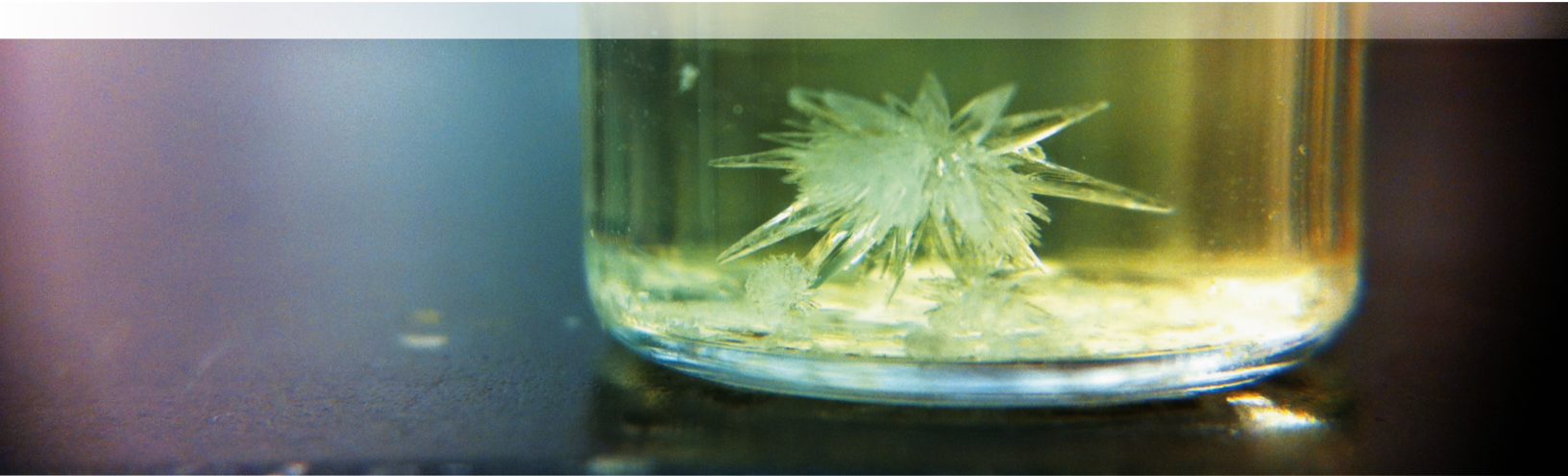
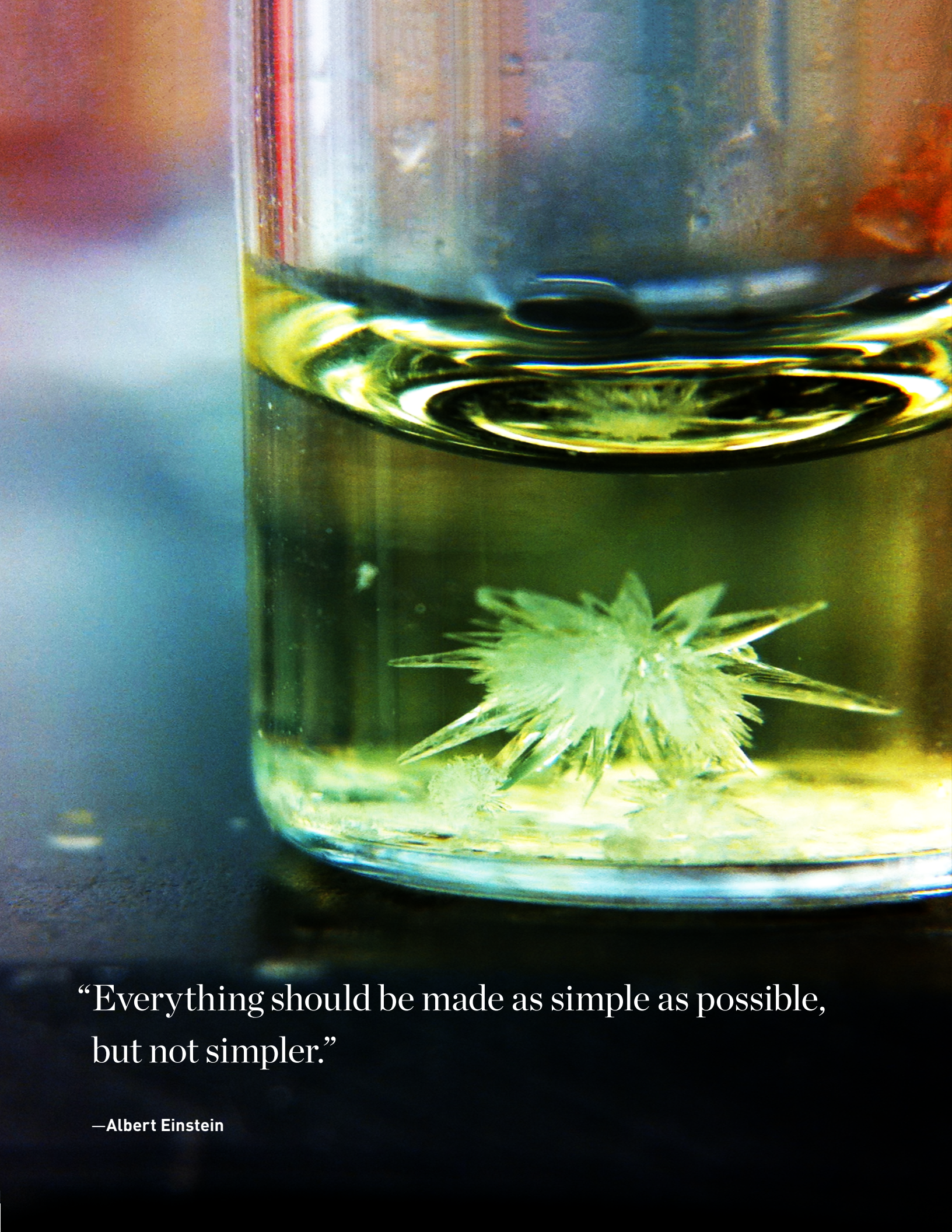


2013

ANNUAL REPORT



SIMONS FOUNDATION



“Everything should be made as simple as possible,
but not simpler.”

—Albert Einstein

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OPPOSITE: RNA precursor molecule crystals developed by the laboratory of Donna Blackmond demonstrate a plausible route to the building blocks of life.

LETTER FROM THE PRESIDENT
AND THE CHAIR

October 2013 brought us to Edinburgh, Scotland, to join in festivities celebrating the philanthropy of steel magnate Andrew Carnegie. While there, we drove to the University of Edinburgh to visit a good friend in its mathematics department, passing a statue of James Clerk Maxwell along the way. Maxwell, the 19th century mathematical physicist, whose equations precisely describe the beautiful relationship between the electric and magnetic fields, laid the foundation for much of modern physics. Though less well known than his contemporary Carnegie, Maxwell’s work enabled a myriad of applications, such as television, radar and the now ubiquitous cell phone. His pursuit of pure knowledge illustrates the profound impact that research in basic science can have on our lives.

Supporting research in mathematics and the basic sciences plays a key role at the Simons Foundation. We do this through a combination of grant-making programs and recently initiated internal research activities. Our staff scientists, many of whom are working researchers themselves, direct our grant-making programs. Outside advisory boards provide counsel and oversight to our programs. Additionally, we implicitly seek the guidance of eminent scientists from diverse fields by inviting them to give lectures and seminars at the foundation.

Taking a step further, at a two-day meeting at Buttermilk Falls Inn in Milton, New York, we met with a group of renowned scientists to discuss specific ideas for research funding. Numerous factors were taken into consideration in assessing a project: the importance of the research, the potential for strong scientific leadership and collaboration, the feasibility

of the work in a finite time scale, the lack of available funding elsewhere and the potential for leveraged funding in the future. This meeting is highlighted in our annual report as it set the stage for programs initiated in 2013 and many that will roll out in the coming years.

As a self-sustaining private foundation, we feel able to take risks with our research investments and thus can afford to take a long view. At the same time, we want to catalyze progress. Scientific questions can lead to answers that not only satisfy our intellectual curiosity but also often provide remarkable applications well beyond the imagination of the scientists themselves, as Maxwell’s work amply demonstrates.

There is an important role for foundations and private donors in supporting science, especially when the National Science Foundation and the National Institutes of Health face shrinking budgets and shifts in political views. There is a bright, talented pool of scientific investigators at outstanding academic institutions, and it is our goal at the Simons Foundation to champion such extraordinary individuals through the funding we provide.

We hope you enjoy reading about our work in the pages that follow.

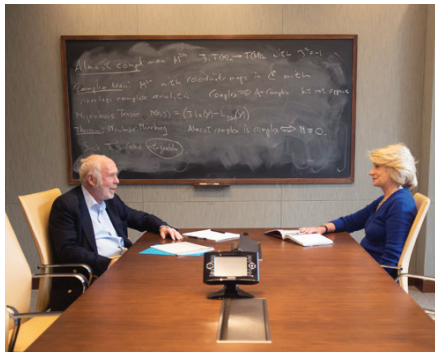
Marilyn H. Simons

Marilyn H. Simons
President

Jim Simons

Jim Simons
Chair

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



Front Row

Left to Right

Jim Simons
Marilyn Simons
David Baltimore

Back Row

Left to Right

Richard Ellis
Marian Carlson
David Eisenbud
Jon Kleinberg

Ingrid Daubechies
Bill Newsome
David Gross
Stephen Quake

Alla Katsnelson
Gerald Fischbach
Erica Klarreich
Jack Szostak

Susan Lindquist
Svante Pääbo
Terrence Sejnowski
David Liu

Charles Sawyers
Eric Lander
Michael Freedman
Edward Witten
David Donoho

Not Shown:
Stanislas Leibler



BUTTERMILK FALLS MEETING

Milton, New York, June 9-10, 2012

The Buttermilk Falls meeting — named for the Buttermilk Falls Inn in Milton, New York, where the Simons Foundation gathered 18 distinguished scientists in the summer of 2012 — was designed as a collegial but intense brainstorming session for new, forward-thinking projects that the foundation might consider supporting. Chaired by esteemed biologist David Baltimore, the meeting comprised two days of presentations spanning subjects from immunotherapy and dark-matter spectroscopy to evolutionary biology and neurophysiology. Not only did the meeting allow an extraordinary group of researchers to exchange ideas in an unconventional setting — an opportunity that is “so rare,” says Baltimore — but it also marked the beginning of a major shift in the way that the Simons Foundation plans to pursue its mission of funding basic science in mathematics, physical science and biology.

Jim Simons, chairman of the board of the Simons Foundation, explains that the foundation invited meeting attendees to suggest “goal-driven collaborative projects,” rather than ask open-ended basic research questions. “We’d been thinking about this as a new direction for the foundation to head — moving toward a more focused mode,” says Simons. “Of course, with really interesting scientific questions, you’re never going to learn everything. Nevertheless, there are questions to be answered that have a natural ending. We thought this way of working should be an important component of the foundation’s work in the foreseeable future.”

The foundation’s leadership worked with biologist Eric Lander to assemble a multidisciplinary guest list of eminent researchers. Rather than urging the guests to suggest applying foundation resources toward goals that would be easily achievable or incremental, the foundation asked them to propose goals that would, if reached, “represent a major scientific milestone” in their fields. These goals might take a decade or more to reach, but as long as the proposals included a concrete endpoint, the Simons Foundation would consider them as potential research areas for this new funding paradigm. The researchers followed this directive closely, bringing to the table such ambitious presentations as re-engineering the human immune system to combat cancer,

identifying the genetic and neurobiological mechanisms of social cognition and quantifying the process of biological evolution using novel computational and data analysis techniques. “It wasn’t just theoretical discussion,” Baltimore says. “These are real problems that are ready to be resolved — and will require resolution.”

The attendees were also encouraged to treat the meeting as a one-of-a-kind incubator for exploring what sorts of innovative projects might best benefit from the Simons Foundation’s unique stance of goal-driven philanthropic support. One of the first topics of discussion was the idea that while federal agencies dominate research funding with tens of billions of dollars every year, private giving may better support focused, large-scale projects that can stimulate true breakthroughs in a research field — or even create entirely new fields. Cognitive neuroscience, for example, was catalyzed by philanthropic grants from nongovernmental institutions interested in developing connections between psychology and neuroscience. “Jim and Marilyn Simons and their collaborators are particularly savvy about what the government is and isn’t doing,” Baltimore says. “It isn’t focused as much on deep, long-term issues in basic research, which is what the Simons Foundation exists to find and support.”

Discussion of collaborative research also permeated the presentations. Attendees explored various strategies for structuring a project devoted to attacking a ‘big idea’ in such a way that maximizes creative cross-pollination of ideas and results, without becoming so inefficient or diffuse that the project goal is never attained. Simons and Baltimore both expressed enthusiasm for gathering top minds ‘under the same roof.’ Other attendees, including Michael Freedman and Terrence Sejnowski, spoke of the advantages of a decentralized network of innovators, or a hybrid model comprising a core team working together in a physical space augmented by off-site collaborators at other institutions. The attendees also made a point of assessing how various projects might benefit from new datasets or technological methods not available in the past. If a blossoming technology such as



inexpensive gene sequencing or big-data analysis could “place a heretofore elusive goal at last in sight,” as the foundation put it to the guests, such a goal ought to be considered that much more seriously.

One of those technological sea changes — the growing problem of dealing with ‘big data’ in basic research — drove discussion for much of the Buttermilk Falls meeting. Physicist and mathematician Ingrid Daubechies proposed the creation of a “collaborative community” made up of mathematicians and scientists from many disciplines who would collectively focus their efforts on developing novel methods to analyze the deluge of high-dimensional data pouring in from research in genomics, neuroscience and other specialties. Almost every presentation at the meeting touched on this data-analysis problem, and Daubechies argued that establishing a physical center devoted to big-data research — where permanent and visiting members would collaborate and “prospect for interesting datasets” — would have “enormous impact” across scientific domains.

