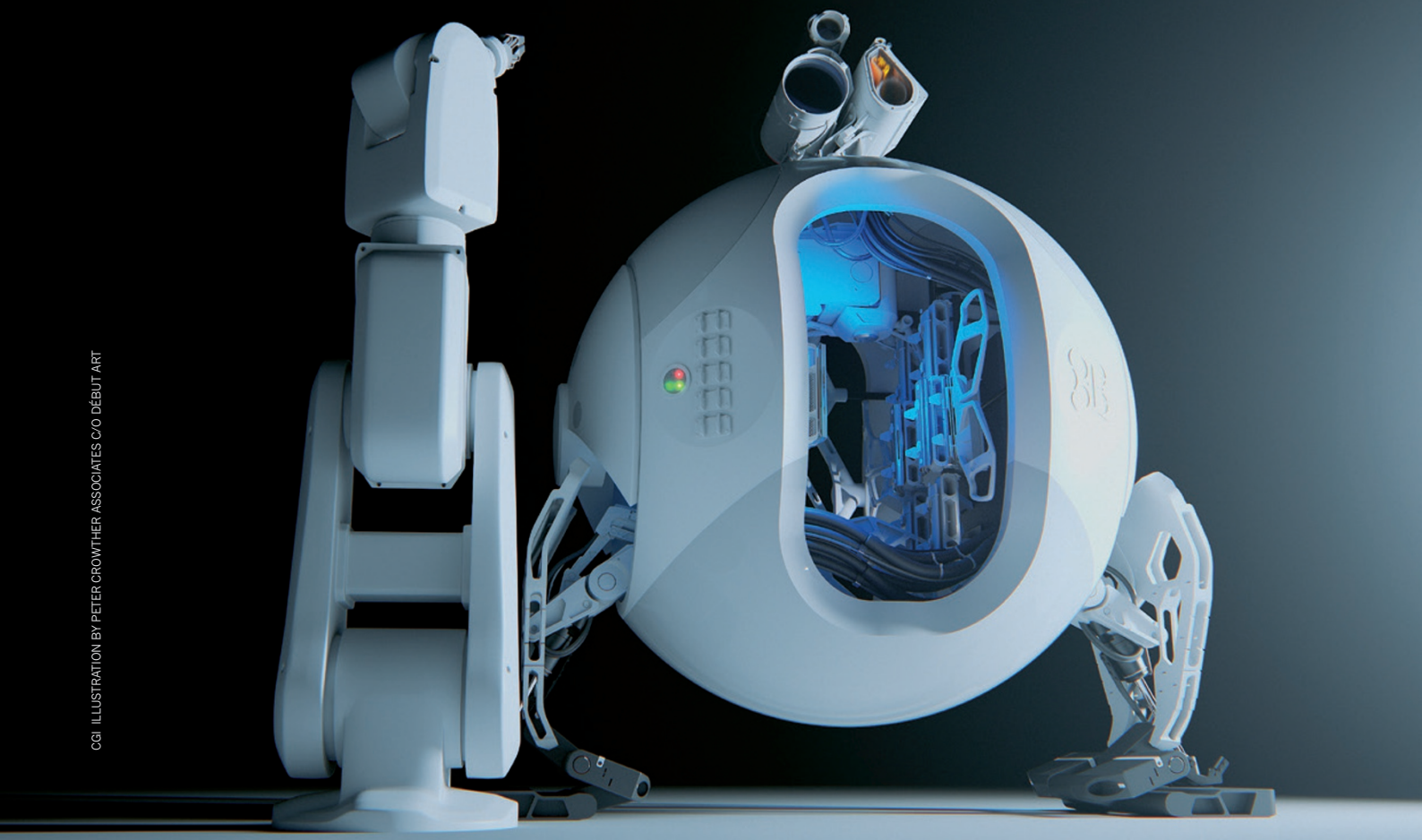
NATURE'S 10

Ten people who mattered this year.



