathematical objects in the form of a beautiful origami sculpture, it's safe to assume that few in attendance ever forgot it.

Demaine's talk was the first offering in the monthly Math Encounters series at the New York City-based Museum of Mathematics (MoMath), described by MoMath's executive director Glen Whitney as "a free public presentation series designed to highlight the richness of mathematics and the unexpected ways in which it touches our lives." The series, which was created in collaboration with the Simons Foundation and is now entering its second year, has already created layman-friendly 'encounters' between geometry and Islamic art, minimal surfaces and soap bubbles, and — in a particularly pop-culture-focused session — four-dimensional manifolds and *The Simpsons*.

Speakers are selected who can articulate mathematical ideas in an engaging yet challenging way — as the sessions are usually attended by a mix of technically proficient math enthusiasts and curious laypeople — and MoMath staff works with them to prepare creative ways to demonstrate their ideas in action, with hands-on activities. In one such workshop, audience members learned that the number of spirals in a pinecone always corresponds to a mathematical pattern called Fibonacci numbers. And even the abstruse-sounding hyperbolic paraboloid from Erik Demaine's talk has a connection to practical reality: it can be used as a model for constructing curved roofs out of straight beams.

"We wanted to create a program that would expose people to these 'aha' moments about math, even if they aren't mathematicians," Whitney explains. "If we can get people to see math where they didn't see it before in their everyday lives, that's a big win for us." It's an approach that Keith Devlin, an acclaimed Stanford University mathematician — who gave the presentation on pinecones and Fibonacci numbers — wishes were more widespread in math education. "The almost total focus in math classes on skills and procedures is misplaced," he says. "We do not devote music classes to a detailed study of musical notation and practicing scales. So why do we continue to reduce mathematics, one of humanity's greatest intellectual achievements, to dull, repetitive practice of skills?"

As Math Encounters enters its second year, Whitney hopes to attract more middle school and high school students to the series. He also expects to move the series from its current home at Baruch College into a larger space in the Museum of Mathematics itself, which will open in late 2012. "The people who come in are very engaged with the topics, and we always end up having to break up lots of little conversations when it's time to go," Whitney says. "I wish we could let people hang out until midnight if they wanted to, just talking about math. In our new space, we may be able to do just that."

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# WORLD SCIENCE FESTIVAL

worldsciencefestival.com

While events have included luminaries like Nobel Laureates Steven Weinberg, Gerard 't Hooft and Frank Wilczek, such eminent participants are often engaged in unexpected ways, like an evening of storytelling.

Roboticist Heather Knight demonstrates DATA, her comedian-robot in the World Science Festival's Cool Jobs presentation.

In an era when humanity derives unprecedented benefits from science, science itself is more estranged from culture at large than ever before. The World Science Festival (WSF) in New York City was conceived to close that gap and to nurture popular interest in a subject that is often regarded as too difficult, or even forbidding.

The brainchild of Tracy Day and Brian Greene, a journalist and a physicist respectively, the WSF is a yearly celebration of scientific culture featuring programs that endeavor to convey the beauty and spirit of the scientific enterprise to laypeople — without compromising its essence.

Launched in 2008, the festival features five days of live, multimedia productions in New York City, parts of the United States, and even abroad. All of science is fair game: from the abstractions of Godel's metamathematics to Einstein's personal correspondence, and from the role of women in science to the biological mechanisms responsible for our sense of smell.