Daubechies’ ideas met with little debate from attendees, and although Jim Simons noted that the data analysis issue was so pervasive that such a center would continue indefinitely — contravening the meeting’s guideline about focusing on finite projects — he also expressed interest in establishing the kind of center Daubechies described. Within months after the meeting adjourned, the Simons Foundation initiated plans to create the Simons Center for Data Analysis (SCDA), inspired by Daubechies’ presentation and the discussions it generated. “It wasn’t what the meeting was intended to focus on,” Simons says, “but the genesis of SCDA was at Buttermilk Falls.”

Biologist Jack Szostak’s presentation was also representative of the scale and ambition of the attendees’ thinking. Entitled ‘The Origin of Life,’ it outlined Szostak’s ideas for reinvigorating research into a scientific question that almost every curious person has asked: *How did life arise from inanimate matter on Earth?* Despite the intellectual appeal of this fundamental mystery, the field has been a scientific backwater for decades, “largely because it doesn’t have immediate practical applications,” Szostak says.

Nevertheless, he argued that the field is on the cusp of several breakthroughs, most notably in identifying a possible pathway by which organic chemicals can self-assemble into nucleotides, which then form the complex self-replicating molecules of RNA and DNA that underpin all life on Earth. Szostak also reported promising discoveries made in his own lab about how chemical vesicles spontaneously assemble and divide, which could suggest a mechanism for how the first living cells began to exhibit similar behavior. Targeted support from an institution like the Simons Foundation, Szostak said, could kickstart and sustain this truly groundbreaking research.

The interdisciplinary nature of origin-of-life research led Szostak and others to propose establishing dedicated investigator positions for researchers at their own laboratories. “A few months after Buttermilk Falls, the Simons Foundation told us to write a detailed proposal, and things moved very quickly after that,” Szostak says. “We had an approved proposal and funding in place, and we were able to start supporting people in this field.” Initial support from the foundation for the first Investigators in the Simons Collaboration on the Origins of Life (SCOL) will extend for eight years.

Other initiatives born from the discussions at Buttermilk Falls include the Simons Collaboration on the Global Brain, which will provide significant support to create a network of researchers exploring the dynamic ‘mesoscopic scale’ of neural circuitry — a little-examined level of brain activity that occurs above the level of single neurons but below the level of whole-brain phenomena that can be observed with functional magnetic resonance imaging.

Two projects not specifically suggested at Buttermilk Falls but inspired by the spirit of the meeting have also been initiated. One, the Simons Collaboration on the Many Electron Problem is aimed at developing effective mathematical models of the dynamics of electrons in complex materials, a central problem in condensed matter physics. The other project, the Simons Collaboration on Algorithms and Geometry, will illuminate connections between mathematics and theoretical computer science.

“While project selection is a fairly lengthy process involving workshops in the proposed area and much outside consultation,” says Jim Simons, “ultimately, it is a question of taste and where we feel we can have the greatest impact. In three or four years, it’s entirely possible that we’ll want to do this sort of gathering again. Generally speaking, getting smart people together to brainstorm is a good idea.”

David Baltimore agrees. “Buttermilk Falls was a rare chance to open up,” he says. “That kind of intellectual and creative expansion ultimately benefits everybody.”

SIMONS CENTER FOR DATA ANALYSIS

When the Simons Foundation gathered top scientists to propose and debate ambitious new research goals at its Buttermilk Falls meeting, no one had in mind a focus on ‘big data.’ But the increasing importance of developing new tools for processing enormous datasets — the kind whose scale and complexity make them resistant or even intractable to standard methods of analysis — informed the meeting throughout.

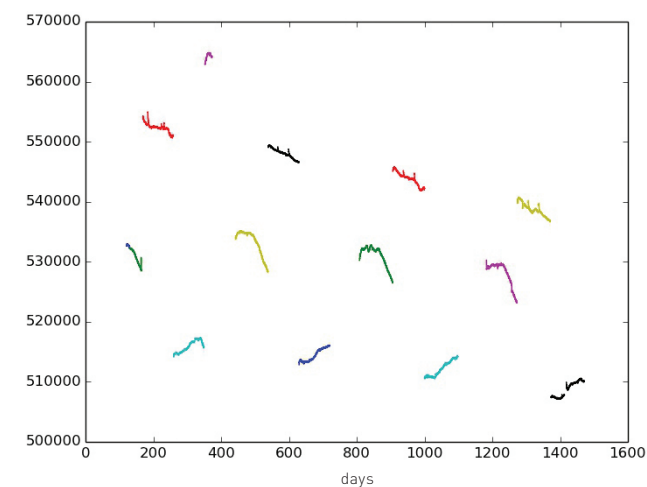
“One of our guests suggested that an in-house data group would be a valuable and necessary companion to some of the more goal-driven initiatives in physics and biology that we discussed,” says Jim Simons. “It struck a chord with me since I had made my living for many years analyzing data to predict markets.”

The Simons Foundation acted quickly on that suggestion and launched the Simons Center for Data Analysis (SCDA) in 2013. The center’s mission is to collaborate with other leading scientific institutions whose research efforts generate data on a massive scale, and to develop new methods of making sense of those data in order to push basic science forward. Although SCDA’s mandate encompasses all scientific disciplines, its initial focus will be on problems stemming from research in genomics and neuroscience.

“There are a host of experimental techniques in these fields that generate enormous amounts of raw, often noisy, data,” says Leslie Greengard, founding director of SCDA. “Our ability to cope with this information influx has not kept pace, and we need to create new tools that will allow us to make sense of the results. This suggests new, unsolved mathematical, statistical and computational questions whose resolution will help us say something about the underlying science.”

Greengard holds an M.D. and a Ph.D. in computer science, and co-developed the fast multipole method, deemed one of the most important algorithms of the 20th century by the Institute of Electrical and Electronics Engineers.

TOP: Representation of the brightness of a star over four years by Weikun Chen. Chen uses data from the Kepler satellite, which continuously monitors more than 100,000 stars similar to our Sun. Within this vast dataset, Chen searches for stars with orbiting planets by identifying stars whose light periodically diminishes, indicating the passing of a planet between that star and the satellite. The y-axis depicts the flux in the star’s light, measured in electrons per second.



This background in both biology and scientific computing makes him “the ideal person to lead our efforts at SCDA,” says Yuri Tschinkel, director of Mathematics and Physical Sciences, who helped coordinate the search committee that hired Greengard. “Data analysis will rely on sophisticated mathematical tools and will generate very interesting problems of its own to investigate.”

Greengard plans to assemble a team of 30 to 40 permanent and visiting researchers, drawn from multiple disciplines, to collaborate closely on data analysis problems. SCDA’s own output will center on disseminating a combination of research publications and software that can address some of the problems faced by scientists working in genomics and neuroscience, and help standardize the experimental and analytical protocols, says Greengard. This would enable individual labs to more easily share and cross-validate their results.

Current projects include analyzing autism genetics data from the Simons Foundation’s Simons Simplex Collection and supporting a new neuroscience initiative called the Simons Collaboration on the Global Brain, which will attempt to analyze how large groups of neurons process internally generated stimuli.

What’s clear is that SCDA, and other institutes like it, will only become more central to the advancement of basic research. “The science of data analysis could be as big as all of physics, all of mathematics,” Tschinkel says. “Data is flooding in from everywhere. It deserves to be attacked from many directions, and that’s exactly what SCDA is best able to do.”

“Where the telescope ends, the microscope begins.
Which of the two has the grander view?”

—Victor Hugo

SIMONS COLLABORATION ON THE ORIGINS OF LIFE

The origins of life is one of the great scientific mysteries of our time. How did we get here? Are we alone in the universe? How did life emerge on the volatile and hostile early Earth? These are just some of the questions that scientists, philosophers and stargazers have been asking for thousands of years.

So when a group of top life science researchers gathered at the foundation’s 2012 Buttermilk Falls meeting to identify and discuss fundamental life science questions, the origins of life was a natural topic of conversation. Charged with pinpointing topics with timely potential for progress where the foundation could make a significant impact, the researchers agreed that the origins of life — a field that has historically struggled for funding — fit the bill.

The result was the launch in 2013 of the Simons Collaboration on the Origins of Life (SCOL), which aims to advance our understanding of the processes that led to the emergence of life — on Earth or elsewhere in our universe.

However, endeavoring to understand how and where life originated in the universe requires expertise in a range of fields. It was clear to SCOL co-directors Dimitar Sasselov, director of Harvard University’s Origins of Life Initiative, and Jack Szostak, investigator at Massachusetts General Hospital and Howard Hughes Medical Institute, that a multidisciplinary collaboration would be in order. The initial group of SCOL scientists comprises an extensive collaboration that includes 15 Simons Investigators and 6 postdoctoral fellows whose disciplines range from chemistry and cell biology to astronomy and geobiology.

“The ability to work within a multidisciplinary group toward a common goal has given rise to interesting collaborations among our researchers,” says Marian Carlson, director of Life Sciences at the Simons Foundation and a member of the SCOL steering committee. “We see this program as enabling people to do creative new things that they otherwise wouldn’t have been able to do. Bringing together people from diverse disciplines can lead to all kinds of synergies.”

“It is the fundamental question of life; how did it all get started? If you’re a life scientist, this is the big one.”

MARIAN CARLSON, Director of Life Sciences

Collaborators study everything from the first chemical reactions that gave rise to life, to signatures of life found in Earth’s oldest rocks, to the likelihood that life originated — or perhaps even exists — on distant planets orbiting other stars.

The answer to this central and most basic question of life science could lead to a deep understanding of Earth, explains Carlson. Yet without active pursuit, the answer would almost certainly elude us.

“It is the fundamental question of life,” says Carlson. “How did it all get started? If you’re a life scientist, this is the big one.”

OPPOSITE: Illustration from the lab of Jack Szostak of a simplified RNA protocell shows in cut-away view a cell’s membrane envelope containing encapsulated nucleic acids. Szostak investigates how the first and simplest cells on the planet — perhaps like this one — began to self-replicate and evolve.

SIMONS COLLABORATION ON THE ORIGINS OF LIFE

DIMITAR SASSELOV, Co-Director

When Dimitar Sassselov began searching for habitable, Earth-like planets 15 years ago, he wasn't sure what he was looking for. "We didn't know how to look for life except for copies of Earth. But since life is such an opportunistic chemical system, it was silly to assume that life on other planets would follow the same chemistry," says Sassselov, professor of astronomy and director of the Origins of Life Initiative at Harvard University and co-director of the Simons Collaboration on the Origins of Life.

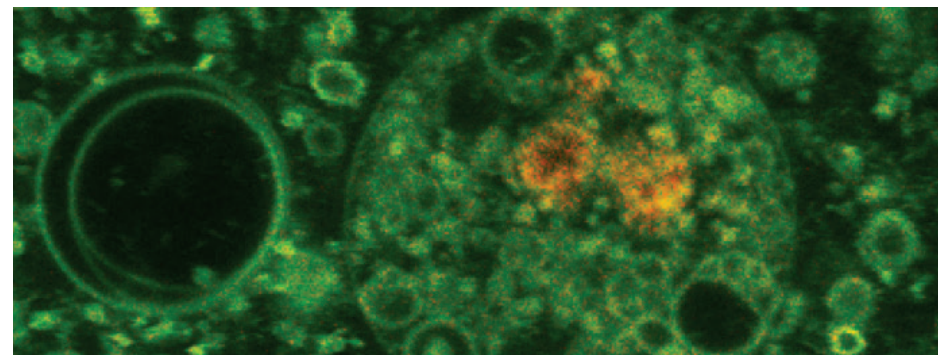
So Sassselov began developing remote sensing methods to study the atmospheres and surfaces of planets light-years away, and presumably quite different, from Earth.

Sassselov studies exoplanets — planets outside our solar system. While he cannot see the exoplanets themselves, he can, by using extremely powerful telescopes to detect light reflected off exoplanets from their stars, examine light signatures of trace gases. The light of any given atmospheric gas has a signature color, and taken together, all the gases present on a planet emit an array of colors called a spectrum.

Researchers look for the molecular signatures of biology by examining planets' spectra, seeking particular combinations of gases that may signify the presence of life.

"We are looking for trace gases that could only exist there in combination if there is biological activity on these planets," explains Sassselov. Knowing the atmospheric signatures that exist on a lifeless planet, Sassselov can identify possible life if other, representative molecules are present.

"My goal is to one day be able to tell you of the discovery of the first living planet, or of life beyond Earth," says Sassselov. "This is one of the biggest questions that science has ever asked, and to have the audacity to think we can even make a dent is such an exciting possibility."



JACK SZOSTAK, Co-Director

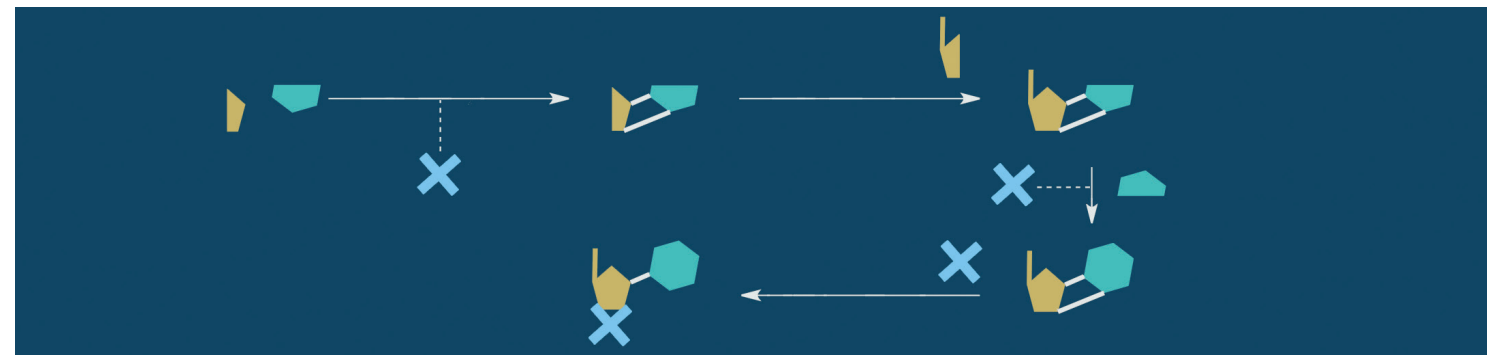
Jack Szostak is contributing to the study of the origins of life by investigating how the first and simplest biological cells began to self-replicate and evolve into more complex structures.