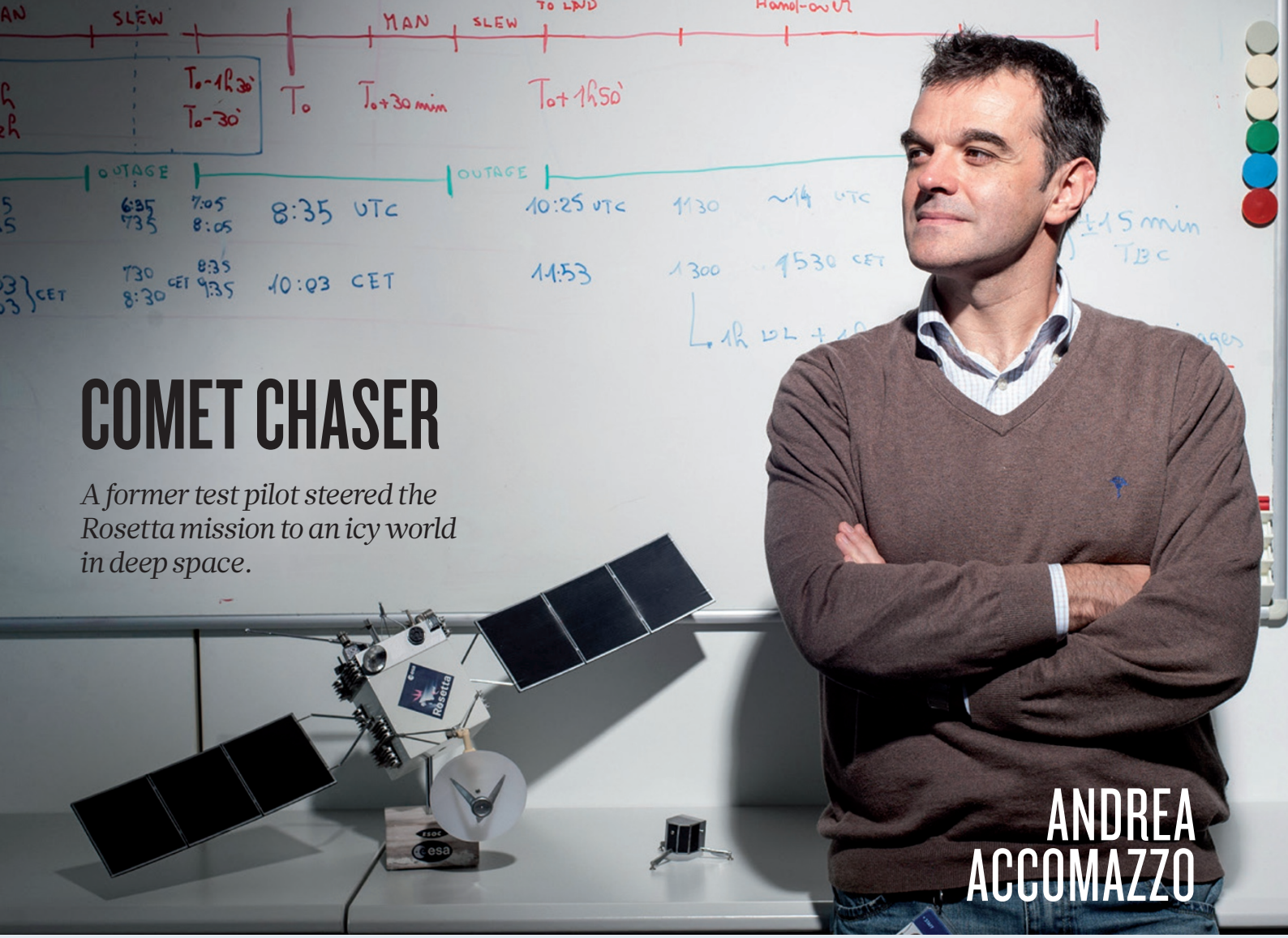
CGI ILLUSTRATION BY PETER CROWTHER ASSOCIATES C/O DÉBUT ART

ANDREA ACCOMAZZO / SUZANNE TOPALIAN / RADHIKA NAGPAL / MASAYO TAKAHASHI / DAVID SPERGEL / MARYAM MIRZAKHANI / PETE FRATES / KOPPILLIL RADHAKRISHNAN / SHEIK HUMARR KHAN / SJORS SCHERES

365 DAYS:
the year in science

COMET CHASER

A former test pilot steered the Rosetta mission to an icy world in deep space.



ANDREAS REEG/AGENTUR FOCUS/EYEVINE

BY ELIZABETH GIBNEY

Nearly two decades ago, Andrea Accomazzo got into trouble with his girlfriend when she found a scrap of paper on his desk. In his handwriting was scrawled a phone number next to a female name: Rosetta.

"She thought it was a girl," says Accomazzo. "I had to explain to my jealous Italian girlfriend that Rosetta is an interplanetary mission that is flying to a comet in almost 20 years."

Ever since, Accomazzo has divided his attention. He eventually married his girlfriend and has also spent the past 18 years pursuing the comet 67P/Churyumov–Gerasimenko. As flight director for the mission, Accomazzo led the team that steered Rosetta to its August rendezvous with the comet, following a 6.4-billion-kilometre journey from Earth. The pinnacle of the project came in November, when Rosetta successfully set down a lander named Philae, providing scientists with the first data from the surface of a comet and making it one of the most successful missions in the history of the European Space Agency (ESA).

Accomazzo did not act alone: it took a large operations team at ESA to manoeuvre Rosetta with enough precision to drop Philae down just 120 metres from the centre of the landing zone. "Given that we'd had a 500-metre error circle, that was not a bad shot," says Fred Jansen, who led the mission. When Philae's anchoring systems failed, the craft bounced into a shady site where it could not charge its solar panels, so the lander lost power after 64 hours. But in that time, it gathered a trove of data that will add to the information collected by Rosetta about the comet's structure and composition. Armed with those insights, scientists hope to better understand the origin and evolution of the Solar System, including whether comets could have brought water and organic molecules to Earth during its infancy.

Accomazzo started off his career focused on a different type of flight. He first trained as a test pilot in the Italian Air Force. But although he loved flying, he found the culture too constraining and after two years he quit to study aerospace engineering. With his quiet, hard-working, sometimes no-nonsense nature, colleagues say that Accomazzo brings a bit of the military with him into mission control.

For Accomazzo, the biggest parallel between flying a fighter jet and Rosetta is the need for split-second judgements. "You have to prepare and train a lot to be able to make the right decision, very quickly," he says. Between launch and landing, his team ran 87 full-day simulations.

Although the Rosetta mission has been a broad success, Accomazzo still cried when he heard that Philae had died, and hopes the lander will revive when the comet approaches the Sun. After swinging around the Sun in August 2015, the comet will head back out towards deep space.

By early 2017, there will be too little sunlight to power Rosetta, and Accomazzo is planning a daring finale. He would love to see the craft skim above the surface of the rubber-duck-shaped comet through the valley that separates its body and head. The team might even try to land the spacecraft on the comet's surface.

The decision might not be up to him. Accomazzo is stepping away from the day-to-day flight operations at Rosetta and is busy preparing for ESA's interplanetary missions to Mercury, Mars and Jupiter. Even with such exciting projects, he finds it hard to leave Rosetta behind. "It's a bit sad," he says. "I don't know how I will be able to cope."

He still dreams of Rosetta. "This morning I woke up at 4 a.m. and thought 'something is wrong,'" he says. "At 7.30 a.m. I got a call — Rosetta had briefly lost signal to Earth at 4 a.m. — I often have this kind of episode. I'm totally linked." ■

CANCER COMBATANT

One clinician always believed that cancer immunotherapy would work — and she was right.