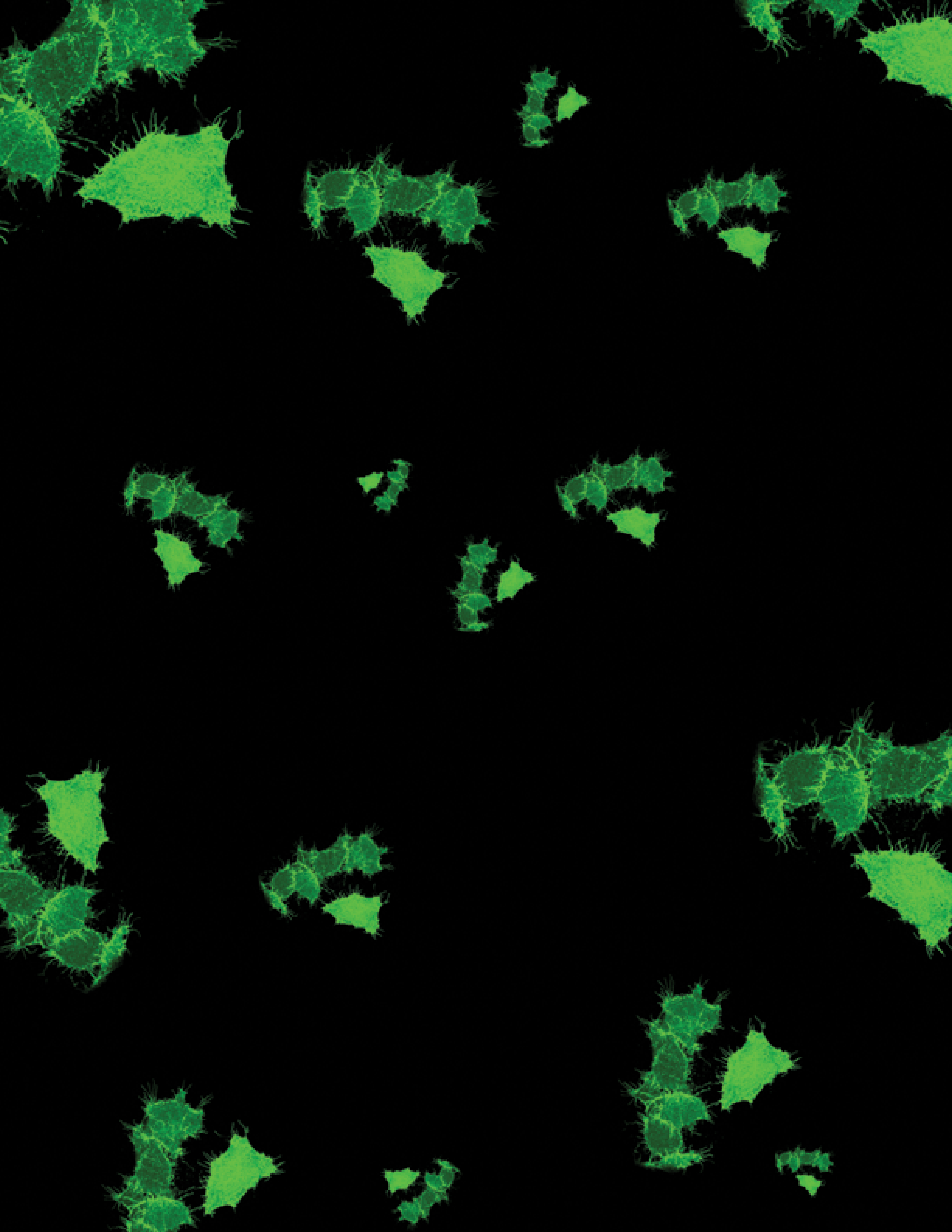
While events have included luminaries like Nobel Laureates Steven Weinberg, Gerard 't Hooft and Frank Wilczek, such eminent participants are often engaged in unexpected ways, like an evening of storytelling. "The programs are quite varied," says Greene. "Some are vibrant discussions among leaders in a given field. Others involve performance where science is brought together with the arts in a manner that amplifies each."

2011 was a characteristic year for the festival. The WSF sponsored the play "Radiance," by esteemed actor Alan Alda, which dramatizes the life of Marie Curie; an exhibition entitled BIORHYTHM, which inquires into how music and sounds evoke specific reactions and emotions; an informal gathering of professional and amateur astronomers for an evening of stargazing at Brooklyn Bridge park; and the production of "Beautiful Minds: The Enigma of Genius," which explores the workings of creativity across a range of disciplines. The goal is to anchor scientists, and science, in a place that is human and accessible.

Establishing connection with young people is also a central objective of the WSF. Many scientists participating in the festival visit New York City public schools to spark enthusiasm among pupils in their formative years.

Over the years, the festival's popularity has grown, and its future is bright. Nearly eighty percent of students attending WSF events have reported being inspired to enroll in more courses in science. Other less conventional measures attest to the festival's efficacy: a video of musician Bobby McFerrin exploring the link between neuroscience and music has logged more than two million viewers to date. Plans for the festival include an expanded website that will serve as a trusted source for information about science. The hope is that coupled with a powerful new internet presence, the WSF's weeklong aggregation of live events will ripple farther than ever before.