"We're trying to understand how, once you have the right molecules — the building blocks for biology — they get together and assemble into cells that can grow and divide and start to evolve," explains Szostak, an investigator at Massachusetts General Hospital and the Howard Hughes Medical Institute and co-director of the Simons Collaboration on the Origins of Life.

Szostak investigates the earliest cellular evolution by building physical models of primitive cells that could have formed on early Earth. His protocells consist of two key components: a cell membrane and some form of genetic material, currently RNA, that may have self-replicated using simple chemistry. Once protocells can replicate, some should contain RNAs that confer an advantage over other protocells, and should therefore begin to take over. "That would be the beginning of Darwinian evolution," says Szostak. And an RNA-based cell is good candidate material for all evolutionary advances, explains Szostak, as it provides a direct connection from the earliest cells to modern biology.

Going forward, Szostak hopes to solve the remaining questions about early RNA replication and then move on to observe the spontaneous emergence of more advanced cellular functions. "Eventually, we'll get a pathway going all the way from planet formation to the synthesis of all the building blocks of biology," he explains. "And that will inform our work on the origins of life. We want to understand how those building blocks became primitive cells and then evolved into the kinds of life we see today."

TOP: Szostak's fluorescence micrograph illuminates a large fatty acid vesicle (green) containing a clay particle coated with RNA (orange). Some clay particles catalyze membrane assembly, leading to the encapsulation of RNA. This same type of clay has previously been shown to catalyze RNA synthesis and could account for the assembly of the first cells. **OPPOSITE:** The product of the above sequence of reactions was discovered by John Sutherland and his group in 2009. The reactions' end product — a building block of RNA — could have led to the first biology on Earth and is composed of a sugar (yellow), a nucleobase (green) and a phosphate group (blue).



JOHN SUTHERLAND

At some point on early Earth, no biological life existed. Then, at a critical juncture, a combination of minerals, chemicals and ultraviolet light gave rise to the first biology. But how that transition occurred has long been a mystery.

In pursuit of an answer, John Sutherland, group leader of the Medical Research Council's Laboratory of Molecular Biology in Cambridge, U.K., focuses on the point at which inorganic materials became biological molecules and how biology continued to evolve after that moment.

Sutherland and his group broke crucial new ground in 2009 by discovering a process by which the building blocks of RNA can be created through chemistry. By re-creating prebiotic conditions and working with the chemistry thought to be present on early Earth, Sutherland filled a gap in origins-of-life theory and bolstered the hypothesis that RNA was the key informational molecule at the origin of life.

Now, extending those findings, Sutherland works to identify specific chemicals that could have both existed on early Earth and had potential to give way to biology. Hydrogen cyanide, found throughout interstellar space and in the atmosphere of moons within our solar system, is of central focus. In the presence of various minerals and ultraviolet light, explains Sutherland, hydrogen cyanide could have triggered a sequence of chemical events that resulted in the first biology.

To test this theory, Sutherland traces reaction pathways from hydrogen cyanide to the emergence of amino acids — the components of nucleic acids and the building blocks of membrane-folding molecules — all through similar chemical processes.

"We're beginning to accumulate a substantial body of evidence that implicates chemistry based on hydrogen cyanide at the origins of life," says Sutherland. "So a highly toxic compound to present-day life nevertheless may have contributed all the elements needed to make the building blocks that assembled at the dawn of life."

DONNA BLACKMOND

An essential factor at play in the chemistry of early Earth is the property of molecular chirality. Chiral molecules exist in two forms that are identical, yet not superimposable on their mirror images, as are left and right hands.

Many biologically important molecules are homochiral, existing only in one of the two possible mirror image formats. Because homochirality has a significant role in molecular recognition, its presence is crucial to basic biological processes. But it is likely that for a time on Earth, the basic life-building molecules such as amino acids and sugars formed both right- and left-handed forms equally.

Today, all sugars are 'right-handed,' and all amino acids are 'left-handed.' But how these molecules emerged in this way remains a mystery.

Donna Blackmond, professor of chemistry at the Scripps Research Institute, is aiming to find out how the first homochiral molecules emerged on the planet. "This is a question that's intrigued people since they realized that molecules had this property of 'handedness,'" says Blackmond.

Blackmond uses several approaches in studying how amino acids and sugars finally tipped in one direction, to the 'hand' that they are today. Her lab experiments with phase behavior of crystalline chiral solids to develop processes that amplify the fraction of one hand over the other. She uses both experimental and theoretical studies to explore the possible chemical reactions that might have amplified one 'hand' over the other.

And Blackmond is collaborating with other prebiotic chemists to weave these chiral amplification processes into other basic prebiotic chemical reactions.

"It's so important to know when and where along the line this evolution happened," says Blackmond. "This one question could help us understand a lot of other questions about how life started."



ROGER SUMMONS

Massachusetts Institute of Technology professor of geobiology Roger Summons has always appreciated working across disciplinary boundaries in order to gain new insights. Not surprisingly, his work in the area of origins of life ranges from lab experiments that re-create conditions on early Earth at the time of life's emergence to comparative research on modern ecosystems dominated by microbes — microscopic single-celled organisms that were the only inhabitants on Earth for 80 percent of its history.

Summons also works to identify signatures of life in Earth's earliest sedimentary rocks that could provide evidence for life's presence on early Earth and enhance our understanding of that life. By examining chemical and isotopic patterns in ancient rocks, Summons searches for signs of microbial processing — or 'metabolizing' — of elements that are central to biology.

While it is unlikely that any unaltered rocks remain from the time life first emerged more than three billion years ago, by identifying the presence of microbially processed carbon and sulfur in the rocks that are now accessible, Summons is working to demonstrate that life was actively metabolizing these elements at particular moments or places during Earth's history. Apparent metabolic activity of ancient microbes might then be viewed alongside metabolic activity of contemporary microbes to try to piece together new clues about the nature of primordial metabolisms.

In the end, Summons says, "the answers are going to come about by people getting together, discussing the results and arguing about it. I'm just one small part of this work, and this is a field where no individual is going to have all the answers."

LISA KALTENEPPER

What kind of environment can support life on a planet orbiting another sun? What does a water world's environment look like? What is the influence of two suns on a planet's environment?

These are just some of the questions that Lisa Kaltenegger, research group leader at the Max Planck Institute for Astronomy in Germany and researcher at the Harvard-Smithsonian Center for Astrophysics, is asking. "We're trying to figure out what conditions can support life and where to find them outside our solar system," says Kaltenegger, who uses atmospheric modeling to experiment with potential environments on distant planets.

Kaltenegger focuses on exoplanets, planets orbiting other stars, that are the right size and distance from their sun to sustain liquid water, one essential element necessary to support life as we know it.

"A planet only appears as a dot of light among the huge darkness of space," says Kaltenegger. "It's close to a very bright source of light, its star, so catching a smaller planet's light is a major technical challenge, one we have solved for larger planets. Now we need larger telescopes — and time to build them — to identify smaller habitable planets."

In April 2013, Kaltenegger was part of a team that announced the first two rocky planets whose size and distance from their sun indicate that they could support liquid water. The planets, Kepler-62e and Kepler-62f, may have the capacity to support life.

"After thousands of years, we are the first generation that will be able to answer the question of whether or not there are other worlds like ours out there, which makes it an amazing time to live in," she says.

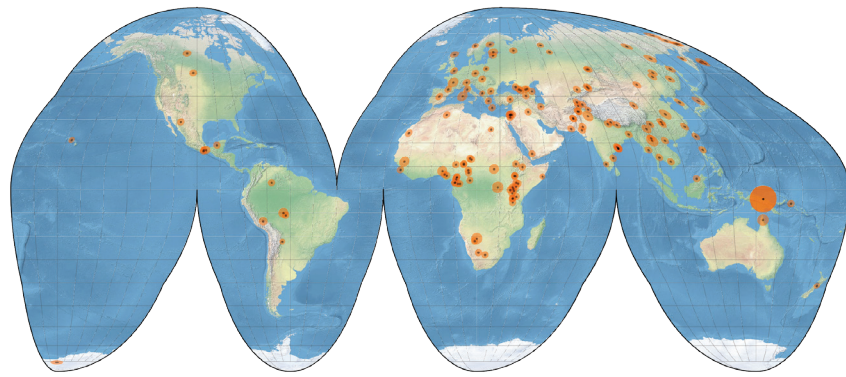
TOP: A rock outcrop in western Australia contains one of the oldest documented stromatolites, a dome-shaped feature resting on an older, flat surface. Roger Summons and his colleagues study these structures, thought to have formed with the growth of a microbial community that existed on an ancient sea floor. **OPPOSITE:** An artist's rendering of the planetary system Kepler-62, discovered by NASA's Kepler team in April 2013. Two of the five planets in the system, Kepler-62e and 62f, are located within the habitable zone of the star and likely possess liquid water. Courtesy of Dimitar Sasselov.



“A time will come when men will stretch out their eyes. They should see planets like our Earth.”

—Christopher Wren

SIMONS GENOME DIVERSITY PROJECT



Diverse human genomes collected all over the globe — from groups ranging from some of the smallest, most isolated, genetically distinct communities to the largest and most accessible ones — are providing researchers with fresh insight into the full range of diversity and variety within the human species. While other projects have produced thorough and greatly informative datasets, the enormous range of human genomes on the planet has not been otherwise documented and explored.

The Simons Genome Diversity Project, led by principal investigator David Reich along with co-investigators Nick Patterson and Svante Pääbo, aims to characterize human genetic diversity with samples from two individuals from each of 125 populations across the globe. “We’re trying to represent as much of the existing genetic variation around the world as we can access,” says Reich. “With some holes, we think we’ve captured much of the diversity that we know about.”

“The question they’re getting at is: What are the outer boundaries of human variation?” says Alex Lash, chief informatics officer at the Simons Foundation. “How much variation can you have from genome to genome and still be considered the same species?”

Chosen populations range from the Sardinians, an Italian ethnic group that has been relatively isolated from European gene flows, to the Khoisan, a small population of hunter-gatherers in southern Africa, to Sherpas, an originally nomadic and now isolated small group in eastern Nepal.

Delving into current human genetic variation could further our understanding of the processes that contributed to creating that variation. For example, researchers might use the new information to trace migration of early humans by comparing genomic similarities among populations of varying geographic proximity. The dataset might also enable discovery about physical and environmental factors that affected human natural selection and genetic evolution in different regions.

“I’m interested in understanding how people got to where they are today, how they diversified from common ancestral populations and how mixtures between populations occurred,” says Reich. “And there are forces of natural selection that shaped people’s genomes and are responsible for the differences and similarities in the people alive today, and I’d be interested in understanding those, too.”

Understanding genetic diversity also holds promise for enhanced understanding of disease, making rapid and accurate medical diagnoses, and developing improved and targeted therapies.

Equally important as capturing a wide array of human genomes was sequencing the data consistently. By processing each sample in the identical way, the project minimized the likelihood of encountering systematic differences between samples — differences that, in other experiments, are created by varying experimental setups. Reich and his team used Illumina HiSeq 2000 sequencers to complete whole-genome sequencing on all 250 samples. All samples were sequenced at one facility using a precise experimental protocol, over a short period of time.

When sequencing and analysis of all the data is complete, Reich and his colleagues plan to offer the dataset in downloadable and analyzable form through repositories at the Simons Foundation, Google and Amazon.

The researchers believe that the consistency, accessibility and diversity of the dataset will make it an essential genomic research tool. “We intend this to be a reference set for the whole world for studying human genetic variation,” says Reich. “We think it’s going to be the primary reference population genetics dataset for years to come.”

TOP: This map by Peter Sudmant of the University of Washington shows the global sources of DNA samples from the diverse populations in the Simons Genome Diversity Project dataset. The size of the circle indicates relative sample size: two for most populations. **OPPOSITE:** A nucleosome is a protein-DNA complex that aids in the compaction and storage of human genetic material and regulates access to information stored in the human genome. The New York Genome Center studies nucleosomes to understand how genetic information is regulated, or mis-regulated, in disease.

NEW YORK GENOME CENTER

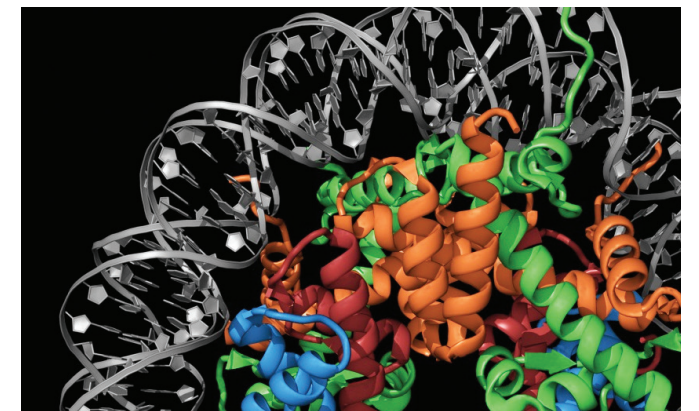
In the summer of 2011, 12 preeminent academic, research and medical institutions across New York state came together to announce a plan to develop a comprehensive genomic sequencing, analysis and research institute. The result was the creation of the New York Genome Center (NYGC), an unprecedented independent nonprofit consortium that leverages the unique resources and talents of its members: leading New York hospitals, medical schools, research centers and authorities on genomic thought.