BY HEIDI LEDFORD

When Suzanne Topalian heard in July that a therapy she had helped to pioneer could now be prescribed to treat people with advanced melanoma, she greeted the news with excitement, but also characteristic resolve. The meticulous cancer researcher and physician was already focused on the field's next challenges: approval for the drug in other countries and against a wider range of cancers. "Although this was reason to celebrate, we're still looking towards the horizon," she says.

The drug in question is part of a hot new class called PD-1 inhibitors, which allow T cells in the immune system to jump into high gear so that they are free to attack tumours. This July, Japanese regulators approved the first such drug — nivolumab, made by Bristol-Myers Squibb of New York — largely on the back of clinical trials that Topalian led. Two months later, the US Food and Drug Administration approved another, called pembrolizumab. Some analysts predict that the drugs will become a cornerstone of cancer treatment, with a market exceeding US$10 billion by 2020.

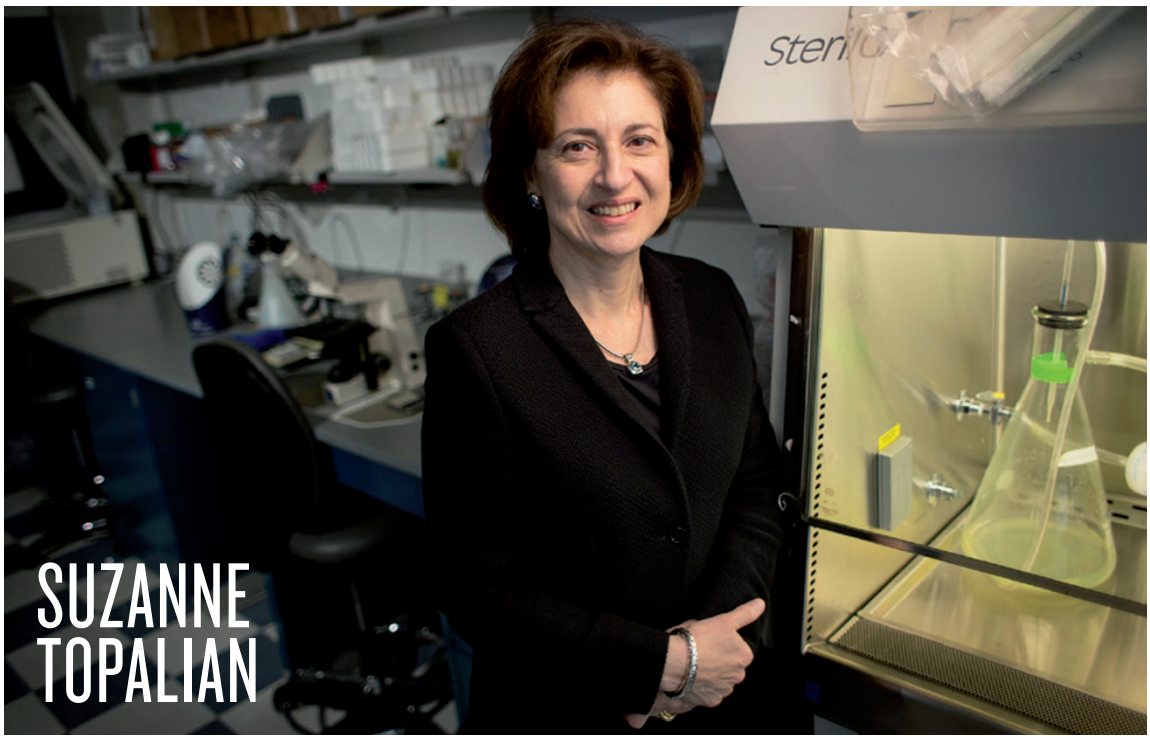
Even as a medical student, Topalian says, she was hooked by the idea of turning the body's own defences against cancer rather than — as most other therapies do — attacking a tumour directly with radiation or drugs. In 1985, she joined the lab of tumour immunologist Steven Rosenberg at the US National Cancer Institute in Bethesda, Maryland. She intended to leave after 2 years; instead, she stayed for 21 and set up her own lab. Rosenberg says that Topalian quickly made her mark as a talented, careful scientist who always kept the big picture in mind. "She was totally passionate about finding effective cancer treatments," he says.

Even when sceptics doubted that cancer immunotherapy would work, and early clinical trials looked disappointing, Topalian was undeterred. "There would always be some patients who responded to those treatments," she says. "It was those exceptional responders who kept hope alive."

In 2006, Topalian left Bethesda to help to launch trials of nivolumab at Johns Hopkins University in Baltimore, Maryland. That work led to a landmark publication in 2012 showing that nivolumab produced dramatic responses not only in some people with advanced melanoma but also in those with lung cancer — the world's most common cause of cancer death (S. L. Topalian *et al. N. Engl. J. Med.* **366,** 2443–2454; 2012). Regulators are now considering approval of the drugs for treatment of lung cancer.

Other researchers are pouring into the field, spurred by successes with PD-1 inhibitors and other cancer immunotherapies, says Jedd Wolchok, an oncologist at the Memorial Sloan Kettering Cancer Center in New York. "It's legitimized a field that was once scorned," he says. ■

CHRIS MADDALONI



REFLECTION FILMS

ROBOT-MAKER

A researcher inspired by social insects gets robots to coordinate on a massive scale.

BY CORIE LOK

When Radhika Nagpal was a high-school student in India, she hated biology: it was the subject that girls were supposed to study so that they could become doctors. Never being one to follow tradition, Nagpal was determined to become an engineer.

Now she is — leading an engineering research team at Harvard University in Cambridge, Massachusetts. But she also has a new appreciation for the subject she once disliked. This year, her group garnered great acclaim for passing a milestone in biology-inspired robotics.