"Science is interwoven with every aspect of life," says Day, "and our belief is that when the general public sees that, they will understand the scientific process of rational inquiry as the human struggle to understand ourselves and our place in the universe."



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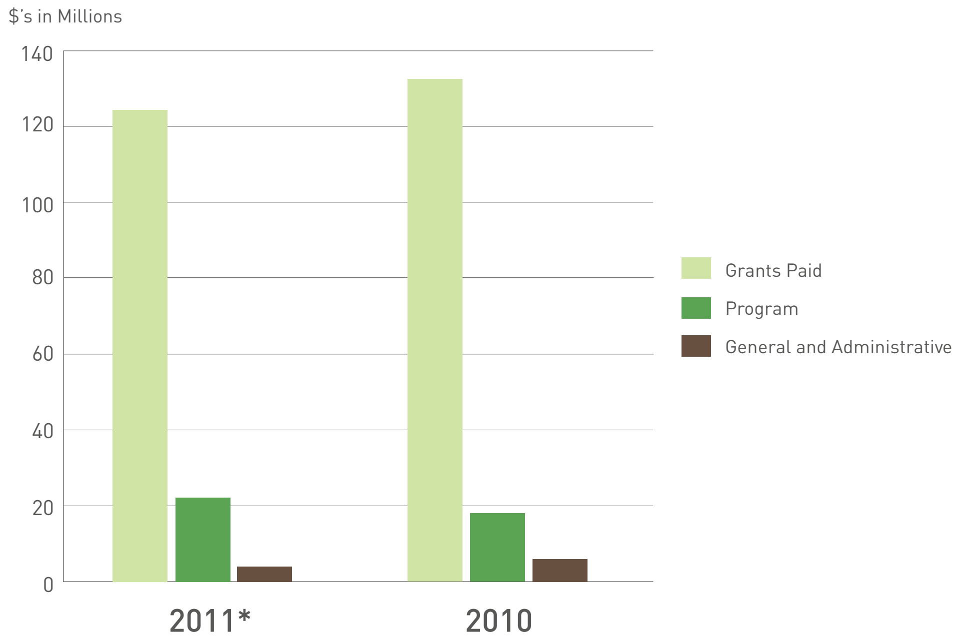
## FOUNDATION FACTS

*Reorganization of death receptors*

CD95 receptor activation by its CD95 ligand induces a reorganization of the receptor, including clustering and internalization. Those processes are involved in the transduction of the apoptotic signal. Here, a HeLa cell expressing CD95 fused to a fluorescent protein and induced by an extracellular soluble CD95 ligand has been imaged. The receptor is mostly present on the plasma membrane of the cell but can also be seen internalized inside the cell.

# FINANCIALS

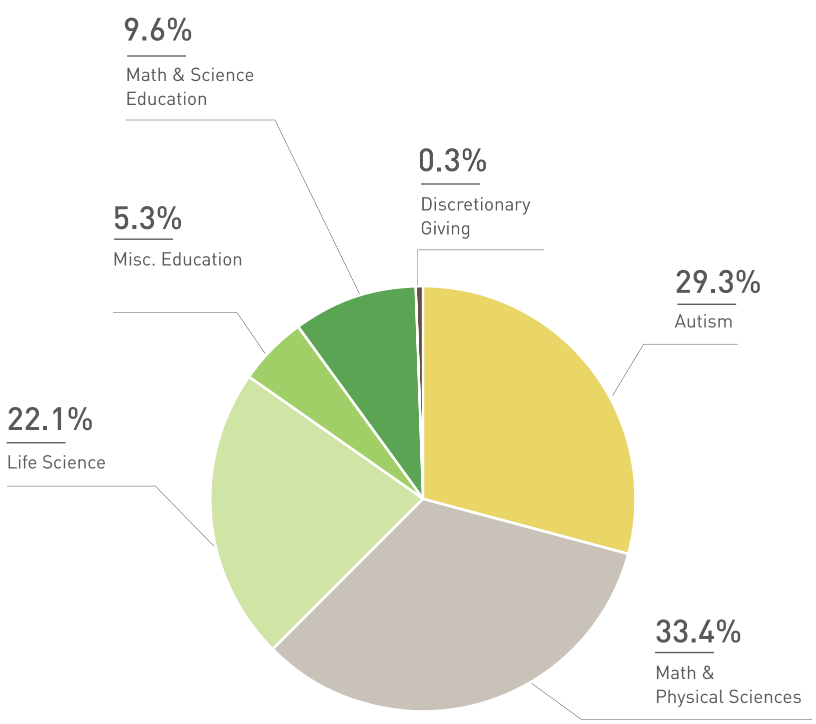
## Proportions of Expenses




* Beginning in 2011, some General and Administrative expenses were allocated to Program Expense

