THE DISCOVERY OF THE HIGGS BOSON

NO RECENT SCIENTIFIC ADVANCE HAS generated more hoopla than this one. On 4 July, researchers working with the world's biggest atom smasher—the Large Hadron Collider (LHC) in Switzerland—announced that they had spotted a particle that appears to be the long-sought Higgs boson, the last missing piece in physicists' standard model of fundamental particles and forces. The seminar at which the results were presented turned into a media circus, and the news captured the imagination of people around the world. "[H]appy 'god particle' day," tweeted will.i.am, the singer for pop group The Black Eyed Peas, to his 4 million Twitter followers.

Yet, for all the hype, the discovery of the Higgs boson easily merits recognition as the breakthrough of the year. Hypothesized more than 40 years ago, the Higgs boson is the key to physicists' explanation of how other fundamental particles get their mass. Its observation completes the standard model, perhaps the most elaborate and precise theory in all of science. In fact, the only big question hanging over the advance is whether it marks the beginning of a new age of discovery in particle physics or the last hurrah for a field that has run its course.

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The Higgs solves a basic problem in the standard model. The theory describes the particles that make up ordinary matter: the electrons that whiz around in atoms, the up quarks and down quarks that make up the protons and neutrons in atomic nuclei, the neutrinos that are emitted in a type of radioactivity, and two sets of heavier cousins of these particles that emerge in particle collisions. These particles interact by exchanging other particles that convey three forces: the electromagnetic force; the weak nuclear force, which spawns neutrinos; and the strong nuclear, which binds quarks.

But there's a catch. At first blush, the standard model appears to be a theory of massless particles. That's because simply assigning masses to the particles makes the theory go haywire mathematically. So mass must somehow emerge from interactions of the otherwise massless particles themselves.

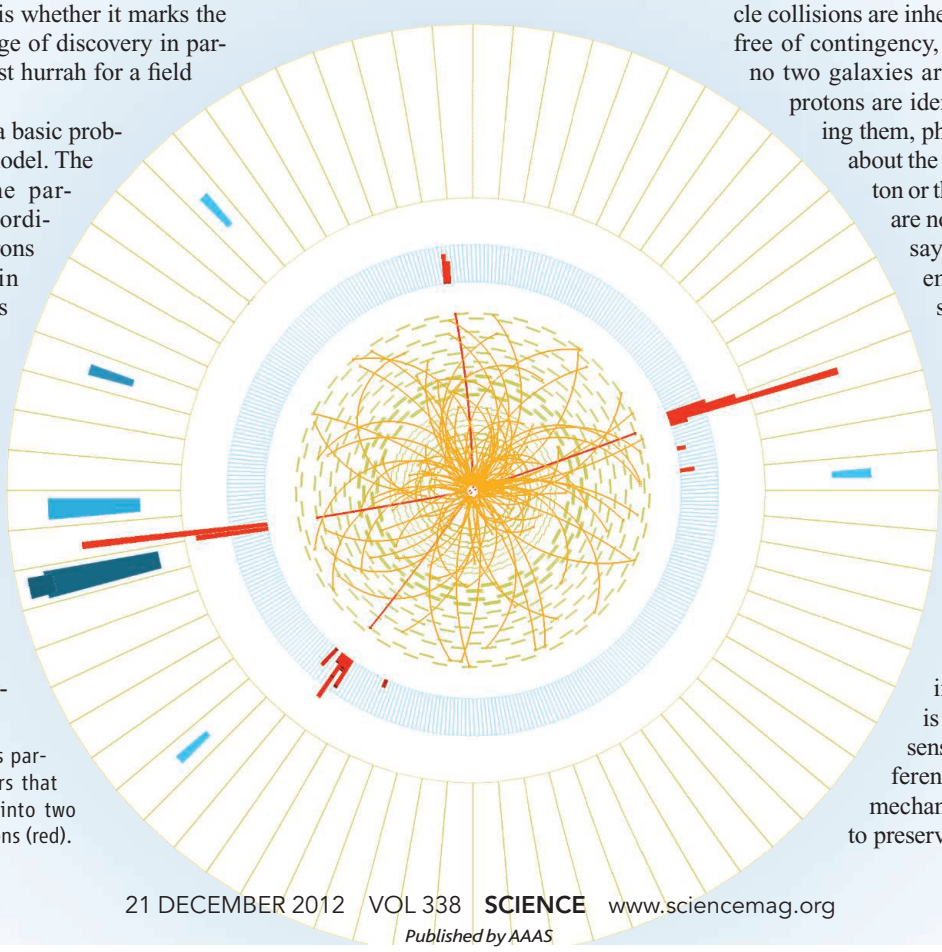
That's where the Higgs comes in. Physicists assume that empty space is filled with a "Higgs field," which is a bit like an electric field. Particles interact with the Higgs field to acquire energy and, hence, mass, thanks to Albert Einstein's famous equivalence of the two, encapsulated in the equation $E = mc^2$. Just as an electric field consists of particles called photons, the Higgs field consists of Higgs bosons woven into the vacuum. Physicists have now blasted them out of the vacuum and into brief existence.