Taking their cue from the way in which ants, bees and termites build complex nests and other structures with no central direction, Nagpal's group devised a swarm of 1,024 very simple 'Kilobots'. Each Kilobot was just a few centimetres wide and tall, moved by shuffling about on three spindly legs and communicated with its immediate neighbours using infrared light. But the team showed that when the Kilobots worked together, they could organize themselves into stars and other two-dimensional shapes (M. Rubenstein *et al. Science* **345,** 795–799; 2014). Achieving that level of cooperation in a swarm this large was a major feat, says Alcherio Martinoli, a roboticist at the Swiss Federal Institute of Technology in Lausanne. Nagpal's approach — combining theoretical proofs with a physical demonstration of swarm behaviour — "is, to me, extremely powerful and something other people should follow", he says.

The hope is that this kind of swarm-robotics research will eventually

EBOLA DOCTOR

An infectious-disease expert battled a killer virus in Africa.

BY ERIKA CHECK HAYDEN

In this year's devastating outbreak of Ebola, Sheik Humarr Khan played a unique part. He was a scientist — part of the team that performed the first genetic sequencing studies of the virus in his native Sierra Leone. He was an infectious-disease doctor who turned down an invitation to leave his country so that he could stay and treat patients. He also became one of its many victims, dying on 29 July.

Ebola brought devastation to Guinea, Sierra Leone and Liberia as it ballooned into an epidemic during 2014. Khan was the lead physician at Sierra Leone's Kenema Government Hospital, where he was treating and studying Lassa, another potentially fatal viral disease, until the hospital was overwhelmed by people with Ebola.

According to those who knew him, Khan believed that research and medicine should serve everyone — not just those able to access and afford it — and he had eschewed offers to make more money working in the capital, Freetown, to stay in the underserved rural region of Kenema. "That was one of the more important examples he set," says John Schieffelin, a physician at Tulane University in New Orleans, Louisiana, who worked with Khan.

Khan became a central figure in the Kenema community and when Ebola struck, he cancelled his plans to teach abroad. When he became sick himself, his doctors decided not to give him the experimental treatment known as ZMapp in case it backfired and caused dangerous side effects. Some staff at the hospital worried that his death would spark civil unrest. "They said that if Dr Khan dies, people in Kenema are going to tear the hospital down," remembers Lina Moses, an epidemiologist also at Tulane who spent much of the year working in Kenema.

The outbreak now looks as though it is levelling off, and drug and vaccine trials are getting under way. The research that Khan was involved in showed how quickly the virus was mutating, and the team he worked with is now installing genetic sequencers throughout West Africa so that they can continue to track its evolution.

But the toll has been great: Ebola has killed around 6,300 people, including many doctors and other health-care workers. Recovering from this loss of scarce experts will be a tremendous challenge, says Estrella Lasry, a tropical-medicine specialist for Médecins Sans Frontières (Doctors without Borders) in New York City. "It's going to take years before the same number of people who died are trained". ■

lead to self-organizing robot teams that can rapidly respond to disasters, say, or aid in environmental clean-up. But getting even this far took much longer than Nagpal and her team originally estimated.

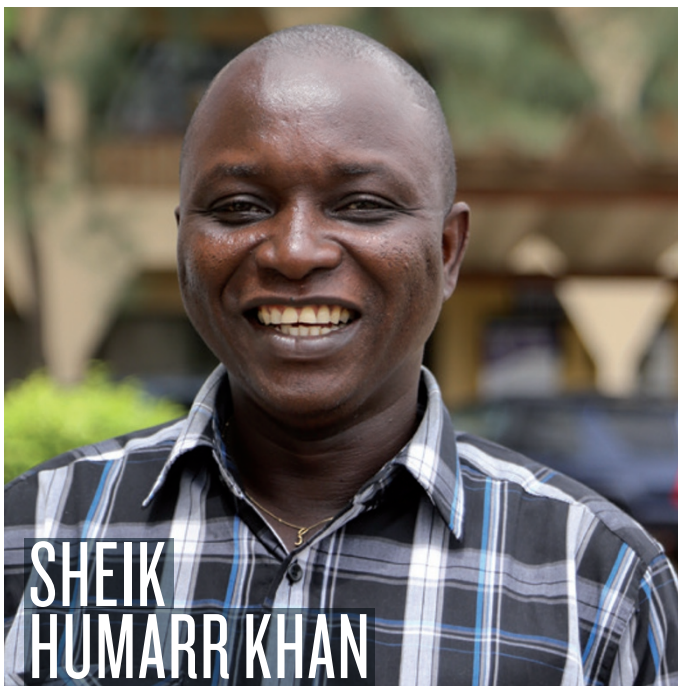
The original idea for the Kilobots is four years old, says Nagpal. Like other swarm-robotics researchers, her team had been doing computer simulations and small laboratory experiments. But then one of her postdocs, Michael Rubenstein, convinced her that it was possible to do much larger experiments, because advances in electronics, materials and three-dimensional printing were making it easier and cheaper than ever to create robots en masse.