“The core mission of NYGC is to save lives by harnessing technology, science and medicine together,” says Robert B. Darnell, president, chief executive officer and scientific director of NYGC.

The concept of an exceptional New York genome center first emerged in 2010 and quickly gained traction with an early matching grant from the Simons Foundation. It was further catalyzed with additional philanthropy from other individuals and institutions.

Now NYGC researchers, having moved into their new facility in September 2013, have already published their first significant findings. In February 2014, scientists from NYGC, Rockefeller University and Memorial Sloan-Kettering Cancer Center together announced the discovery of a strong link between an unusual genetic mutation and a rare liver cancer, fibrolamellar hepatocellular carcinoma. The clear identification of this association may now enable the development of a targeted therapy for this deadly liver cancer and for other more common cancers as well.

To accomplish feats like this, the center, located in Tribeca, houses state-of-the-art sequencing technology, analytic and bioinformatics tools and resources for academic and clinical research. Part of becoming a hub for genomic research means embracing the rapid scientific advancements revolutionizing the field.



“The amount of data now available is mandating a big change,” says Darnell. “The new sequencing and analysis technology is changing the way we do genomic science.”

“It’s not just a matter of sequencing data,” says Toby Bloom, deputy scientific director of informatics at NYGC. “In providing a space for researchers from different institutions to analyze data together, we’re hoping to make this facility not only a sequencing hub but also an informatics and analysis center for the whole New York area.”

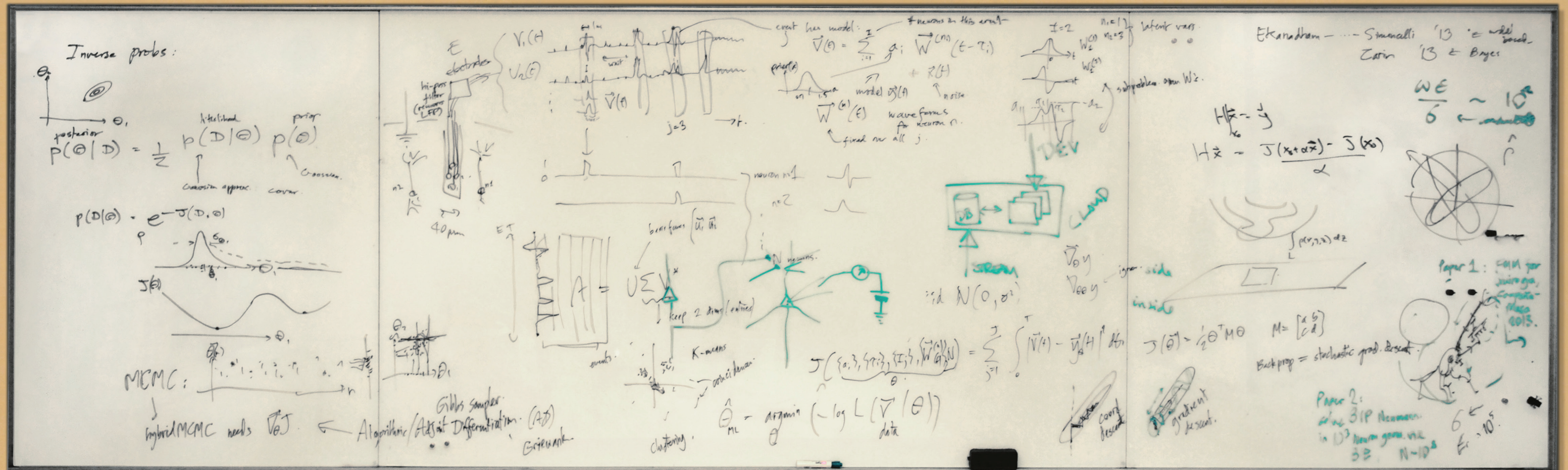
The center necessarily relies on collaboration. “Different kinds of scientists have to work together — from people sharing interesting samples, to people doing high-quality sequencing, to computational biologists and high-level computer scientists, all the way up to people in big data,” says Darnell. “No single person is sufficient to drive the revolution in genomics.”

Darnell is determined to continue the center’s support of researchers who use genomic science and to provide them with the most up-to-date technology.

“We’re staying abreast of — and pushing — current technology to be as expansive, forward-thinking and responsive as possible.”

“It behooves us to place the foundations of knowledge in mathematics.”

—Roger Bacon



Researchers at the Simons Center for Data Analysis tackle the problem of 'spike sorting': a basic task converting raw data measured in an electrophysiological experiment into a disambiguated set of signals from active neurons. Technological advances in the design and construction of electrodes have made spike sorting a big-data question.

MATHEMATICS & PHYSICAL SCIENCES FIRST ANNUAL MEETING

Five years ago, in 2009, the newly launched Mathematics and Physical Sciences (MPS) division at the Simons Foundation issued its first requests for applications. Since then, the MPS program has funded nearly 700 grantees, including 34 Simons Investigators and 132 Simons Fellows, who study topics across the division’s primary subject areas: mathematics, theoretical physics and theoretical computer science.

Not until this fall, however, at October’s inaugural MPS annual meeting, did MPS Investigators and Fellows have the opportunity to come together in one physical space to begin to grow a shared community. Spanning two days, the meeting brought together 72 foundation-supported researchers to learn, discuss and forge new collaborations.

The meeting featured nine lectures, all held in the Gerald D. Fischbach Auditorium at the Simons Foundation in New York City. Diverse topics were covered, ranging from Christopher Hacon’s talk on the geometry of polynomial equations to Shafi Goldwasser’s survey of new concepts in cryptography and Roger Blandford’s lecture about the accelerating universe.

Daniel Spielman’s lecture on his recent proof of the Kadison-Singer conjecture was a meeting highlight. Formulated in 1959, this conjecture is one of the key foundational questions of quantum physics and has turned out to have many fascinating implications for mathematics and theoretical computer science. Spielman’s solution was a major breakthrough of 2013, and the lecture was memorable for both its clarity and its conciseness.

Leslie Greengard, founding director of the Simons Center for Data Analysis, gave the meeting’s keynote address. Greengard’s work on fast algorithms and scientific computing has had a tremendous impact on many fields in science and engineering, including solid-state physics, computational chemistry and biology. His research combines ideas from theoretical mathematics, physics and computer science, and the broad vision presented in his talk appealed to all participants.

The meeting also provided a unique opportunity for scientists to interact across disciplinary boundaries. Sharon Glotzer,

“It was great to meet the other Simons Investigators and share details about the mathematical puzzles we’re each obsessed with solving.”

SHARON GLOTZER, Simons Investigator and physicist

a Simons Investigator and physicist, embraced the opportunity to learn from researchers in other fields. “It was great to meet the other Simons Investigators and share details about the mathematical puzzles we’re each obsessed with solving,” says Glotzer. “And I learned some interesting things about cryptography from one of the talks that I’m still thinking about, trying to relate it to things I’m working on.”

With the growth of the Simons Investigators program, next year’s meeting will be larger and will likely expand in scope. This core group of attendees, funded for up to ten years, plus the foundation’s Math+X Chairs, funded for up to six years, will be invited back to annual meetings at the foundation for years to come, forming a steady cohort of attendees.



INTERNATIONAL GIVING

The Simons Foundation Mathematics and Physical Sciences (MPS) division increased its targeted grant-making activities to international institutions in 2013, building on an already substantial outreach effort to support high-level basic research in quantitative scientific fields. This year, MPS awarded grants to ten institutes around the globe, from the Middle East, Russia and India to China, South America and Europe. “MPS’s focus is on institutes that have high visibility scientifically,” says Yuri Tschinkel, director of Mathematics and Physical Sciences. “There is also a geographic diversity that we are striving for. India and China have been at the forefront of pure math research for many years, and Brazil is a powerhouse as well.”

The targeted institutional grants are not designed to replace the funding that these prominent institutes already have, but rather to enable new activity. “We always look at the impact of our gifts. And we have been getting a lot of positive feedback from scientists visiting these institutions — so we’re on the right track,” Tschinkel says.

The four institutional grants highlighted below illustrate the foundation’s geographically diverse — and diverse approaches to — funding of mathematics and computer and physical sciences around the globe.

NATIONAL CENTRE FOR BIOLOGICAL SCIENCES
Bangalore, India

Working together with the foundation’s Life Sciences division, MPS has enabled India’s National Centre for Biological Sciences (a division of the Tata Institute of Fundamental Research) to establish the Simons Center for the Study of Living Machines (SCSLM). This new center will provide an intellectual home for theorists — often with backgrounds in math, physics and computer science — to interact with experimental biologists. The center’s research will exploit mathematical tools such as nonlinear dynamics, game theory and the theory of computation to investigate and describe cells and organisms as “living machines:

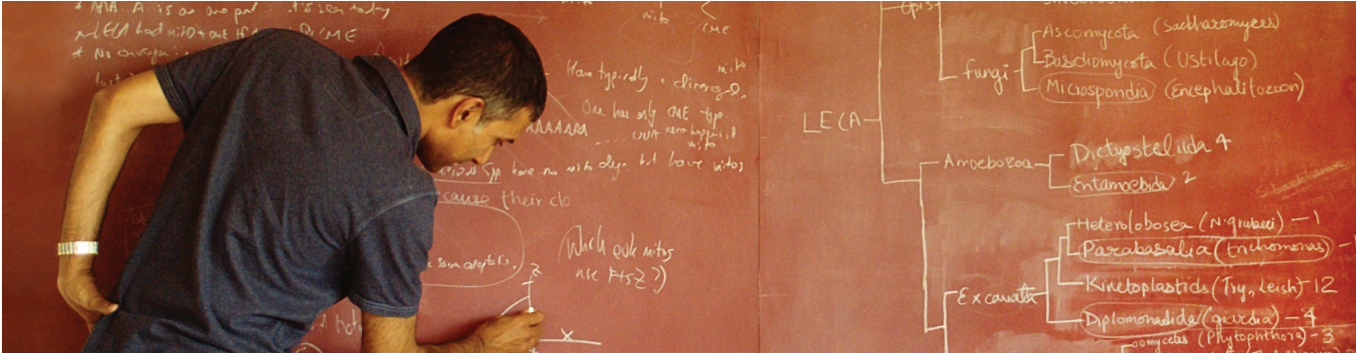
imperfectly optimized products of natural selection which consume energy to achieve specific goals,” in the words of SCSLM’s mission statement.

The connections between theoreticians from other disciplines and biological experimentalists have been strengthening for the past decade, according to Mukund Thattai, director of SCSLM. “This is a very exciting time, reminiscent of the state of physics in the early 20th century,” Thattai says. “At one level, new kinds of biological experiments are generating massive amounts of data. But at a deeper level, biology is doing what it has always done: throwing up a constant stream of mysteries, revealing completely unexpected phenomena and tantalizing clues about how life works at all scales. Until recently, biologists had all the fun because they were the ones able to attack these deeper issues, while theorists were left to watch from the sidelines. This has changed now.”

MATHEMATICAL RESEARCH INSTITUTE OF
OBERWOLFACH
Oberwolfach, Germany

International collaborations between researchers can be difficult for even high-profile institutions to fund, but MPS grants allow the institutions to foster visiting scientists from anywhere on earth. The foundation’s grant to Germany’s Mathematical Research Institute of Oberwolfach (MFO) promises to be especially effective, according to Tschinkel. The new Oberwolfach Simons Visiting Professors program will support 40 researchers from outside Europe to attend one-week-long multidisciplinary workshops at MFO in combination with a research visit to a European University.

“The Simons Visiting Professorships offer a unique opportunity to deepen ties between leading researchers from overseas and researchers in Europe and to follow up on research ideas generated at Oberwolfach workshops,” says Gerhard Huisken, director of MFO. “They create synergies in combining these activities in a single overseas trip, thus allowing an optimal use of resources of all institutions involved.”



TSINGHUA UNIVERSITY
Beijing, China

Supporting collaboration between far-flung mathematicians is also the goal of the targeted grant to the Tsinghua University Education Foundation in China. The funds will support travel expenses of scholars from the U.S. and Europe to speak at weekly workshops at the Tsinghua Sanya International Mathematics Forum (TSIMF) in 2014. Past workshops have been attended by hundreds of world-renowned mathematicians, economists and scientists, including Fields Medal winners Vaughn Jones and David Mumford and Nobel Prize-winning physicist David Gross.

“The mission of [TSIMF] is to raise the level of mathematical research in China while providing a platform for scientific innovation by bringing together leading mathematicians and core researchers from related disciplines,” says Shiu-Yuen Cheng, chairman of the mathematics department at Tsinghua University. “Travel support is crucial to achieving this mission, especially in this era of dwindling grant supports. The Simons award will greatly facilitate these important international exchanges at the forum.”

INTERNATIONAL CENTER FOR THEORETICAL
PHYSICS (ICTP)
Trieste, Italy

Scientists and mathematicians in the developing world can all too often feel isolated from their peers — a problem that the late Nobel Prize-winning Pakistani physicist Abdus Salam experienced directly and sought to mitigate 50 years ago by founding the Associate Scheme at ICTP. Associateships provide travel and living expenses for promising scientists in the developing world to visit ICTP three times for up to 210 days over six years. In 2013, a new

category of Simons Associates was created to expand the ICTP Associate Scheme. “Simons Associates will be able to use part of their funds to bring postdocs or students with them to ICTP,” says Fernando Rodriguez Villegas, director of the Associates Scheme. “It allows some more flexibility for the associates, and it makes the program better as a whole.”

Although the Associates Scheme is one of ICTP’s longest-running outreach programs, Villegas stresses the importance of the Simons Foundation’s new support. “It’s a complicated balancing act to have a very high level of science being done at the institute together with helping scientists in the least-developed parts of the world, such as sub-Saharan Africa,” Villegas says. “It is sometimes difficult to understand what it’s like to come from an impoverished background as a scientist. Associates often tell us that the program is crucial for their careers. So ICTP is a godsend for an incredible number of people, and the Simons grant is a fantastic gift.”