That feat marks an intellectual, technological, and organizational triumph. To produce the Higgs, researchers at the European particle physics laboratory, CERN, near Geneva, built the $5.5 billion, 27-kilometer-long LHC. To spot the Higgs, they built gargantuan particle detectors—ATLAS, which is 25 meters tall and 45 meters long, and CMS, which weighs 12,500 tonnes. The ATLAS and CMS teams boast 3000 members each. More than 100 nations have a hand in the LHC.

Perhaps most impressive is the fact that theorists predicted the existence of the new particle and laid out its properties, right down to the rates at which it should decay into various combinations of other particles. (To test whether the particle really is the Higgs, researchers are measuring those rates now.) Physicists have made such predictions before. In 1970, when only three types of quarks were known, theorists predicted the existence of a fourth, which was discovered 4 years later. In 1967, they predicted the existence of particles that convey the weak force, the W and Z bosons, which were found in 1983.

Particle theorists offer various explanations of their knack for prognostication. Particle collisions are inherently reproducible and free of contingency, theorists say. Whereas no two galaxies are exactly the same, all protons are identical. So when smashing them, physicists need not worry about the peculiarities of this proton or that proton because there are none. Moreover, theorists say, in spite of its mathematical complexity, the standard model is conceptually simple—a claim that nonphysicists might not buy.

The standard model ultimately owes its predictive power to the fact that the theory is based on the notion of mathematical symmetry, some theorists say. Each of the three forces in the standard model is related to and, in some sense, necessitated by a different symmetry. The Higgs mechanism itself was invented to preserve such symmetry while



Pieced together. In this particle collision, it appears that a Higgs boson decays into two electrons and two positrons (red).

CREDIT: CERN/L. TAYLOR/T. MCCAULEY

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giving mass to force-carrying particles like the W and the Z. Simply put, symmetry arguments are powerful predictive tools.

No matter the reason for particle physicists' predictive prowess, with the Higgs boson apparently in the bag, they have no similar prediction to test next. They have plenty of reason to think the standard model is not the final word on fundamental physics. The theory is obviously incomplete, as it doesn't incorporate the force of gravity. And the theory itself suggests that interactions between the Higgs and other particles ought to make the Higgs hugely heavy. So physicists suspect that new particles lurking in the vacuum may counteract that effect. But those arguments aren't nearly as precise as the one necessitating the Higgs boson.

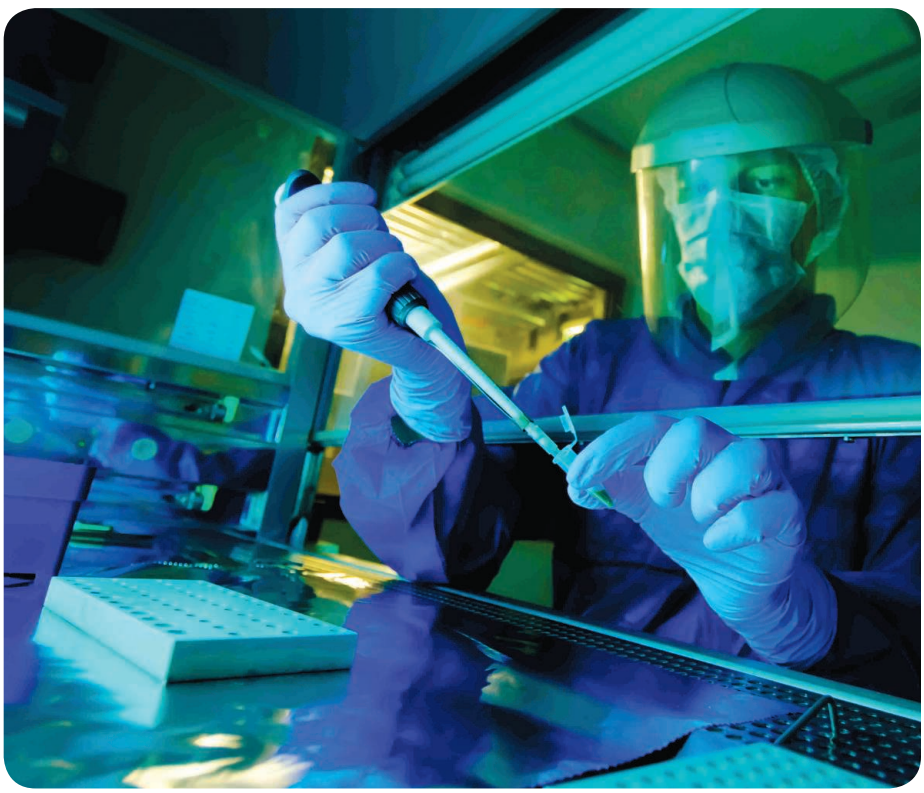
In fact, scientists have no guarantee that any new physics lies within the reach of the LHC or any conceivable collider. The standard model could be all of the inner workings of the universe that nature is willing to reveal. The discovery of the Higgs is a breakthrough. Will particle physicists ever score a similar breakthrough again?