## Grant Payment by Category

For year ended 12/31/2011



# FINANCIALS (UNAUDITED)

## Balance Sheet

| ASSETS | 12/31/2011 | 12/31/2010 |
|---|---|---|
| CASH AND CASH EQUIVALENTS | 50,484,501 | 33,126,300 |
| INVESTMENT PORTFOLIO | 1,911,592,457 | 1,828,290,093 |
| PROPERTY AND EQUIPMENT, NET | 12,722,157 | 13,368,353 |
| PREPAID EXCISE TAXES | 176,947 | 44,200 |
| OTHER | 3,024,425 | 1,639,805 |
| TOTAL | 1,978,000,487 | 1,876,468,751 |
| **LIABILITIES** | | |
| ACCOUNTS PAYABLE | 3,680,853 | 3,249,854 |
| DEFERRED RENT LIABILITY | 3,817,819 | 3,817,819 |
| GRANTS PAYABLE | 390,158,217 | 257,627,654 |
| DEFERRED EXCISE TAX LIABILITY | 9,725,215 | 8,214,743 |
| OTHER TAXES PAYABLE | 8,500,000 | - |
| TOTAL | 415,882,104 | 272,910,070 |
| **NET ASSETS** | | |
| **UNRESTRICTED NET ASSETS** | 1,562,118,382 | 1,603,558,681 |

## Income Statement

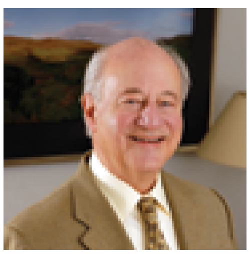
| REVENUE | FOR 12 MONTHS ENDED 12/31/2011 | FOR 12 MONTHS ENDED 12/31/2010 |
|---|---|---|
| CONTRIBUTIONS | 79,402,229 | 270,395,621 |
| INVESTMENT INCOME | 172,384,483 | 214,790,243 |
| TOTAL | 251,786,712 | 485,185,864 |
| **EXPENSES** | | |
| GRANTS PAID | 123,802,345 | 132,374,789 |
| CHANGE IN GRANTS PAYABLE | 132,530,564 | 13,715,874 |
| PROGRAM | 22,359,211 | 18,271,050 |
| GENERAL AND ADMINISTRATIVE | 2,965,898 | 5,497,736 |
| DEPRECIATION AND AMORTIZATION | 854,301 | 593,386 |
| TAXES | 10,586,098 | 2,382,710 |
| OTHER (INCOME) EXPENSES | 128,595 | 5,828,993 |
| TOTAL | 293,227,012 | 178,664,538 |
| **NET INCOME (LOSS)** | (41,440,300) | 306,521,326 |

# DIRECTORS

## Marilyn Hawrys Simons, Ph.D. | PRESIDENT

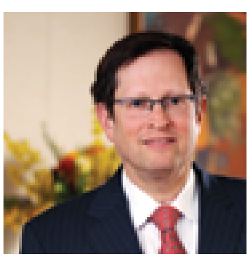
Marilyn Hawrys Simons is the president of the Simons Foundation. Under her leadership, the foundation has grown rapidly since its inception in 1994 to become one of the country's leading private funders of basic scientific research.

Ms. Simons also has more than 25 years of experience actively supporting non-profit organizations in New York City and on Long Island. In addition to her work to advance basic science research, Ms. Simons has been involved in K–12 education for underserved communities. Ms. Simons is vice president of the board of Cold Spring Harbor Laboratory, an outstanding U.S. research facility specializing in molecular biology and genetics. She is president of the board of the LearningSpring School, a New York City school for children ages 5–14 diagnosed on the autism spectrum. She is also a member of board of trustees at the East Harlem Tutorial Program, an after school program in New York City.