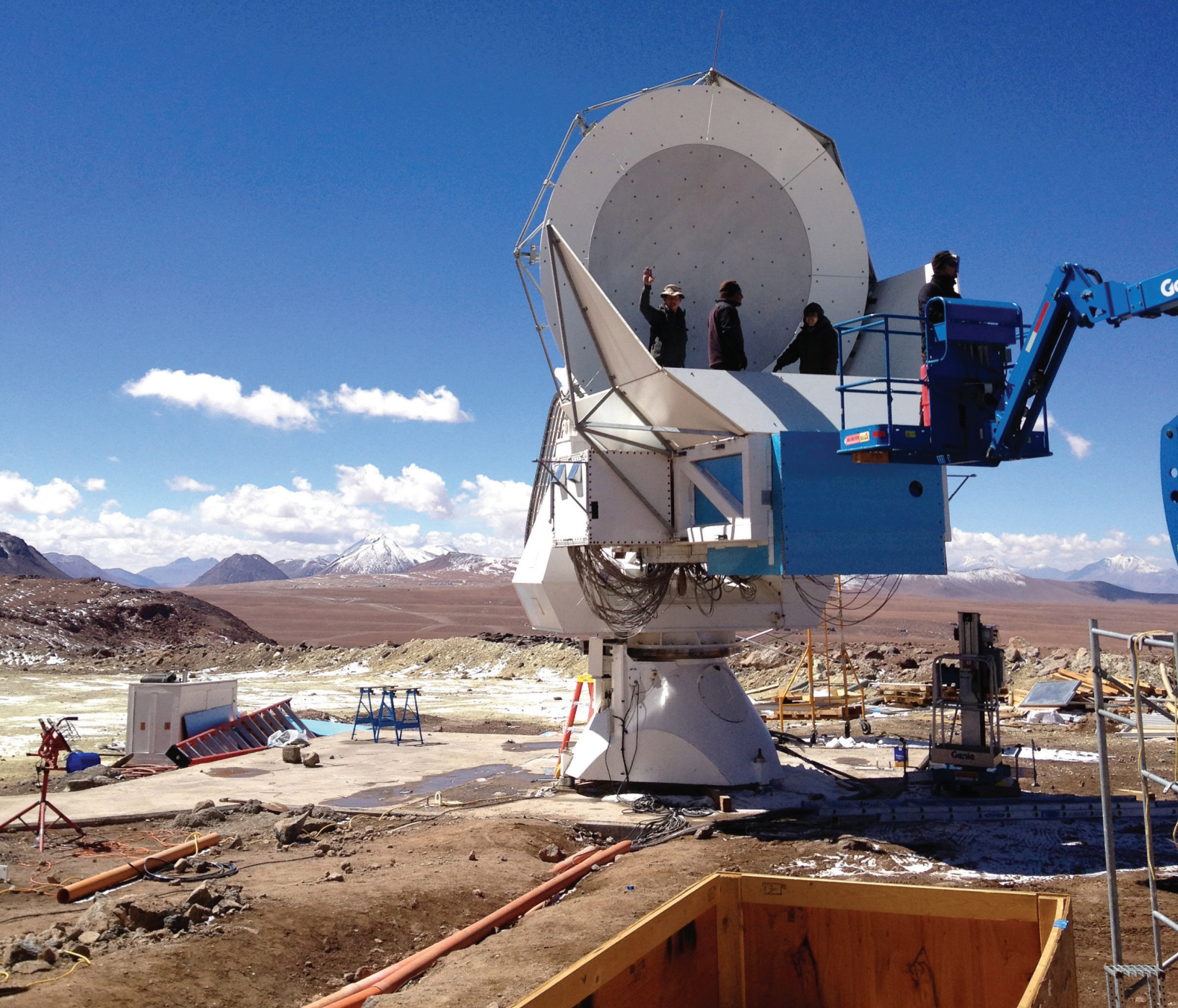


TOP: Mukund Thattai, faculty member at the Simons Center for the Study of Living Machines (SCSLM) in Bangalore, India, explores the processes that led to the evolution of complex cells more than two billion years ago.

BOTTOM: Amit Das of the SCSLM studies how proteins are organized on the surfaces of cells.

“I have looked further into space than ever a human being did before me.”

—William Herschel



POLARBEAR

High in Chile’s Atacama Desert, above almost half of the Earth’s atmosphere, a Polarization of Background Radiation (POLARBEAR) telescope probes the sky for signatures of ‘inflation,’ the hypothesized moment following the Big Bang when the universe expanded exponentially.

The site, dry and desolate, has a unique climate that is ideal for searching for signatures of inflation. “It’s really like being on another planet,” says Brian Keating of the University of California, San Diego. “It’s a very special place to do astronomy.”

Keating, with co-investigator Adrian Lee of the University of California, Berkeley, is building an array of three POLARBEAR telescopes to investigate the origin of the universe, one of the greatest scientific mysteries of all time. “What we’re trying to do, essentially, is detect the Big Bang itself,” explains Keating.

Inflation is a key idea of modern cosmology. It has a clear experimental signature, and researchers theorize that during the period of inflation, quantum fluctuations would have produced ripples in space-time known as gravitational waves. These waves, in turn, would have left behind particular light waves called primordial B-modes, whose polarization makes them uniquely identifiable as relics of the Big Bang.

The first POLARBEAR instrument, the Huan Tran Telescope, began operating in March 2012. It will soon be joined by two others that Keating and Lee are building while they continue to implement improvements to the instrumentation of the Huan Tran. Together, the three telescopes will be known as the Simons Array. When complete, the array will provide a clearer and more accurate view of primordial B-modes and thus of the earliest moments of the universe.

OPPOSITE: Investigators working on the POLARBEAR project in Chile’s Atacama Desert inspect the project’s first telescope. By 2015, this telescope will be joined by two others to create the Simons Array. **TOP:** The first POLARBEAR telescope searches the skies for signatures of inflation, the moment after the Big Bang when the universe expanded exponentially.



Keating played a major role in the design of an experiment known as BICEP, which has recently reported evidence for B-modes from inflation. “The inflationary signal has been claimed to exist,” says Keating. “But we need to study it at high resolution to tease out the details of inflation — its energy scale, duration and dynamics. These are just some of the topics the Simons Array will explore.”

While it seems likely that inflation did occur, Keating explains, a negative result would provide significant insight into the origins of the universe as well. “The inflationary signal is not yet known to exist,” he says. “So it may then be that inflation did not occur and there must be some other origin of the universe. And if that’s the case, it would be very exciting to understand why the universe is incompatible with an inflationary origin.”

The Simons Array will also search for cosmic neutrinos. Neutrinos are an essential component of the standard model of particle physics, but despite their importance, their masses are unknown. “By searching for telltale distortions that the neutrinos produce, it may be possible to definitively measure their masses,” Keating says. Cosmic neutrinos may also be a significant component of dark matter, which composes most of the mass of the universe but has been detected only by its gravitational effects on conventional matter.

Construction of the new telescopes is slated to begin within a year. “What draws me to this project is the ability to study the very largest things in the universe, to really disentangle deep mysteries,” says Keating. “To me, there’s nothing more fundamental that you could study in all of science.”

“Human subtlety ... will never devise an invention more beautiful, more simple or more direct than does nature.”

—Leonardo da Vinci

QUANTUM ENTANGLEMENT

Simons Symposium

What happens if you jump into a black hole? Is it a smooth ride past the event horizon, the boundary beyond which light cannot escape? Or is there a sharp wall of energy that immolates everything that crosses it? This controversial idea of a 'black hole firewall', first proposed in 2012, was one of the topics participants discussed at the Simons Foundation Quantum Entanglement Symposium in February 2013, organized by Shamit Kachru, Hiroshi Ooguri and Subir Sachdev.

Each Simons Symposium brings researchers together for an intense week of conversation and collaboration centering on a particularly timely topic in mathematics, theoretical physics or computer science. Quantum entanglement, famously described by Albert Einstein as “spooky action at a distance,” is a counterintuitive phenomenon in quantum mechanics in which multiple particles can start to behave as a unit. When particles are entangled, measurements taken on one particle will correlate with measurements taken on other particles, no matter how far apart they are.

Entanglement is a major focus for researchers in both high-energy physics and condensed matter physics. Because the fields developed independently, the techniques they use to study entanglement are different, so bringing researchers from both areas together for the symposium was very fruitful. “It’s always useful to meet with people in other areas, compare tools and discover unexpected applications of other tools,” Ooguri says.

One example of this unexpected convergence of ideas involved talks by condensed matter theorist Ashvin Vishwanath and string theorist Joseph Polchinski. Vishwanath spoke about using ideas from quantum entanglement to classify new spin systems in large-scale interactions of particles, and Polchinski talked about possible resolutions of the black hole firewall problem.

“Remarkably, the inequalities that Polchinski was using were the same as Vishwanath had used to describe and classify these quantum spin systems on a lattice,” Sachdev says.

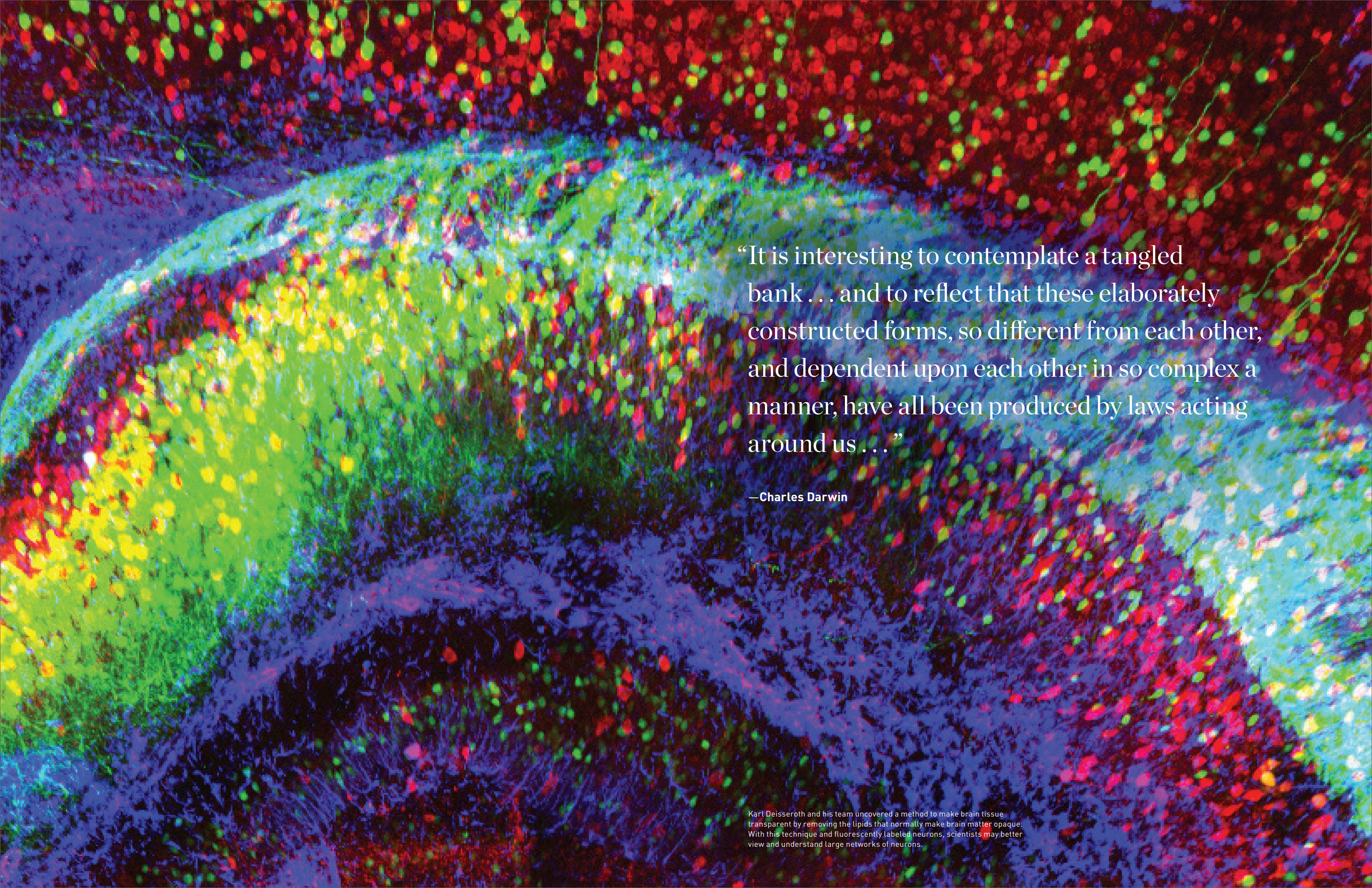
The ‘holographic principle’ was also discussed at length during the symposium, providing a different perspective on entanglement. In this context, the holographic principle is a remarkable set of ideas that relate aspects of a higher-dimensional space-time universe with gravity to some properties of a quantum field theory defined on a lower-dimensional universe without gravity. Results from gravity physics in the higher-dimensional space offer insights into quantum mechanical properties of the lower-dimensional universe, and vice versa.

This line of inquiry has concrete implications for the real world. In a talk at the symposium, Gary Horowitz argued that entanglement and the holographic principle can be used to understand the properties of cuprate superconductors, which lose electrical resistance at much higher temperatures than conventional superconductors and exhibit many other properties incompatible with the standard theory of superconductors. Taking entanglement into account gives researchers a more subtle understanding of the way materials carry current and may even help with the development of new classes of high-temperature superconductors.

In addition to lectures on the latest research into entanglement, the symposium offered its interdisciplinary participants the opportunity to engage in less structured discussions, which have proved to be highly productive. Participants report that these cross-disciplinary interactions have already led to fruitful new collaborations.