–ADRIAN CHO

A HOME RUN FOR ANCIENT DNA

Two years ago, paleogeneticists made our short list for Breakthrough of the Year for publishing the complete sequence of the nuclear genome of the Neandertals. In 2011, the same lab shared our spotlight for piecing together the genome of the Denisovans, an archaic human that lived in Siberia at least 50,000 years ago. But those ancient DNA sequences and others were blurry snapshots next to the high-resolution genomes that researchers can now sequence from living people. Much of the fragile DNA from fossils is degraded into single strands that automatic sequencers can't copy. Researchers were resigned to deciphering only parts of the code of ancient genomes, whether from archaic humans, animals, or pathogens.

This year, however, a persistent postdoc developed a remarkable new method that enabled his team to revisit the Denisovan DNA and sequence it 31 times over. The resulting genome, of a girl who lived in Siberia's Denisova Cave, reveals her genetic material in the same sharp, rich detail that researchers typically get from the DNA of living people. This technological feat promises to give a major boost to the field of ancient DNA, as researchers begin to apply the method to other samples and species.



CREDIT: MAX PLANCK INSTITUTE FOR EVOLUTIONARY ANTHROPOLOGY

Single-minded. Postdoc Matthias Meyer (*above*) developed a new method to prepare single strands of ancient DNA; the technique gave researchers an unprecedented view of an ancient girl's genome.

Ancient DNA researchers typically have adapted the tools used to sequence DNA from living humans, which start with samples of double-stranded DNA. But ancient DNA usually breaks into single strands. So postdoc Matthias Meyer at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, set out to sequence single-stranded ancient DNA from scratch. He failed at first, but then managed to bind special molecules to the ends of a single DNA strand, holding it in place for sequencing. As a result, using only 6 milligrams of bone from the Siberian girl's pinky finger, Meyer and colleagues were able to copy 99.9% of her genome at least once and 92% of the genome 20 times—the benchmark for reliably identifying nucleotide positions.

The results confirmed that Denisovans interbred with the ancestors of some living humans; people living in parts of island Southeast Asia have inherited about 3% of their nuclear DNA from Denisovans. The genome literally offers a glimpse of the girl, suggesting that she had brown eyes, brown hair, and brown skin. It also allowed the team to use DNA to estimate that the girl died between 74,000 and 82,000 years ago—the first time researchers had used genomic information to date an archaic human. The high quality of the genome gives researchers a powerful new tool to fish for genes that have recently evolved, providing a "near-complete" catalog of the handful of genetic changes that separate us from Denisovans, who were close kin to Neandertals.

These details are all the more remarkable because the Denisovans are so poorly known from fossils: Only a tiny scrap of finger bone and two molars have been reliably assigned to them so far. In contrast, the Neandertals are known from hundreds of fossils but from a much less complete genome.

Neandertal experts may catch up soon. Meyer and colleagues have been trying "Matthias's method" on fossil samples that previously failed to yield much DNA. A detailed Neandertal genome comparable to the Denisovan one is expected in 2013.

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ITALIAN QUAKE VERDICTS RATTLE RESEARCHERS

Can scientists risk talking publicly about risk—especially when lives are on the line? It's a question that many researchers began asking this year as Italian prosecutors pressed manslaughter charges against four scientists, two engineers, and a government official accused of conducting superficial analyses and making misleading public statements about earthquake hazards in the days before a deadly 2009 temblor struck the city of L'Aquila, killing more than 300 people. In October, each of the seven defendants was found guilty and sentenced to 6 years in prison; all are appealing the convictions, a process that could take years.

The verdicts shocked and enraged many researchers—and prompted them to revisit a long-standing challenge: how to communicate with the public and policymakers about risk, especially in technical areas with high uncertainty and the potential for great loss of life. From bioterrorism and disease outbreaks to hurricanes and earthquakes, researchers are called upon by government officials to help forecast the probability of dangerous events and devise plans to keep the public safe. They often struggle to translate nuanced statistical models into plainspoken, practical advice. Should a 40% probability that an event might occur make it "low-risk" in common parlance, for instance—or should that be a "medium" risk? And what difference would that make to a person trying to decide whether to flee an oncoming storm, or a government official trying to prepare for a possible bioterror attack?