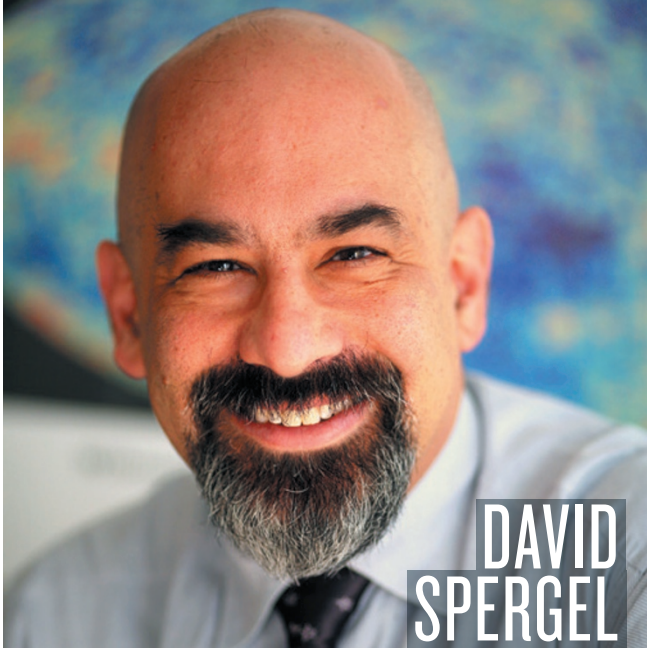
The team struggled to go from building 20 autonomous robots — their largest group at the time — to the full-sized swarm of 1,024 Kilobots. The key turned out to be simplicity, says Nagpal. "The individuals would be less calibrated, have lower-quality components and would have less control over what they do," she says, but they would still need to carry out complex tasks by working together. "Somehow, at the top, we would have to think of algorithms that didn't depend on precision at the individual level."

Nagpal is now trying to develop large robot swarms that can self-assemble into structures in three dimensions. And she will continue to draw her inspiration from nature, she says — a practice she learned from her graduate-school adviser, computer scientist Gerald Sussman at the Massachusetts Institute of Technology in Cambridge. Sussman convinced her to set aside her distaste for biology when he pointed out that cells are the ultimate computers, able to take in data from signalling molecules, and to carry out complex chemical calculations to decide how to act. And then there are the extraordinary things that happen when these cell-computers come together, says Nagpal.

"At the end, you get this functioning organism and it's so amazing that you forget that it's even composed of cells," she says. This is a key goal in swarm-intelligence research: using the collective to accomplish much more than the individual. "Looking at biology makes me think differently about computer science," she says. ■

PARDIS SABETI





JOHN JAMESON/PRINCETON UNIV.

COSMIC SCEPTIC

An astrophysicist found errors in a major discovery about cosmic inflation.

BY RON COWEN

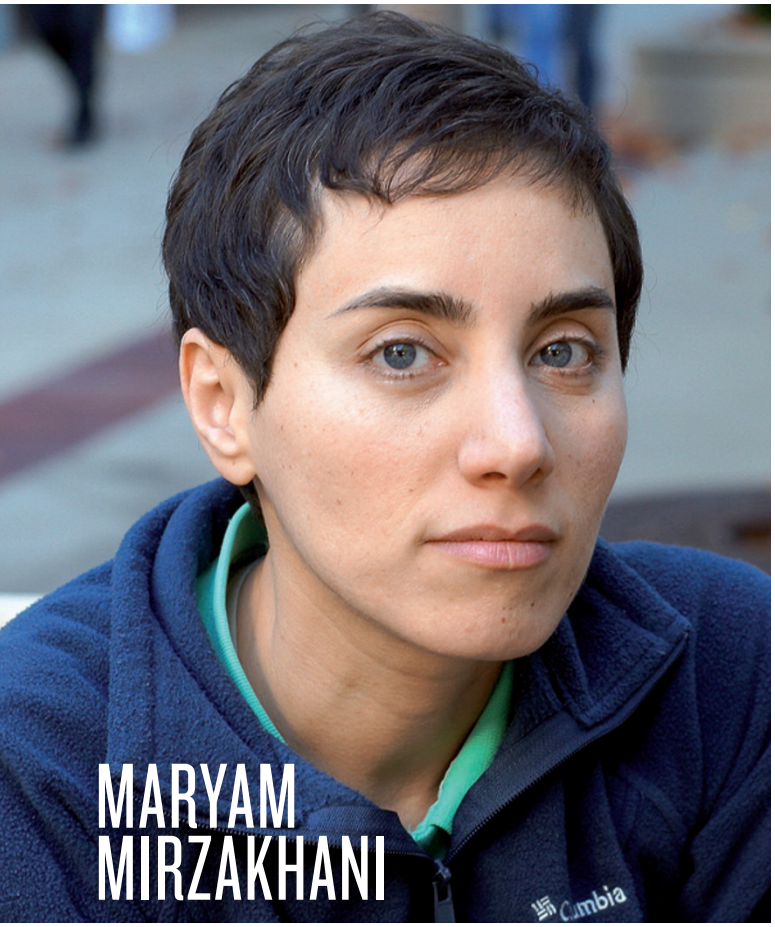
David Spergel first spotted the blunder while on a train in late March. Ten days earlier, researchers had made front-page headlines by holding a press conference announcing the probable detection of gravitational waves from the far reaches of space. That long-sought signal provided evidence that the infant Universe had undergone a brief but enormous expansion called cosmic inflation, and the result had prompted talk of a Nobel prize for the team, which was led by John Kovac of the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts.

Spergel was troubled from the start by the evidence that Kovac's team had gathered from the BICEP2 telescope at the South Pole. As an astrophysicist who studies the early Universe at Princeton University in New Jersey, he worried that the signal might be an artefact. On the train, en route to giving a lecture in New York City, he realized that the BICEP2 team had made a mistake when accounting for how nearby dust might alter the long-distance signal. He raised his concerns in his talk, and in May he co-authored a paper that pointed out the flaws (R. Flauger *et al.* Preprint at http://arxiv.org/abs/1405.7351; 2014).

Spergel, who sports a shaved head and a voice that can fill a room, decided that he needed to speak out. "I wanted to let the broader physics community know there were reasons to have doubts," he says.

Social media amplified his criticisms. A video of his New York talk drew nearly 2,000 views, alerting others to the controversy. Soon, talk of a Nobel prize for the BICEP2 team was eclipsed by discussions about how it had made a cosmic mistake.