The black hole firewall paradox is far from resolved, and entanglement is far from being understood, but researchers hope that connections made at the symposium will have short- and long-term implications for mathematics and physics research.

OPPOSITE: A representation by Guifre Vidal, of the Perimeter Institute for Theoretical Physics, of a tensor network: a mathematical description of the entanglement properties of a quantum mechanical wave function representing the state of many interacting particles.



“It is interesting to contemplate a tangled bank . . . and to reflect that these elaborately constructed forms, so different from each other, and dependent upon each other in so complex a manner, have all been produced by laws acting around us . . .”

—Charles Darwin

Karl Deisseroth and his team uncovered a method to make brain tissue transparent by removing the lipids that normally make brain matter opaque. With this technique and fluorescently labeled neurons, scientists may better view and understand large networks of neurons.

SFARI GENETICS PROGRESS

As evidence mounts that autism is a highly heterogeneous disorder, with hundreds of genes implicated in its development, SFARI Investigators are elucidating the complex interplay between autism genetics and biology.

Over the past few years, researchers have identified at least two dozen high-confidence autism genes by searching for spontaneous, or *de novo*, mutations within the Simons Simplex Collection (SSC), a repository of data from more than 2,600 families consisting of one child with autism and unaffected parents and siblings.

Now, a team led by Evan Eichler of the University of Washington in Seattle has mined this resource in a new way, searching for mutations inherited directly from parents. Eichler’s lab searched for copy number variants (CNVs) — genomic regions that are missing or duplicated — among 411 SSC families.

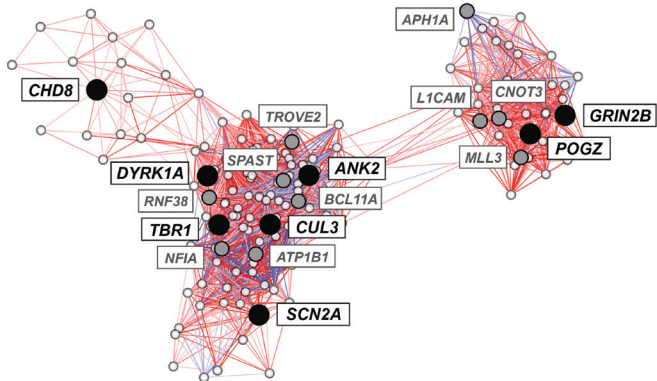
Their study, published in the October 3, 2013, issue of the *American Journal of Human Genetics*, found that children with autism inherit more parental CNVs than do their siblings. The difference is even more pronounced in families whose unaffected siblings have high social skills, suggesting that the CNVs indeed play a role in the affected child’s autism.

The researchers were able to identify much smaller CNVs than had been found in previous studies, allowing them to home in on specific autism candidate genes. These genes, many of which are involved in learning and brain plasticity, compose a different list than previous studies have discovered. “The data give us another hook to understand the genes relevant to autism,” Eichler says.

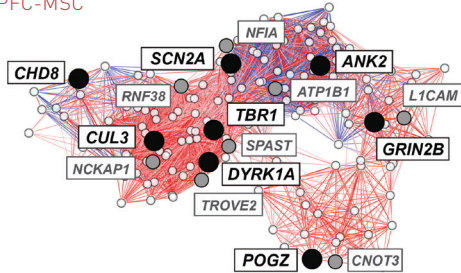
Two other collaborations, published November 21, 2013, in *Cell*, have started to bridge the gap between candidate genes and biological processes. Many autism researchers believe that the hundreds of autism genes converge on a much smaller set of biological pathways.

A team led by Daniel Geschwind of the University of California, Los Angeles, has mapped hundreds of autism

A. Period 3-5 PFC-MSC



B. Period 4-6 PFC-MSC



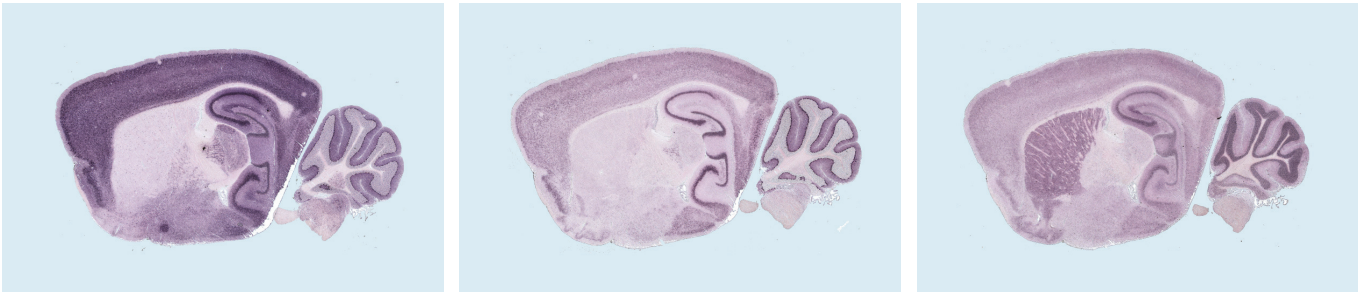
candidate genes onto a network the laboratory has developed over the past decade, consisting of modules of genes that work together to carry out particular functions.

The team found that unlike intellectual disability genes, which seem to be widely scattered across different modules, autism genes tend to cluster in several modules involved in the development of upper-layer cortical projection neurons, with one such module involved in development of a deeper cortical layer. These neurons connect regions of the cerebral cortex within and across hemispheres. The clusters “give us a window to look at the specific timing and the potential mechanism by which these genes are acting,” Geschwind says.

In the second *Cell* paper, Matthew State of the University of California, San Francisco, and his team tackled the same overarching problem using a different approach. The researchers built gene clusters around nine high-confidence autism genes and then checked another 120 autism candidate genes to see whether they appeared in any clusters.

The researchers found that many of the genes are expressed in clusters corresponding to mid-fetal development of cortical projection neurons, also in a deep brain layer. State calls the overlap between the two laboratories’ findings “gratifying.” These findings, he says, make the leap from a multiplicity of autism genes to “a very specific idea of where to do the next experiment.”

MOUSE MODELS OF AUTISM



As information pours in about genetic variants that heighten susceptibility to autism, SFARI has turned its attention to a natural next step: developing and sharing mouse models for these genetic risk factors. With The Jackson Laboratory in Bar Harbor, Maine, SFARI is providing mouse models of several important autism-related mutations.

Mouse models provide an essential platform for studying the neural circuits underlying autism spectrum disorders. But while researchers are producing many interesting mouse models, these models are often not made widely available. Some researchers are reluctant to share their models, as their careers may depend on publishing studies that use them, and others are simply unwilling to expend the time and resources entailed in sending mice to other labs.

“It’s onerous for a lab to generate and ship a mouse model,” says Marta Benedetti, SFARI senior scientist.

What’s more, once a colony of mice has been shipped to a laboratory, it must typically be subjected to a lengthy quarantine.

To streamline this process, SFARI is providing funding to establish some of the mouse models most relevant to autism and to distribute these models to researchers. The Jackson Laboratory is widely trusted by research institutions, and its mice are typically not subject to quarantine.

OPPOSITE: When and where do mutations in autism risk genes disrupt brain development? Researchers used BrainSpan, a database that shows when genes are turned on or off in the developing human brain, to identify the time and place autism risk genes are activated, or deactivated, in concert, suggesting a common function. This figure shows highly correlated expression of many autism risk genes (connecting red lines) in the prefrontal cortex at periods 3-5 and 4-6, corresponding to weeks 10-24 post-conception. (Willsey, *et al.* 2013) **TOP:** These mouse brain images (Peca, *et al.* 2011) show the expression of three related genes: SHANK1, SHANK2 and SHANK3. Of these, only SHANK3, the gene implicated in the autism-related disorder Phelan-McDermid syndrome, is highly expressed in the striatum, a region in the middle of the brain associated with repetitive compulsive behaviors.

The Jackson Laboratory, as a result of its partnership with SFARI, now stores six mouse models of autism risk factors: duplications and deletions in 16p11.2, deletions in CNTNAP2, a model for Timothy syndrome and two models for Phelan-McDermid syndrome. Additional mouse models are in the planning stages. SFARI is partnering with the Dup15q Alliance, a philanthropic group, to provide funding for developing a mouse model for chromosome 15q duplication syndrome, which is linked to autism.

One advantage of centralizing the storage and distribution of mouse colonies, Benedetti says, is that each model is bred from just one strain of mice, eliminating the major variable of genetic background when comparing across mouse models. Currently, researchers use a variety of strains, which makes it harder to interpret research findings. Having uniform strains of autism mouse models should make it easier to figure out which signaling pathways or neural circuits are disrupted in autism, Benedetti says.

SFARI is encouraging investigators to share mice with The Jackson Laboratory even before publishing their mouse models, so the laboratory can be ready to distribute the mice immediately after publication. Now that SFARI has removed many of the logistical roadblocks to sharing mice, Benedetti hopes researchers will be even more forthcoming with their models.

“If you share, you’re a good member of the scientific community,” she says. “That’s how science goes — it wouldn’t progress if you didn’t share your reagents.”

SFARI 2013 RESEARCH ROUNDUP

To catalyze high-quality autism research, SFARI supported nearly 250 SFARI Investigators on four continents in 2013. Some have been studying autism for many years, and others have migrated to autism research from other fields, but together they have carried out hundreds of research projects that advance our understanding of autism, studying cognition and behavior, genetics, molecular mechanisms and improvements in diagnostics and therapeutics. The following represent some highlights of SFARI Investigators' research over the past year.

Early warnings. Infant boys later diagnosed with autism show diminishing attention to other people's eyes between 2 and 6 months of age, suggested a new study published November 6, 2013, in *Nature*. The phenomenon is the earliest known behavioral sign of autism.

The researchers, SFARI Investigator Ami Klin and Warren Jones of Emory University in Atlanta, compared the gazes of 11 young boys later diagnosed with autism and 25 typically developing children at various stages of development as they watched videos of a woman cooing and playing patty-cake. While the controls grew more interested in the woman's eyes over time, the children who went on to have an autism diagnosis steadily lost interest in the woman's eyes as they grew older. By age 24 months, they spent about half as much time looking at her eyes as the controls did.

Previous studies had suggested that signs of autism may emerge as early as 6 months. The new study shows that in fact indications appear as early as 2 months. Before that age, however, children later diagnosed with autism seem to display the same level of interest in people's eyes as typically developing children, suggesting that early infancy represents "a remarkable opportunity for treatment," the authors write.

Further research will be required to determine whether these findings hold true for larger populations of children who go on to develop autism.

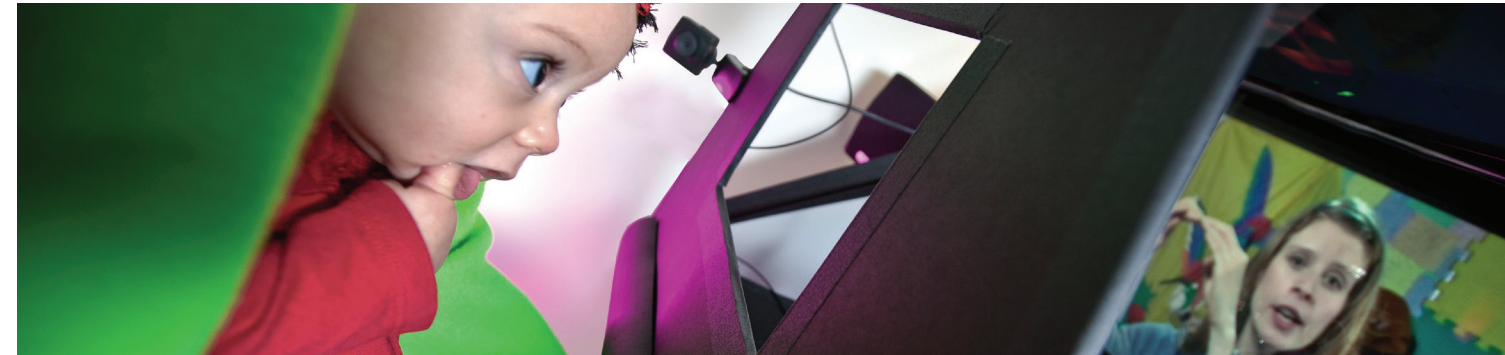
Long genes. Autism candidate genes are on average about four times longer than other genes expressed in neurons, researchers reported in the September 5, 2013, issue of *Nature*. The functions of these long genes may be disrupted by mutations or environmental factors that impair topoisomerases, enzymes that the researchers showed are crucial to the expression of long genes.

The research team, co-led by SFARI Investigator Benjamin Philpot of the University of North Carolina at Chapel Hill, had previously shown that a topoisomerase inhibitor called topotecan can activate UBE3A, a gene associated with Angelman syndrome, a disorder related to autism. In the new study, the researchers treated cultured mouse and human neurons with topotecan. The chemical, they found, reduced the expression of 155 genes, all of them long, and increased the expression of 28 shorter genes. It inhibited the expression of nearly all genes longer than 200 kilobases. Many of the inhibited genes are involved in neuronal development and synaptic function.

The study showed that 27 percent of the genes affected by topotecan are known autism-risk genes, a much higher percentage than chance would dictate. The team is now testing other drugs that disrupt topoisomerases, to try to identify environmental contributors to autism.

A new light on compulsion. Researchers have taken a step toward identifying the specific brain circuits involved in compulsive behaviors. SFARI Investigators Guoping Feng and Ann Graybiel of the Massachusetts Institute of Technology made certain neurons responsive to light in the brains of compulsively grooming mice and then showed that it is possible to 'turn off' the compulsive behaviors by activating those neurons with a light beam.