Until now, the answers to such questions were largely academic, or at least low-risk from a legal perspective. After the Italian verdicts, however, some scientists worry that the words they utter might land them in prison. "I'm afraid that many scientists are learning to keep their mouths shut," earth scientist Thomas Jordan of the University of Southern California in Los Angeles, told *Science* earlier this year. "This won't help those of us who are trying to improve risk communication between scientists and the public."

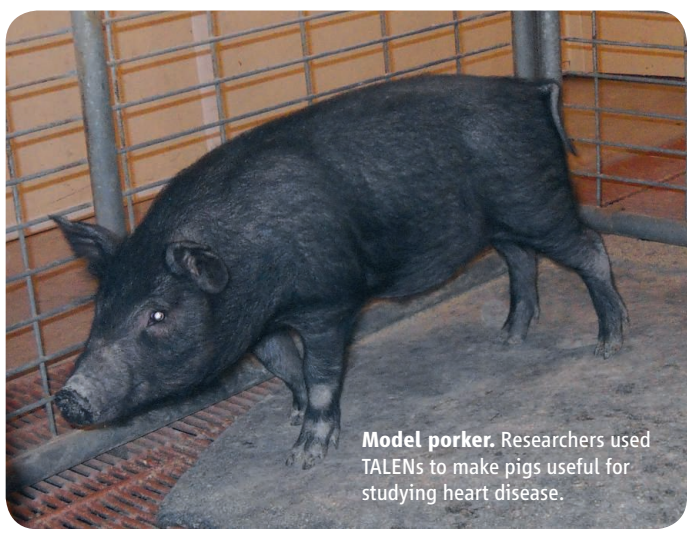
Some science groups are working to make sure researchers don't go silent. National academies of science in Europe, for example, are collaborating on efforts to extract lessons from the L'Aquila case, with an eye toward heading off similar legal jeopardy elsewhere. "Probability-based statements are per se fraught with uncertainty," the French and German academies noted in a statement earlier this year. But "scientists cannot—and should not—absolve themselves" of the responsibility to communicate clearly, it added. The risk that scientists ultimately decide to say nothing, such efforts suggest, may be the greatest risk of all.

–DAVID MALAKOFF

GENOMIC CRUISE MISSILES

This year, genome engineers got their hands on some potentially powerful new tools that promise to put the modification of DNA within easy reach of biologists studying a variety of organisms, including yeast and humans. One of these tools, called TALENs (for "transcription activator–like effector nucleases"), can destroy or alter specific genes in zebrafish, *Xenopus* toads, and livestock. A TALEN is a protein that cuts DNA in specific places, and the ensuing repair modifies the target gene. One group of researchers used the technique to create a miniature pig useful for studying heart disease. Others are modifying the genomes of rats, crickets, and even human cells from patients with disease. Crystal structures of these effector proteins attached to DNA have revealed how the proteins find their targets. And at least three teams have come up with a way to make many of these proteins fast and cheaply. This progress has prompted more investigators to give this approach a try.

Such a boom in genome engineering was unthinkable just a few years ago. For most higher organisms, changing or deleting DNA has generally been a hit-or-miss proposition. Researchers could not readily control where an added gene would insert itself into a genome or which DNA they delete in so-called knockout experiments. As a result, pinpointing what specific genes do and correcting disease genes in people have posed major challenges.



Model porker. Researchers used TALENs to make pigs useful for studying heart disease.

A decade ago, a new technology called zinc finger nucleases provided a way to target specific genes. Researchers leaped to develop this tool. But zinc fingers proved difficult to make, and one company holds all the key patents. So excitement swelled again in 2009, when two teams discovered a one-to-one correspondence between the repetitive regions of transcription activator–like effector proteins and the DNA bases they attach to, thus providing a new way to target genes. In 2012, studies drove home that TALENs work as well as zinc fingers do but are far easier and cheaper to make. Some researchers now think TALENs will become standard procedure for all molecular biology labs.

RUNNER-UP

Meanwhile, another gene-targeting technology is beginning to make a name for itself. One drawback of zinc finger nucleases,

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TALENs, and another genome-editing tool called meganucleases is that they must be reengineered for each new DNA target. These proteins have two parts: the DNA targeting section and the DNA-cutting section. The new technology substitutes RNA—which is simpler to make than a piece of a protein—for the DNA targeting section. It also makes use of a bacterial protein called Cas9, which is part of a natural bacterial defense system called CRISPR, to do the cutting.

Researchers have shown in a test-tube that they can combine these two RNAs into a single one that both matches the DNA target and holds Cas9 in place. Using this system, they were able to cut specific target DNA, demonstrating the potential of Cas9 to work like TALENs. Now, those researchers are trying this approach in organisms other than bacteria, and other genome engineers are quite excited about their prospects, suggesting that it may one day challenge zinc finger nucleases and TALENs as the core genome engineering technology.