When the BICEP2 researchers published their findings in June (P. A. R. Ade *et al. Phys. Rev. Lett.* **112,** 241101; 2014), they were more tentative than at the press conference — although not enough to satisfy Spergel. A forthcoming analysis of satellite data may soon settle the controversy. For cosmologist Marc Kamionkowski of Johns Hopkins University in Baltimore, Maryland, the episode shows the danger of announcing major results too early. Although the BICEP2 researchers may have had good reasons to hold a press conference, he says, "they or others in a similar situation in the future may lean towards awaiting some vetting". ■



COURTESY OF MARYAM MIRZAKHANI

SURFACE EXPLORER

A mathematician's award shines a light on a lack of women in the field.

BY ERICA KLARREICH

When Maryam Mirzakhani was a mathematics graduate student at Harvard University in 2003, she went to her adviser, Curtis McMullen, with a question. McMullen had just solved a long-standing problem related to the behaviour of billiard balls on a type of abstract table that can be folded up into a doughnut surface with two holes. It was a major discovery, but Mirzakhani asked why he had proved it just for surfaces with two holes, rather than for complex surfaces with even more. She was drawn to the largest possible problem — even if she had no idea, back then, just how hard it would be to solve. "Maybe sometimes not knowing enough is a blessing," she says, "because then you just do your thing."

Mirzakhani, now at Stanford University in California, turned this problem over in her mind for almost a decade, until she found an answer. In a 172-page paper written in 2012 with Alex Eskin of the University of Chicago, Illinois, she extended McMullen's result to all surfaces with two or more doughnut holes, tying together disparate mathematical fields such as geometry, topology and dynamical systems (A. Eskin and M. Mirzakhani Preprint at http://arxiv.org/abs/1302.3320; 2013). "It's a spectacular result," says Howard Masur, a mathematician at the University of Chicago. In August, Mirzakhani was awarded the Fields Medal, often called mathematics' Nobel prize, for this and other advances in pure mathematics. Among her other findings is a surprising link between hyperbolic

ICE-BUCKET CHALLENGER

A patient advocate helped to kick-start the social-media stunt of the year — with huge returns for research.

BY SARA REARDON

In the two-and-a-half years since he was diagnosed with amyotrophic lateral sclerosis (ALS), 29-year-old Pete Frates has lost the ability to speak or move. But in November, the former university baseball coach was the guest of honour at a sporting-goods shop near his home in Beverly, Massachusetts, where he sat with his newborn daughter in his lap and watched a Christmas celebration that featured an actor dressed as Santa Claus dousing himself with snow.

Santa was paying homage to the 'Ice Bucket Challenge', in which people post and share videos of themselves dumping ice water over their heads to raise awareness and donations for ALS research. Frates first promoted the idea in August, through posts to Facebook and YouTube that he dictated using eye-tracking software. Since then, it has become one of the most lucrative social-media fund-raisers ever for biomedical research — and has led advocates for other little-known diseases to wonder whether similar efforts could also help them to raise money.

The ice-bucket idea did not originate with Frates's posts — similar challenges had been used in other social-media campaigns. But his efforts, along with posts by Pat Quinn of Yonkers, New York, who also has ALS, did a lot to help the challenge go viral. Both men urged Internet users to show solidarity by posting videos. The meme morphed into a fund-raising campaign: either dump water on your head or donate money to ALS research, then challenge friends to do the same. Many people chose both.

So far, participants from around the world have posted at least 17 million ice-bucket videos on Facebook, and raised more than US$115 million — almost three times the $40 million the US National Institutes of Health spent on ALS research last year.

Critics say that the Ice Bucket Challenge is a fad and that its focus on a disease affecting around 500,000 people worldwide could draw attention away from deadlier threats, such as heart disease, which kills 7.4 million people every year. Nevertheless, the strategy has caught the attention of other advocacy groups. The National Organization for Rare Disorders in Danbury, Connecticut, held a seminar in October on viral fund-raising campaigns, and is planning a follow-up session owing to its popularity.

Back in Massachusetts, the Frates family still hopes that the Ice Bucket Challenge will one day pay off for ALS. "When there is a treatment," says Pete's father, John Frates, "it will go back to August 2014." ■

geometry — the geometry of saddle shapes — and string theory.

Mirzakhani is humble — when she got word of her award, she assumed it came from a hacked e-mail account — and extremely private. She kept a low profile after her prize was announced, but the news was greeted with an explosion of interest elsewhere. It raced through social media and the press, reaching outlets such as the fashion magazine *Elle* and the feminist blog Jezebel. Most of the discussion was not about abstract surfaces, however: it was about how the Iranian-born mathematician was the only woman to receive the Fields Medal since the prize was first awarded in 1936.

The commotion threw a spotlight on the vast under-representation of women in mathematics: according to a 2012 survey of US universities by the American Mathematical Society, women make up only 30% of PhD students — a number that has not budged for years — and only 12% of tenured faculty members at PhD-granting universities. Those who do become tenured mathematics professors receive a disproportionately small number of scholarly awards.

Mirzakhani says that she has not encountered any outright discrimination against women, but that there are subtle cultural forces that can undermine their confidence, such as a shortage of peers and a perception among girls that mathematics isn't "cool". She hopes her award will inspire confidence in female mathematicians — and others believe that it will change how they are perceived. From now on, "no one will be able to think about the Fields Medal without picturing Maryam Mirzakhani", says Ruth Charney, a mathematician at Brandeis University in Waltham, Massachusetts, and president of the Association for Women in Mathematics. "It's a clear signal that there are women doing absolutely top-notch mathematics — in case anyone wasn't sure."

Mirzakhani is sure, and she predicts more female Fields Medal winners soon. Meanwhile, she is focusing on pushing her analysis of billiard surfaces even further. She regards herself as a discoverer, not an inventor, of mathematics. "I see it as exploring some unknown territory," she says. "It's an adventurous thing, trying to find the connections." ■

ARUN SANKAR K/AP/PRESS ASSOCIATION IMAGES

KOPPILLIL RADHAKRISHNAN

ROCKET LAUNCHER

India's space chief led the country's charge to Mars.