The study, published in the June 7, 2013, issue of *Science*, examined a genetic mouse model that grooms so obsessively it develops skin lesions. The researchers targeted neurons that connect the orbitofrontal cortex, which plays a role in decision making, to the striatum, which is involved in



motor planning and execution. Studies suggest that both these brain regions show abnormal activity in people with obsessive-compulsive disorder.

The team found that shining a light beam to activate the orbitofrontal neurons decreased the mice's compulsive grooming by increasing activity of certain inhibitory neurons within the striatum. When the light was turned off, the compulsive grooming resumed. This population of inhibitory neurons in the striatum normally acts as a 'brake' on motor behaviors, but because the compulsive mice had fewer of these neurons, their ability to dampen compulsive behavior was reduced. Stimulation of these inhibitory neurons by light activation of the orbitofrontal neurons restored the neural brake, and normal behavior, to the mice.

Mutational hot spots. Mutation is a random process, but the likelihood that a mutation will occur varies across the genome. A new study led by SFARI Investigator Jonathan Sebat of the University of California, San Diego, suggests that the genome is full of 'hot spots,' regions where the mutation rate can be as much as 100 times higher than it is in other, less mutable regions. A number of autism risk genes lie within these hot spots, the researchers reported in the December 21, 2012, issue of *Cell*.

Sebat's team sequenced the genomes of ten pairs of identical twins with autism and their parents and looked for spontaneous, or *de novo*, single-letter mutations that appeared in both children but not in their parents. The researchers found that about 1 percent of the genome is particularly susceptible to mutation. High mutation probability is common among disease genes, the team found. The researchers also discovered that genes that are typically expressed in the brain are significantly more mutable than average.

The researchers are now sequencing the genomes of an additional 110 families, about half of which include a child with autism. They plan to share the data from this study in the National Database for Autism Research, a free data repository for autism researchers.

Convergent mutations. A study has identified an unexpected commonality in two autism-related mutations of the gene neuroligin-3 (NLGN3), a molecule involved in the organization and functioning of synapses, the junctions between neurons. Both mutations, researchers report in the May 8, 2013, issue of *Neuron*, dramatically impair signaling in the endocannabinoid system, a collection of lipids and receptors that regulate appetite, memory, mood and pain sensation.

Previous studies had linked autism to two NLGN3 mutations: NLGN3-R451C, in which a single amino acid is changed, and NLGN3-KO, in which the entire gene is missing. However, the studies had suggested that the two mutations have different effects on synaptic function. To zero in on how the two mutations contribute to autism, the new study, carried out by SFARI Investigators Robert Malenka and Thomas Südhof of Stanford University, and by Csaba Földy, also at Stanford, looked for a synaptic phenotype that is shared by the two mutations.

The team found that both mutations impair the activity of inhibitory neurons that release a chemical messenger called cholecystokinin. This messenger affects a type of long-term endocannabinoid signaling called tonic signaling, which the authors describe as "an enigmatic component of overall endocannabinoid signaling" and whose very existence as a separate process has been unclear. The study establishes NLGN3 as the first known molecule essential for tonic endocannabinoid signaling and implicates this signaling in autism — "a tantalizing idea," the researchers write, as the endocannabinoid system in the brain is an attractive target for therapeutic approaches.

TOP: Infant eye-tracking by Ami Klin's laboratory at Emory University's Marcus Autism Center shows promise as a tool for early detection of autism in children as young as 6 months of age.

MATH FOR AMERICA

Nearly a decade ago, Math for America (MfA) began building a corps of outstanding mathematics teachers by supporting excellent New York City public secondary school educators, and by training new ones. The program aimed to improve mathematics education by forming — and sustaining — two related groups of educators: MfA Master Teachers, experienced educators who have demonstrated long-term excellence in the classroom, and MfA Fellows, mathematically talented individuals just starting their teaching careers.

Today, with the addition of the MfA Early Career Fellowship and the MfA School Leader Fellowship, there are more than 800 MfA teachers across seven major U.S. cities. MfA brings the best teachers together so they can share knowledge, advance teaching skills and define excellence in mathematics and science teaching.

“As a member of the MfA community, I am surrounded by educators who are devoted to treating their career not just as a job, but rather as a profession,” says Jessica Gomez, a 2012 MfA Fellow who teaches 9th grade integrated algebra. “The learning and improving never stops.” MfA Fellows receive five years of support, with the first dedicated to earning a master’s degree in education.

Master Teachers, funded for four years, receive fellowships that provide these advanced educators with opportunities to design and lead high-quality professional workshops, mentor early-career teachers and share innovations and best practices.



In 2013, MfA expanded its Master Teacher Fellowship to encompass not only mathematics teachers, but all public secondary school science teachers as well.

MfA believes that elevating the status of the profession is one of the key elements of making teaching an attractive and sustainable career choice. Now, interaction across disciplines is another professional benefit that MfA can provide its members.

“We spent nine years honing the program for math teachers,” says John Ewing, president of MfA. “MfA has a role to play in bringing people together from different areas to collaborate professionally and learn from one another. As we expand into science, we form a growing community that is changing the landscape of math and science education.”

Expansion into science teaching has proven smooth and rewarding. Of this year’s nearly 240 new MfA teachers, about half are science educators, experienced teachers of biology, physics, chemistry, earth science, computer science and middle school (general) science. “Being part of the MfA community makes me excited, and ready to push myself to learn more and grow in my practice,” says Michael Zitolo, a high school physics teacher who was accepted as an MfA Master Teacher in Science in fall 2013. “And I’m surrounded by hundreds of other educators who feel exactly the same way.”

In the future, one of MfA’s goals will be to expand its Master Teacher corps to 800, and the whole MfA New York program to 1,000 teachers. And Ewing hopes that other groups will adopt MfA’s model. New York state has already initiated a Master Teacher program modeled directly on MfA.

“If we could get ten other states to adopt the MfA model, we’d be on our way to making this a nationwide program that really changes the way people think about math and science teachers,” says Ewing. “And eventually, I would hope it could change the way people think about all teachers in general.”

QUANTA MAGAZINE

In 2012, the Simons Foundation launched Simons Science News, an online science news publication focusing on covering the basic sciences. With a goal of supplying journalistic coverage of the hard sciences to practitioners and laypeople alike, its rapid success exceeded all expectations.

The enterprise was so successful, in fact, that the foundation relaunched the online publication this year with a new design, a new name and an expanding staff of writers and contributing journalists, including renowned science writers Carl Zimmer and Jennifer Ouellette.

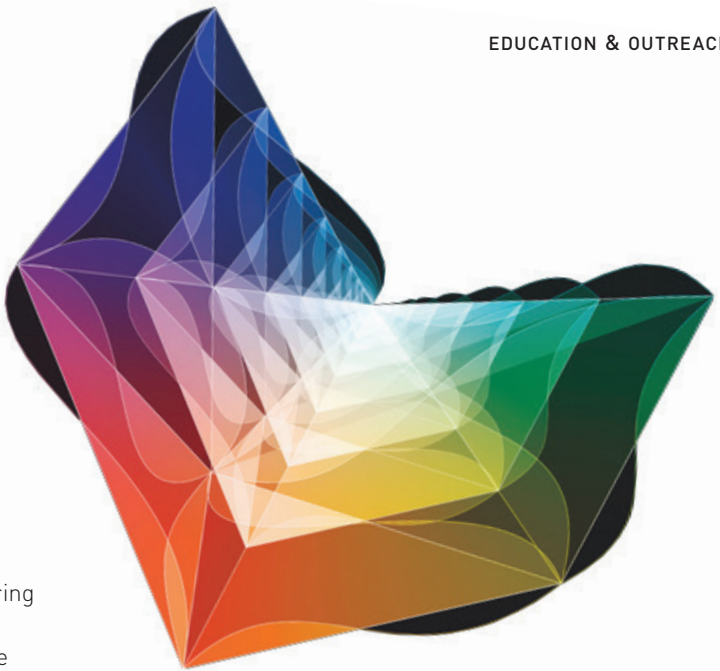
Under the leadership of Thomas Lin, a former editor on *The New York Times* science desk, Quanta Magazine has begun producing material that fills an important niche in the media landscape. “We had a sense that there was a real appetite for these independent hard-science features,” Lin says.

Finding a new name for the magazine was no mean feat. In the end, the foundation decided on ‘Quanta’ because of the magazine’s focus on the quantitative aspects of basic science research. “Quanta can be thought of as the small, constituent particles or parts that make up larger systems and phenomena,” Lin says. “Basic science often operates at this level, but tends to receive less attention from the mainstream media.”

The magazine’s new name, redesign and dedicated homepage space all underscore for visitors to simonsfoundation.org that while Quanta Magazine covers topics related to the foundation’s mission, the articles are pieces of independent journalism.

Quanta’s traffic increased more than tenfold in 2013, aided by strong syndication relationships with *Scientific American* and *Wired*. While many Quanta articles are frequently shared on social media sites such as Twitter and Facebook, two stories achieved ‘viral’ status in 2013.

OPPOSITE: Manish Parmar, an MfA Fellow, teaches high school physics at the NYC iSchool in Manhattan. **TOP:** An artist’s rendering of the amplituhedron, from ‘A Jewel at the Heart of Quantum Physics’, by Natalie Wolchover. The amplituhedron is a newly discovered mathematical object resembling a multifaceted jewel in higher dimensions. Encoded in its volume are the most basic features of reality that can be calculated: the probabilities of outcomes of particle interactions.



An exclusive article by staff writer Natalie Wolchover describing the discovery of an abstract mathematical object called the amplituhedron, which dramatically simplifies calculations of particle interactions and challenges the notion that space and time are fundamental components of reality, crossed over from Quanta into popular sites like Gawker, and even received a mention in Conan O’Brien’s late-night TV monologue. “It transcended what you’d think of as the traditional boundaries of a science story,” Lin says.

Another article, by contributor Erica Klarreich, told the story behind an unknown mathematician’s remarkable new result in the centuries-old twin primes conjecture. This piece was widely shared on Facebook and other social networks and became one of Wired.com’s most highly trafficked posts for the month of May.

To buttress its commitment to independence and accuracy, Quanta also formed an advisory board this year. Members include noted scientists, mathematicians and journalists. “We are constantly trying to improve Quanta,” says Lin, “and we are delighted and grateful that these distinguished scientists and journalists have agreed to lend their expertise.”

Foundation president Marilyn Simons agrees that making Quanta a world-class publication helps the goals of the Simons Foundation. “In my life, I have been lucky to hear many outstanding scientists share their insights with clarity and enthusiasm, in a way that I could understand as a non-scientist,” she says. “I’m confident that Quanta will bring that opportunity to the many interested people who are curious to learn more about cutting-edge science.”

SIMONS FOUNDATION LECTURES



On March 13, 2013, Kerry Emanuel of the Massachusetts Institute of Technology presented 'Hurricanes: Present and Future', a talk that laid out the science behind tropical cyclones. Emanuel described how such science can also inform observed variability of storms and how storms may create feedback with climate phenomena such as El Niño–Southern Oscillation and global climate change. The lecture was part of the Science of Climate series, which explores the relationship between mathematics and climate science.

Emanuel's talk was also the inaugural Simons Foundation Lecture (SFL), and the Science of Climate series was the first of many curated sets of lectures established to bring together scientists from the New York City area. Since then, SFLs have covered a wide array of topics related to Simons Foundation programs, from mathematics and computer science to life science and autism research.

To gather a good mix of area researchers with an interest in the subject matter, SFL organizers typically reach out to local and regional research institutions and academic departments in the fields of astrophysics, chemistry, evolutionary biology, paleontology, physics and neuroscience, among others. And because of popular interest and the foundation's desire to share cutting-edge science broadly, the lectures were quickly opened to the interested public.

"Many attendees are people who don't have these kinds of lectures at their institutions and certainly don't have the opportunity to speak with people from diverse institutions," says Gerald D. Fischbach, chief scientist and fellow of the Simons Foundation. "So I think it's filled a latent need in the city, and I hope it's going to grow more and more popular."

One highly anticipated lecture was given by Catherine Lord and Steven Hyman for the Autism: Emerging Concepts series — 'Evolving Perspectives on Autism' outlined the recent tremendous progress in understanding autism spectrum disorders.

Hyman is director of the Stanley Center for Psychiatric Research at the Broad Institute of the Massachusetts Institute of Technology and Harvard University. During his talk, he discussed recent advances in genomic technology that have shed light on many underlying mechanisms of autism and related neurobiological disorders.

Lord, a clinical psychologist and neuroscientist, is director of the Center for Autism and the Developing Brain and a seminal autism researcher who co-developed the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised, two essential tools in the diagnosis and assessment of autism.



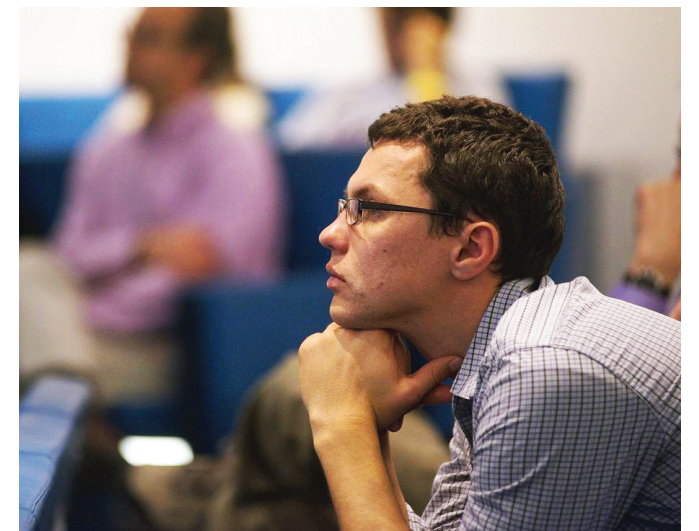
Hyman presented a genetic framework for understanding autism, and Lord discussed a behavioral approach. Lord proposed that improving techniques for measuring the behavior of individuals with autism across developmental stages is an essential element in advancing our understanding of the disorder. Some potential behavioral metrics, she suggested, include eye contact, parent reports of behavior and brain function measurement.