CRASH PROJECT OPENS A DOOR IN NEUTRINO PHYSICS

Sometimes it's not the result itself so much as the promise it holds that matters most. This year, physicists measured the last parameter describing how elusive particles called neutrinos morph into one another as they zip along at near–light speed. And the result suggests that in the coming decades neutrino physics will be every bit as rich as physicists had hoped—and may even help explain how the universe evolved to contain so much matter and so little antimatter.

RUNNER-UP

Born in certain nuclear interactions, neutrinos come in three types or flavors that change into one another in so-called neutrino oscillations. The rates and extents to which the flavors mix depend on six parameters: the three differences between the neutrinos' masses, and three "mixing angles." In March, the 250 researchers with the Daya Bay Reactor Neutrino Experiment in China reported that last unknown parameter, the mixing angle known as θ_{13} (pronounced "theta one three"), equals 8.8°, give or take 0.8°.

The result itself is remarkable, as it's not every year that physicists measure a new fundamental parameter. The real excitement, however, stems from the result's broader implications. The measurement proves that all three mixing angles are greater than zero. That fact, in turn, implies that the oscillations of antineutrinos might differ from those of neutrinos, something that would not be possible had θ_{13} equaled zero.

That's a big deal. Such a difference would be an example of an asymmetry between matter and antimatter known as CP violation. Physicists have already observed CP violation among particles called quarks, but they know that it isn't pronounced enough to explain why particles of normal matter vastly outnumber particles of antimatter in the universe. Physicists think that if there is CP violation among neutrinos, then it may be more analogous to the effect that created the matter-antimatter imbalance in the universe.

In fact, researchers in the United States, Japan, and Europe are engaged in experiments in which they use particle accelerators to fire neutrinos hundreds of kilometers through Earth to huge particle detectors. Current efforts seek to pin down, for example, the masses of the neutrinos and not just the differences between them. And scientists in all three regions are planning bigger experiments to search for CP violation among neutrinos. The Daya Bay result gives those efforts an enormous shot in the arm.

The result also marks a coup for Chinese physicists. The Daya Bay team studied the neutrinos emanating from the reactors at the Daya Bay Nuclear Power Plant and two neighboring plants in Shenzhen. In making a definitive measurement, they beat out teams working at reactors in France and South Korea and accelerator-based experiments in Japan and the United States.

The measurement of θ_{13} wasn't the only result in particle physics this year. Researchers working with the world's largest atom smasher, the Large Hadron Collider (LHC) in Switzerland, discovered the Higgs boson, the last piece of physicists' standard model. But if LHC researchers do not find new particles beyond those in the standard model, then neutrino physics could be the future of particle physics—as the fact that neutrinos even have mass isn't part of the standard model. If so, the Daya Bay result may mark the moment when the field took off.

That was fast! Construction of China's Daya Bay Reactor Neutrino Experiment began in 2007. With 2 months' worth of data, it scooped competitors in Japan, France, Korea, and the United States.

CREDIT: SUN ZIFA/COLOR CHINA PHOTO/AP IMAGES

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GENOMICS BEYOND GENES

A decadelong, $288 million study reported this year in more than 30 papers showed the human genome to be quite a bustling place, biochemically speaking. The work—called the Encyclopedia of DNA Elements (ENCODE)—builds on the Human Genome Project, which deciphered the order of the bases that are our DNA's building blocks and found that less than 2% of those bases defined genes.

ENCODE researchers took an intensive look not just at genes but at all of the DNA in between. Their results drive home that much of the genome that at one time was dismissed as "junk DNA" actually seems to play an essential role, often by helping to turn genes on or off. They pinpointed hundreds of thousands of landing spots for proteins that influence gene activity, many thousands of stretches of DNA that code for different types of RNA, and lots of places where chemical modifications serve to silence stretches of our chromosomes, concluding that 80% of the genome was biochemically active. These details provide a much better road map for investigators trying to understand how genes are controlled. Some researchers have already used these insights to clarify genetic risk factors for a variety of diseases, including multiple sclerosis and Crohn's disease.

When these papers were published in September, the media went wild. ENCODE was hailed in *The New York Times* as a "stunning resource" and "a major medical and scientific breakthrough" with enormous and immediate implications for human health. *The Guardian* called it "the most significant shift in scientists' understanding of the way our DNA operates since the sequencing of the human genome."