BY T. V. PADMA

Koppillil Radhakrishnan knew the odds were against him when India's Mangalyaan space probe closed in on Mars this year. As head of the Indian Space Research Organisation (ISRO), he was well aware that half of all attempts to reach Mars have ended in failure.

But the ISRO had taken lessons from other countries' mistakes, and it set modest aims for its first interplanetary mission, which it billed as a technology demonstration. When Mangalyaan settled successfully into Mars orbit on 24 September, India joined the elite group of nations with the ambition and technical capability to explore the Solar System.

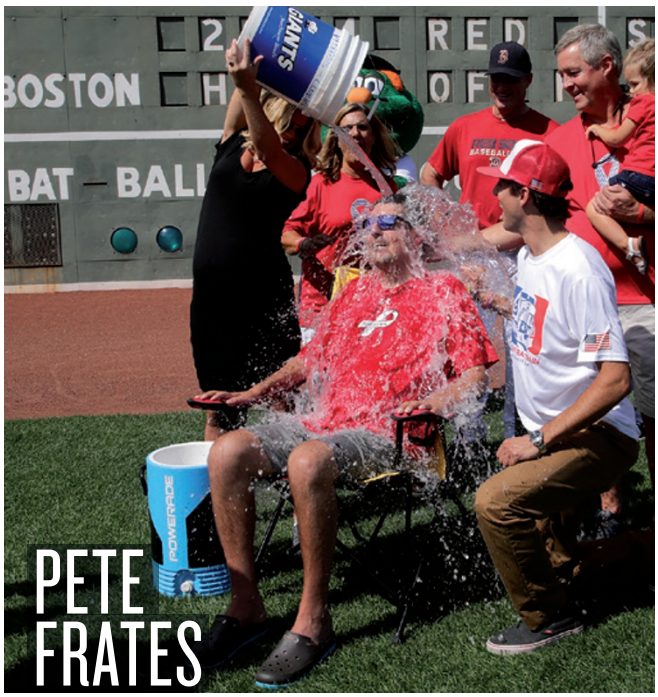
In his 43 years as an engineer and manager at the ISRO, Radhakrishnan has led a diverse set of projects, from developing remote-sensing satellites to setting up India's tsunami-warning system. The Mars mission was a gamble, but it caused less heartache than the ISRO's work on a cryogenic rocket engine that had failed during a launch in 2010 and finally succeeded this year. "The Mars mission was a slightly more joyous occasion," he says, while playing down his own role. "I was like a conductor of an orchestra."

The Mars mission has put the spotlight on Asia's space ambitions. India plans in the next three years to launch its second Moon mission, and China aims to bring lunar samples back to Earth by 2017.

India's success this year drew widespread applause. "This is good for India and its economy, demonstrating the ability to develop and implement high-technology enterprises," says Raymond Arvidson, a planetary scientist at Washington University in St. Louis, Missouri.

Radhakrishnan says that India's space plans should not be judged against those of other countries: "We are not racing with anyone. We are only racing with ourselves." But he will soon leave the race. Radhakrishnan will retire at the end of the year, leaving him free to pursue his love for classical South Indian singing and dancing. He has not had much time for that during the ISRO's hectic pursuit of Mars. ■

BARRY CHIN/THE BOSTON GLOBE VIA GETTY



PETE FRATES

MAMI NAGAOKI/AP/PRESS ASSOCIATION IMAGES

STEM-CELL TESTER

An ophthalmologist injected hope into the stem-cell field during a troubled year.

BY DAVID CYRANOSKI

For an hour on Friday 12 September, Masayo Takahashi sat alone, calmly reflecting on the decade of research that had led up to this moment.

An ophthalmologist at the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan, Takahashi was about to watch a sheet of epithelial cells that she had grown be transplanted into the back of a woman's damaged retina. She had made the cells from induced pluripotent stem (iPS) cells, which have been widely touted for their potential to generate genetically-matched tissue for treating a range of diseases. The transplant would be the first test of that promise in people, and therefore a major milestone for the stem-cell field. As she sat, Takahashi quietly considered all those who had helped her get to that point ("so many people — it would be like the credits rolling at the end of a movie"), and the scandal in the stem-cell field that had threatened to derail the project earlier in the year. "It was like a sacred hour," she says.

Takahashi had been trying to use stem cells to repair retinal damage for ten years — and trying to downplay hype about the cells for almost as long. Her work received a boost when, in 2006, stem-cell scientist Shinya Yamanaka at Kyoto University in Japan discovered how to make iPS cells, which are much easier to make than other human pluripotent cells. Collaborating with Yamanaka, Takahashi worked out how to turn the iPS cells into sheets of retinal epithelial cells. She then tested the resulting cells in mice and monkeys, passed regulatory hurdles, recruited patients, and practised growing cells from those patients. Finally, she

STRUCTURE SOLVER

A biologist brought the cell's molecular machines into sharper focus.

BY EWEN CALLAWAY

Sjors Scheres is surrounded by ribosomes. A picture of one fills his computer screen, and thousands more are stuffed on his hard drive. His CV is studded with high-profile papers from this year showing some of the clearest images ever produced of these complex protein-making machines. So it is all the more surprising when Scheres, a structural biologist, says that he isn't all that interested in ribosomes. "It's all about the math," he says, with relish. "That's what my main contribution is."

That mathematics is helping to drive a revolution in structural biology. Once dominated by a method called X-ray crystallography, the field is now in the thrall of a technique called cryo-electron microscopy, or cryo-EM. Scheres's calculations have led to software that transforms grainy cryo-EM images into exquisitely detailed pictures, allowing biologists to visualize molecular machines more easily and accurately than ever before.