Another 2013 SFL highlight came in November: Joseph Incandela, preeminent particle physicist and leader of the Compact Muon Solenoid particle detector experiment at CERN, presented The Discovery and Study of a Higgs Boson at the Large Hadron Collider. The talk provided an overview of the work being done at the Large Hadron Collider and described the discovery of the Higgs boson — a heavy subatomic particle whose existence suggests the relative masses of other elementary particles.

Series topics planned for 2014 include the global brain, which will explore the simultaneous recording and observation of large populations of neurons, the social brain and its evolution and function, and an expansion of the SFL's popular Biotech Symposia, which cover technical approaches, new methods and innovative algorithms in the life sciences.

Lectures include a question and answer session and are sometimes followed by a reception. The promenade surrounding the auditorium is scattered with blackboards, whiteboards and discussion areas, creating opportunities for attendees to interact with lecturers and also to learn from other attendees.

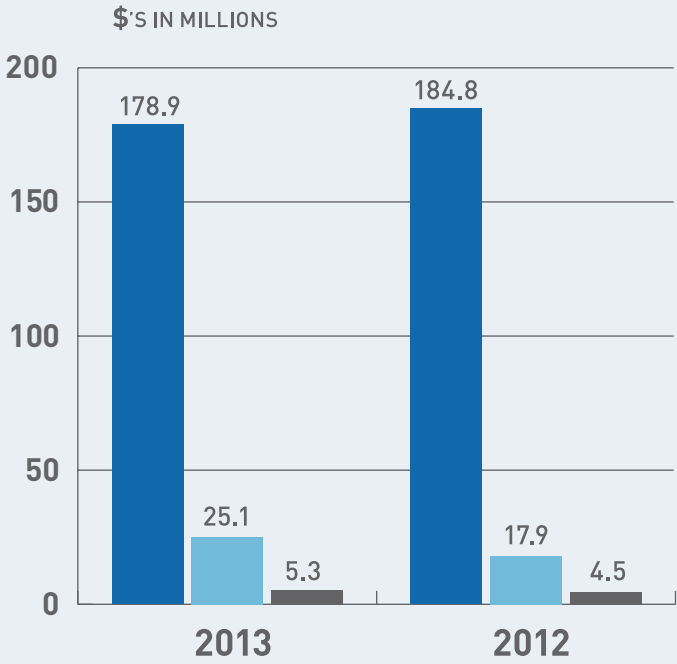
"I think this is a great initiative," says Incandela. "The atmosphere was terrific and the venue was wonderful. It will provide learning opportunities for researchers, and it is a great way to connect people and generate ideas."



FINANCIALS

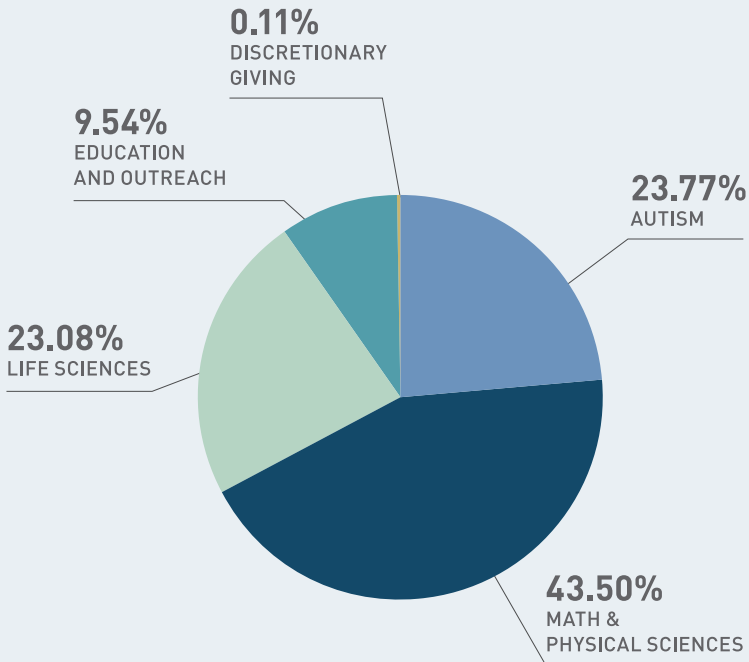
PROPORTIONS OF EXPENSES

- Grants Paid
- Program
- General and Administrative



GRANT PAYMENT BY CATEGORY

FOR YEAR ENDED 12/31/2013



BALANCE SHEET

ASSETS	12/31/2013	12/31/2012
CASH AND CASH EQUIVALENTS	72,365,145	37,585,988
INVESTMENT PORTFOLIO	2,072,501,411	2,020,036,639
PROPERTY AND EQUIPMENT, NET	22,673,962	23,706,251
PREPAID EXCISE TAXES	-	340,000
OTHER	3,146,097	6,969,450
TOTAL	2,170,686,615	2,088,638,328
LIABILITIES		
ACCOUNTS PAYABLE	3,959,125	3,956,818
DEFERRED RENT LIABILITY	5,059,369	5,467,062
GRANTS PAYABLE	345,316,453	415,799,499
DEFERRED EXCISE TAX LIABILITY	12,322,669	12,166,503
OTHER TAXES PAYABLE	10,300,000	9,700,000
TOTAL	376,957,616	447,089,882
NET ASSETS		
UNRESTRICTED NET ASSETS	1,793,728,999	1,641,548,446

INCOME STATEMENT

	FOR 12 MONTHS ENDED 12/31/2013	FOR 12 MONTHS ENDED 12/31/2012
REVENUE		
CONTRIBUTIONS	84,000,000	150,328,193
INVESTMENT INCOME	211,626,040	155,275,629
TOTAL	295,626,040	305,603,822
EXPENSES		
GRANTS PAID	178,889,844	184,781,415
CHANGE IN GRANTS PAYABLE	(69,469,676)	24,747,780
IN-KIND DONATION	750,538	775,581
PROGRAM	25,129,417	17,921,418
GENERAL AND ADMINISTRATIVE	3,837,723	3,193,927
DEPRECIATION AND AMORTIZATION	1,429,268	1,294,900
TAXES	2,926,632	4,863,830
OTHER (INCOME) EXPENSES	(48,259)	1,382,838
TOTAL	143,445,487	238,961,689
NET INCOME		
	152,180,553	66,642,133



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“Science makes people reach selflessly for truth and objectivity; it teaches people to accept reality, with wonder and admiration, not to mention the deep awe and joy that the natural order of things brings to the true scientist.”

—Lise Meitner

OPPOSITE: Nikolay Prokof’ev’s depiction of a small subset of skeleton Feynman diagrams, pictorial representations of the mathematics that govern the behavior of subatomic particles. When extrapolated to an infinite-order limit, these diagrams help us understand the quantum mechanical behavior of systems comprising many interacting electrons.

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Marilyn Hawrys Simons is president of the Simons Foundation. Under her leadership, the foundation has grown to become one of the country’s leading private funders of basic scientific research. Simons is vice president of the board of Cold Spring Harbor Laboratory, treasurer of the board of the Learning Spring School and a member of the board of trustees at the East Harlem Tutorial Program. She received a B.A. and a Ph.D. in economics from Stony Brook University.



David Eisenbud, Ph.D.
Director, Mathematical Sciences Research Institute

David Eisenbud is director of the Mathematical Sciences Research Institute in Berkeley, California. Previously, Eisenbud was director of the Mathematics and Physical Sciences division at the Simons Foundation. A former president of the American Mathematical Society, Eisenbud serves on the board of Math for America and is a member of the U.S. National Committee of the International Mathematical Union. In 2006, he was elected a fellow of the American Academy of Arts and Sciences. Eisenbud holds a Ph.D. in mathematics from the University of Chicago and has been on the faculty at the University of California, Berkeley, since 1997.



Gerald D. Fischbach, M.D.
Chief Scientist of the Simons Foundation and Fellow of the Simons Foundation

Gerald D. Fischbach joined the foundation in 2006 to oversee SFARI and is now the foundation’s chief scientist and first fellow. He was formerly dean of the faculty of health sciences at Columbia University and director of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health (NIH). Fischbach began his research career at the NIH and later served on the faculty of Harvard Medical School, where he became chair of the neurobiology department, a position he also held at Massachusetts General Hospital. Fischbach was also head of the department of anatomy and neurobiology at Washington University School of Medicine. He was a nonresident fellow of the Salk Institute for more than 20 years. Fischbach’s research has focused on trophic interactions between nerve cells and the targets they innervate.



Mark Silber, J.D., M.B.A.
Executive Vice President and Chief Financial Officer, Renaissance Technologies

Mark Silber is executive vice president and chief financial officer of Renaissance Technologies LLC. Silber joined Renaissance 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 B.A. from Brooklyn College, a J.D. and an 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.

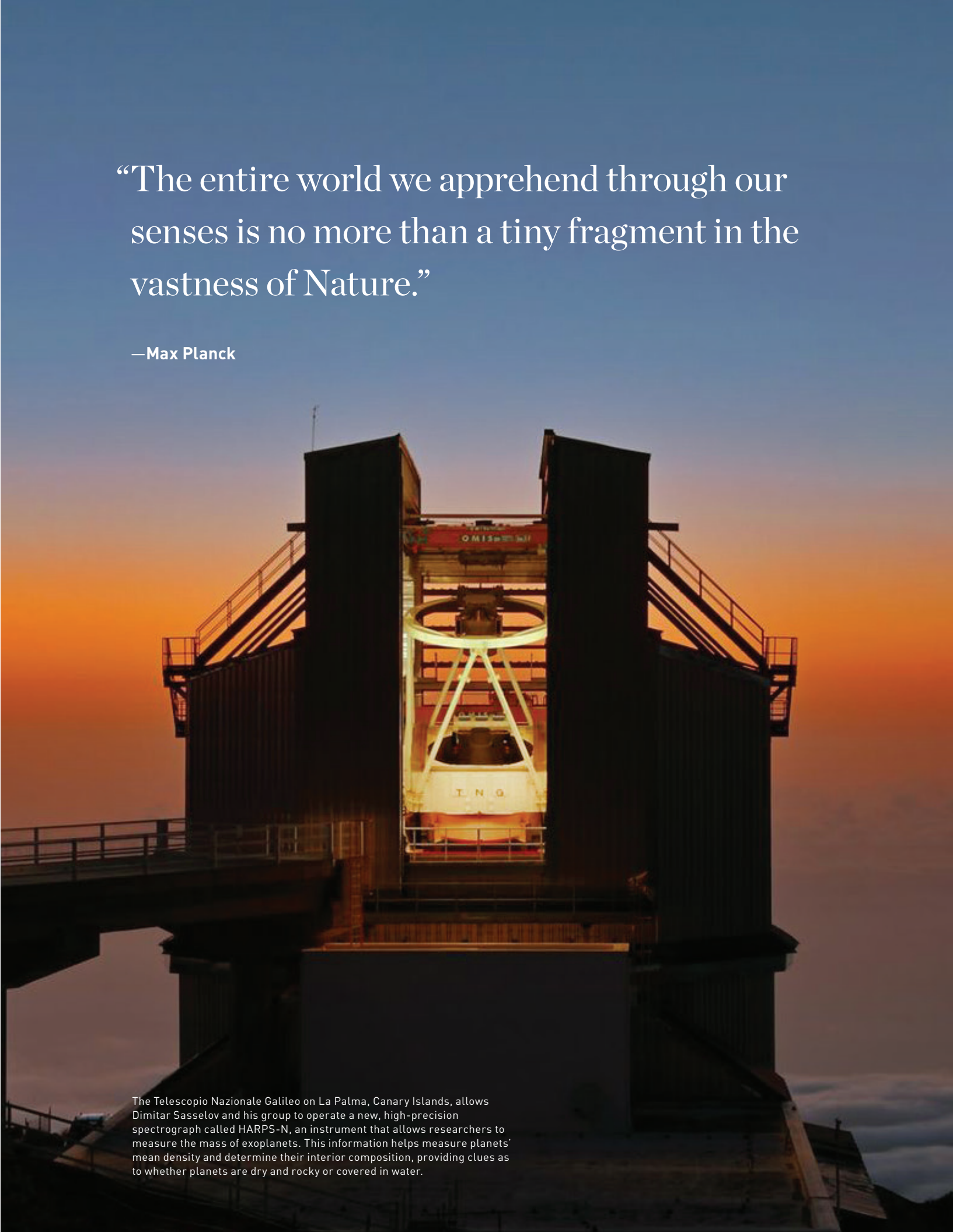


James H. Simons, Ph.D.
Chairman

James Simons is chairman of the Simons Foundation and board chair and founder of Renaissance Technologies. Prior to his financial career, Simons was chairman of the mathematics department at Stony Brook University, taught mathematics at the Massachusetts Institute of Technology (MIT) and Harvard University, and was a cryptanalyst at the Institute for Defense Analyses. Simons holds a B.S. from MIT and a Ph.D. from the University of California, Berkeley. In 1976, he won the Veblen Prize of the American Mathematics Society for his work in geometry. He is a trustee of the Stony Brook Foundation, Rockefeller University, MIT, Brookhaven National Laboratory, the Mathematical Sciences Research Institute, New York Genome Center and the Institute for Advanced Study, and is a member of the National Academy of Sciences, the American Academy of Arts and Sciences and the American Philosophical Society.

“The entire world we apprehend through our senses is no more than a tiny fragment in the vastness of Nature.”

—Max Planck



The Telescopio Nazionale Galileo on La Palma, Canary Islands, allows Dimitar Sasselov and his group to operate a new, high-precision spectrograph called HARPS-N, an instrument that allows researchers to measure the mass of exoplanets. This information helps measure planets’ mean density and determine their interior composition, providing clues as to whether planets are dry and rocky or covered in water.

SIMONS FOUNDATION

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