But several scientists in the blogosphere called the coverage overhyped and blamed the journals and ENCODE leaders for overplaying the significance of the results. For example, ENCODE reported that 76% of DNA is transcribed to RNA, most of which does not go on to help make proteins. Various RNAs home in on different cell compartments, as if they have fixed addresses where they operate, suggesting that they play a role in the cell. Critics argue, however, that it was already known that a lot of RNA was made, and that many of these RNAs may be spurious genome products that serve no purpose. Likewise, one ENCODE researcher found 3.9 million regions across 349 types of cells where proteins called transcription factors bind to the genome—but again, it's unclear how much of that binding is functional.

Nonetheless, ENCODE stands out as an important achievement that should ease the way for more insights into the genome. By combining these data with sampling from another data-intensive effort, the 1000 Genomes Project, researchers discovered that 8% of our DNA appears with little variation throughout the human population—a strong sign that it was important for our evolution. Overall, ENCODE's newly discovered functional regions overlap with 12% of the specific DNA bases linked to higher or lower risks of various diseases, suggesting that the regulation of genes—not just the makeup of the genes themselves—might be at the heart of these risks. Scientists have used this information to home in on relevant genes and cell types in several disorders. Experiments can now unearth the molecular basis of these connections and, from there, identify potential treatments. If that potential is realized, then ENCODE will have earned its accolades as a "stunning resource."

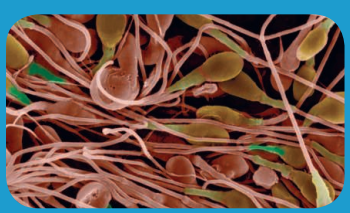
ENCODE
BY THE NUMBERS

147	cell types studied
80%	functional portion of human genome
20,687	protein-coding genes
18,400	RNA genes
1640	data sets
>30	simultaneous papers
442	researchers
$288 MILLION	funding for pilot, technology, model organism, and current project

AREAS TO WATCH

ONE CELL AT A TIME

Single-cell DNA sequencing burst onto the scene this year, with advances in microfluidics, the isolation of rare cells, and the ability to decipher these tricky one-shot genomes—milestones that should help break the field wide open in 2013. Even more exciting, some say, are prospects for learning about how cells—particularly brain cells—work by studying the RNA in individual, intact cells.



In the coming year, single-cell sequencing promises to reveal a lot about how cancer cells vary within a tumor and how many copies of genes reside in each cell. Expect continued progress in developing this technology for medical diagnostics for cancer and prenatal applications. Meanwhile, several groups are assessing what genes are doing by measuring in individual cells the messenger RNA that carries their instructions to a cell's protein factories.

PLANCK MAPS THE COSMIC MICROWAVE BACKGROUND

The European Space Agency's Planck satellite will produce the most precise map yet of the afterglow of the big bang, the cosmic microwave background radiation (CMB). The discovery of the CMB in 1965 bolstered the notion that the universe was born in an explosive big bang. Measurements of tiny variations in its temperature in 1992 supported the idea that the universe expanded at greater than light speed in a brief spurt of "inflation." And the precise mapping of those variations in 2003 helped nail down the composition of the universe: 5% ordinary visible matter, 22% as-yet invisible dark matter, and 73% space-stretching dark energy. Planck will test the now-standard cosmology in greater detail—and could find evidence that the relatively simple scenario isn't quite the whole story.

CONNECTOMES

In 2013, the Human Connectome Project will get into full swing. This $38.5 million effort, funded by the U.S. National Institutes of Health, aims to scan the brains of 1200 healthy adults, including 300 pairs of twins, to investigate individual variations in the connections between brain regions and how they might account for individual differences in cognition and

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SCARY ENGINEERING TAMES MARTIAN TERROR

It looked like a wreck waiting to happen, but the new "sky crane" landing system designed to deliver the massive Curiosity rover safely onto Mars performed flawlessly on 5 August (PDT). Curiosity landed a mere 2.4 kilometers from the center of the bull's-eye after a 563-million-kilometer journey from Earth—even though engineers had no way to test Curiosity's "entry, descent, and landing" (EDL) system from beginning to end under martian conditions.

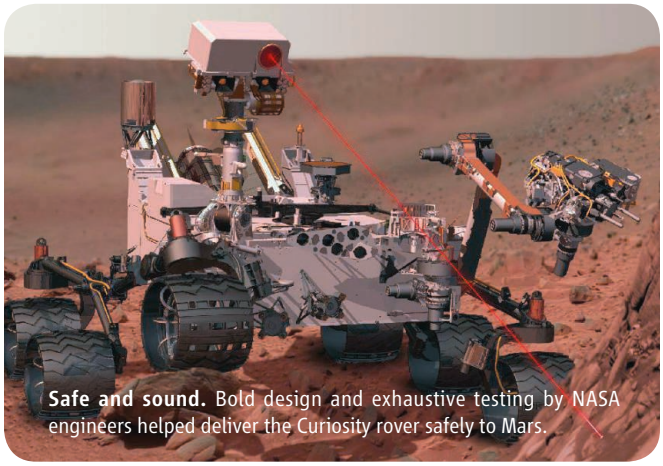
RUNNER-UP

Curiosity mission engineers at NASA's Jet Propulsion Laboratory in Pasadena, California, pulled off a stunning EDL after thinking far outside the box. Six times before, NASA had landed intact spacecraft on Mars (and once it didn't work out so well). Three landers came down like 1950s sci-fi spaceships, rockets blazing and landing on legs. The three rovers bounced onto Mars inside NASA's version of a beach ball. But Curiosity—clamped inside its entry vehicle—weighed in at 3.3 metric tons, too massive for either of the traditional approaches.