Scheres started his PhD trying to get a portion of a gene-regulation protein to form tidy crystals — a prerequisite for X-ray crystallography, which involves pummelling the crystals with X-rays, then using the resulting diffraction patterns to deduce the protein's shape. But he abandoned the project when his protein, like so many others, defied crystallization. He was drawn instead to cryo-EM, in which a beam of electrons is used to visualize flash-frozen protein solutions. Three-dimensional structures are then created by merging electron micrographs taken from different angles. But at the time, the technique was known as 'blob-ology' because the images it produced were so patchy, Scheres says.

In 2010, when Scheres joined the Laboratory for Molecular Biology (LMB) in Cambridge, UK, microscopes were being developed that could detect electrons more efficiently and take snapshots of proteins at hundreds of frames per second. But Scheres knew that better computer programs would be needed to make sense of the flood of data, so he shut himself in his office to try to write one. "I didn't have a group. I was just programming," he says. The resulting software, named RELION, brought the blobs into focus: it did a much better job of marrying images

Ones to watch 2015

XIE ZHENHUA
CHINA'S TOP CLIMATE OFFICIAL
After this year's climate accord between the United States and China, Xie and the world's biggest greenhouse-gas polluter will be a focus of attention at climate talks.

ALAN STERN
PRINCIPAL INVESTIGATOR OF NASA'S NEW HORIZONS MISSION
Stern will be firmly in the spotlight in July when his mission becomes the first to reach Pluto. Just don't tell him it's not a planet.

JOANNE LIU
INTERNATIONAL PRESIDENT OF MÉDECINS SANS FRONTIÈRES (MSF)
MSF has shone in the global response to the Ebola epidemic, and Liu will be a big player in next year's efforts to end it.

BERNARD BIGOT
NOMINATED AS NEXT DIRECTOR-GENERAL OF ITER
Bigot wants to radically reform the troubled multi-billion-euro international project to build a huge reactor that would demonstrate the feasibility of fusion energy.

RICK HORWITZ
EXECUTIVE DIRECTOR, ALLEN INSTITUTE FOR CELL SCIENCE
As head of a new US$100-million venture funded by philanthropist Paul Allen, Horwitz must push cell biology to a new frontier.

was ready to try the transplants in people with a common condition called age-related macular degeneration, in which wayward blood vessels destroy photoreceptors and vision. The transplants are meant to cover the retina, patch up the epithelial layer and support the remaining photoreceptors. Watching the procedure, "I could feel the tension of the surgeon", Takahashi says.

In the end, everything went smoothly — but Takahashi will not reveal whether it has been a success until a year after the transplant. She does say that the tissue seems to have maintained its brownish colour, a sign that it has not been attacked by the immune system. The patient, a woman in her 70s, had already lost most of her vision and is unlikely to get it back; but Takahashi's team is keen to see whether the transplant is safe and prevents further retinal deterioration.

Takahashi had planned to operate on six patients in an informal clinical study. But a law that went into effect in Japan last month opens the door to a fast-track formal trial that would move the technology, if successful, to open clinical use. She is now considering which path to take.

The transplant was a high point for the field after a major low. Earlier in the year, controversy over two stem-cell papers published in *Nature* and unrelated to Takahashi's research had enveloped the CDB. The papers, which reported a quick recipe for making pluripotent stem cells, were first lauded and then shunned after it emerged that some figures had been manipulated. The spotlight fell on Haruko Obokata, the papers' first author, who continued to argue that the method worked. The episode took a tragic turn when Yoshiki Sasai, who supervised Obokata at the CDB, killed himself in August. In the wake of the scandal, the centre was drastically restructured and its research budget was slashed.

As all this unfolded, Takahashi found her own work under intense scrutiny: she was accused of rushing the procedure in an effort to make money, and concerns were raised over whether the cells were safe. A month before the scheduled surgery, the health ministry suddenly announced that several new safety tests would be required. At times, Takahashi says, she felt "beaten".

Now upbeat, however, Takahashi is aiming to clear a much higher bar — transplanting layers of photoreceptors together with the epithelial sheets — to restore a small degree of vision to people with macular degeneration. The photoreceptors would have to make connections with neurons, something that Takahashi realizes will be a challenge. For that, she will use the ability to grow three-dimensional retinal tissue *in vitro* — a technique, she notes with sadness, that was pioneered by Sasai.

Other scientists at the centre share the grief, and say that Takahashi's success was a welcome distraction. "It was definitely encouraging for all CDB people," says developmental biologist Masatoshi Takeichi, former director of the centre. ■

into a three-dimensional molecular structure than did existing tools.

"We left him alone for a couple years, and he came up with all this beautiful software," says Venki Ramakrishnan, a molecular biologist at the LMB. Ramakrishnan had won the 2009 Nobel Prize in Chemistry for his work in determining the structure of the bacterial ribosome using X-ray crystallography. But it takes years to obtain such structures because ribosomes are made up of dozens of different proteins and RNA molecules. Cryo-EM offers a quicker route, and this year, Ramakrishnan collaborated with Scheres to produce detailed structures of yeast and human ribosomes. Now, his lab has converted almost exclusively to the new technology. "For us it's a perfect saviour," he says. "We can be defined by the biological questions, rather than what we can crystallize."

Scheres is now looking for more difficult structures to crack. He found one in a project with a team at Tsinghua University in Beijing, to determine the structure of γ-secretase, a protein implicated in Alzheimer's disease. The protein is relatively small and prone to movement, which blurs cryo-EM images — but Scheres has already produced one structure and is working on improvements. "It is kind of a boom time in cryo-EM," says Richard Henderson, a structural biologist at the LMB who helped to develop the new electron microscopes, "and Sjors deserves a lot of the credit for getting it going." ■

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