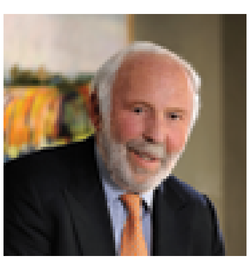
## Gerald D. Fischbach, M.D. | DIRECTOR, LIFE SCIENCES AND DIRECTOR, SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Dr. Fischbach joined the Simons Foundation in 2006 to oversee the Simons Foundation Autism Research Initiative and is now the foundation's director of Life Sciences. He formerly served as dean of the Faculties of Health Sciences at Columbia University, and was director of the National Institute of Neurological Disorders and Stroke at the NIH from 1998–2001. Dr. Fischbach began his research career at the NIH, serving there from 1966–1973. He subsequently served on the faculty of Harvard Medical School from 1973–1981. From 1981–1990, Dr. Fischbach was the head of the Department of Anatomy and Neurobiology at Washington University School of Medicine. In 1990, he returned to Harvard Medical School where he was the chairman of the Neurobiology Departments of Harvard Medical School and Massachusetts General Hospital until 1998. Dr. Fischbach was a non-resident fellow of the Salk Institutes for over 20 years, and today serves on the board of the Spinal Muscular Atrophy Foundation. Throughout his career, he has investigated trophic interactions between nerve cells and the targets they innervate.



## Mark Silber, J.D., M.B.A. | VICE PRESIDENT

Mark Silber is executive vice president and CFO of Renaissance Technologies LLC, a New York–based private investment adviser. Mr. Silber joined the company in 1983 and is responsible for the overall operations of its finance, administration and compliance departments. He was formerly a certified public accountant with the firm of Seidman & Seidman, now BDO USA. He holds a bachelor's degree from Brooklyn College, a J.D. and L.L.M. in tax law from New York University School of Law, and an M.B.A. in finance from New York University Graduate School of Business Administration.



## James H. Simons, Ph.D. | CHAIRMAN

James H. Simons, Ph.D., is chairman of the Simons Foundation. Dr. Simons is also 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 the Massachusetts Institute of Technology and Harvard University, and was a cryptanalyst at the Institute for Defense Analyses in Princeton, New Jersey. Dr. Simons' scientific work was in geometry and topology; his most influential work involved the discovery and application of certain measurements, now called Chern-Simons invariants, which 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 1976. He is a trustee of the Stony Brook Foundation, Rockefeller University, Massachusetts Institute of Technology, Brookhaven National Laboratory, the Mathematical Sciences Research Institute and the Institute for Advanced Study, and a member of the American Academy of Arts and Sciences and the American Philosophical Society.

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Baylor University
Boston University
Brandeis University
Brigham Young University
Brown University
Bucknell University
California Institute of Technology
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Claremont McKenna College
Cleveland State University
Colgate University
College of Staten Island/CUNY
Colorado State University
Columbia University
Cornell University
Davidson College
Drexel University
Duke University
Euclid Lab
Florida Atlantic University
Florida State University
Furman University
George Washington University
Georgia Institute of Technology
Harvard University
Illinois State University
Independent University of Moscow
Indiana University
Instituto Nacional de Matemática Pura e Aplicada
Johnson C. Smith University
Kennesaw State University
Lafayette College
Lehman College/CUNY
Louisiana State University
Massachusetts Institute of Technology
Mathematical Sciences Research Institute
Missouri University of Science and Technology
Monmouth University
Museum of Mathematics
New York University
North Carolina State University
Northwestern University
Oklahoma State University
Old Dominion University
Peking University
Pennsylvania State University
Princeton University
Purdue University
Queens College/CUNY
Rider University
Rochester Institute of Technology
Rutgers, The State University of New Jersey
Stanford University
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Texas A&M Research Foundation
Texas Christian University
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University of Wisconsin-Madison
University of Wisconsin-Milwaukee
Vanderbilt University
Wake Forest University
Washington University
West Chester University of Pennsylvania
William Marsh Rice University
Yale University

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Museum of Mathematics
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Institute for Advanced Study
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Marine Biological Laboratory
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# GRANTS TO INSTITUTIONS

## Autism

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Autism Consortium

Baylor College of Medicine

Beth Israel Deaconess Medical Center

Boston University

Brown University

California Institute of Technology

Children's Hospital Boston

Children's Hospital of Philadelphia

Cold Spring Harbor Laboratory

Columbia University

Columbia University Medical Center

Duke University

Emory University

Feinstein Institute for Medical Research

George Washington University

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Gordon Research Conferences

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Harvard University

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Johns Hopkins University School of Medicine

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Massachusetts Institute of Technology

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