So Curiosity engineers considered how their earthly brethren move big things around. Taking their inspiration from cranes and helicopters, they created the sky crane: a platform festooned with retrorockets with the rover, wheels deployed, dangling 7.5 meters below at the end of three cables. The scary-looking contraption could handle a landing mass too large for a beach ball, while safely setting a massive rover down on inclined slopes that would stymie a legged lander. Instruct the platform to cut the cables on touchdown and fly away, and you've got a safe landing—in principle.

To make it all work in practice, engineers test, test, and test again. But Curiosity engineers had a problem: Their EDL system—a blazing meteor-like entry, a parachute descent, and the sky-crane landing, all designed to slow their spacecraft from a hypervelocity speed of 21,240 kilometers per hour to a standstill 7 minutes later—couldn't be tested on Earth. Earth's gravity and atmosphere are too different from those of Mars. So they tested components separately as much as they could, for example, by opening the parachute in the world's largest wind tunnel. Then they tested the system end to end millions of times in a computer. In the end, reality played out as the simulations did—a sign that NASA had taken one more step toward solving the far weightier problem of landing astronauts on Mars.

Engineers got a break when mission planners asked them to have Curiosity touch down up close and personal with the geologically intriguing central mound of Gale crater, a tight spot that no previous mission could have targeted. Instead of streaking in as uncontrolled as a bullet, Curiosity revived a "heritage" concept from the days of the Apollo moon program, when astronaut-bearing capsules guided themselves during reentry into Earth's atmosphere. Sensing any deviations from its intended flight path, the Curiosity entry vehicle would fire side thrusters to correct its course as it plunged toward the surface. The rover's spot-on landing reassured planners that NASA can now send a rover to collect samples on Mars and later land a second mission in the same spot to pick up the samples and loft them into Mars orbit for eventual return to Earth.



Safe and sound. Bold design and exhaustive testing by NASA engineers helped deliver the Curiosity rover safely to Mars.

behavior. Several other projects are zooming in to examine neural connectivity at the cellular level. Advocates and critics have debated how much these maps will advance our understanding of brain function. By this time next year, far more data will help inform the debate.

PIERCING A FRIGID UNDERWORLD

The depths of Antarctica are about to be brought to light. In February, after 14 years of off-and-on drilling through 4 kilometers of East Antarctic ice, Russian scientists stopped just short of the surface of a mysterious subglacial lake likely cut off from the rest of the planet for millions of years. This month, the team returns to Lake Vostok with plans to bring back samples of ice—and, they hope, to discover signs of long-buried indigenous life. U.S.-led and U.K.-led teams are embarking on their own expeditions to study subglacial Antarctic waters. The U.S. team will head to the Whillans Ice Stream, where Antarctic ice joins the Southern Ocean; the U.K. team, to Lake Ellsworth, also on the Western Antarctic Ice Sheet.

CANCER IMMUNOTHERAPY

Recently developed drugs that harness the body's immune system to fight cancer have beaten back the disease in a small subset of tumor-ridden patients. Researchers predict that combining two such immunotherapies that target different pathways could pack an even more powerful punch. In 2013, look for early results from clinical trials that pair two antibodies that thwart pathways that tumor cells co-opt to hide from the immune system, and for reports on human studies that combine this brake-lifting strategy with treatments that rev up the body's immune response.

PLANT POWER

Expect basic plant research to pay off this year, with farmers making use of drought-resistant crops and companies selling the first algae-based diesel fuel. Researchers expect to pin down details of the molecular and genetic components that interact to regulate the growth of plants. Mechanical forces will prove to play a key role in this regulation. Melding genomic, developmental, and ecological studies should help reveal how natural variation can succeed—or fail—to enable plants to adapt to climate change.

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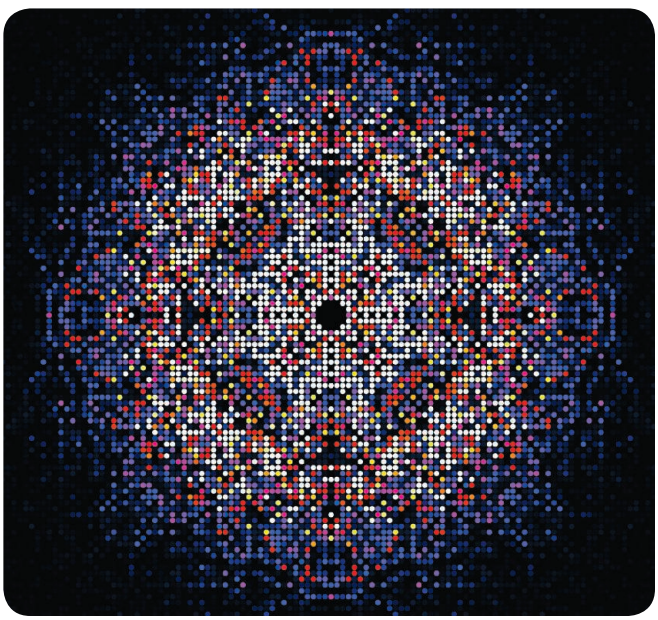
FIRST PROTEIN STRUCTURE FROM AN X-RAY LASER

One hundred years ago, physicists showed how x-rays ricocheting through a crystal could reveal the crystal's atomic-scale structure. This year, scientists pushed such "x-ray diffraction" nearly to its ultimate limit when, for the first time, they used an x-ray laser to determine the structure of a protein. The advance shows the potential of x-ray lasers to decipher proteins that conventional x-ray sources cannot.



In sum. Researchers used 178,875 individual laser pulses to generate this diffraction pattern and decipher the structure.

X-ray diffraction has long been the mainstay of structural biology. When many copies of a molecule are arranged in an orderly array called a crystal lattice, they scatter the x-rays from an incoming beam in concert. The pattern of scattering reveals the structure of the crystal, including that of the molecule. Using circular particle accelerators called synchrotrons to generate x-rays, biologists have determined tens of thousands of protein structures.

Some proteins, such as those found in cell membranes, do not readily form crystals big enough to be studied with synchrotrons, however. So, scientists hope they can probe those tough cases with new x-ray lasers, which are powered by straight-shot linear accelerators and shine a billion times brighter than synchrotron sources. In November, researchers unveiled the first protein structure revealed with such a laser.

RUNNER-UP

Working with the Linac Coherent Light Source (LCLS) at SLAC National Accelerator Laboratory in Menlo Park, California, researchers from Germany and the United States determined the structure of the inactive "precursor" form of an enzyme that's key for the survival of the single-celled parasite that causes African sleeping sickness, *Trypanosoma brucei*. To produce micrometer-sized crystals of the enzyme, they overexpressed it in cultured cells. They dropped the crystals through the beam of the LCLS, which turned on in 2009. A pulse of x-rays would obliterate a crystal even as it produced a diffraction pattern. Adding up 178,875 individual patterns, researchers determined the precursor's structure, which includes a kind of molecular safety cap that deactivates it. That information could help scientists find a drug to tie up the active form of the enzyme.

With just one new structure in the bag, it's not yet clear that x-ray free-electron lasers (XFELs) will compete with synchrotrons in structural biology. For one thing, researchers were not able to determine the structure of the enzyme de novo from the diffraction data alone, but had to use the known structure of the active enzyme as a starting point. For another, an XFEL serves far fewer users than a synchrotron does. Still, the "diffraction before destruction" approach takes a qualitative step past what synchrotrons can do. Earlier this year, researchers in Japan turned on their own XFEL, and researchers in Europe are building one that should power up in 2015.

The grand goal is to push x-ray diffraction to its ultimate limit and use an x-ray laser to decipher a protein structure by zapping individual molecules. It's not certain that can be done, but some researchers say the new result suggests that objective may not be too far out of reach.

BRAIN-MACHINE INTERFACES START TO GET A GRIP

This week researchers in Pennsylvania reported that a 53-year-old woman paralyzed from the neck down by a genetic neurodegenerative condition had learned to manipulate a robotic arm with her thoughts. Surgeons had implanted two 4×4-millimeter grids of hair-thin electrodes in her brain to capture signals from an area involved in planning hand movements. A computer translated those signals into commands to move the robotic arm, which was engineered to have nearly all the same movement capabilities as the real thing. In videos, the woman uses the arm to grasp and move various objects, removing plastic cones stacked on a base and restacking them one by one on another base, for example. The demonstrations represent the most complex movements yet performed by a paralyzed human patient using a brain-machine interface (BMI), as such sophisticated prosthetics are often called.

RUNNER-UP

By demonstrating more fluid and natural movements, this case study improves on another impressive report earlier this year. In that study—the first published demonstration that paralyzed human patients can use a BMI to execute complex movements in three dimensions—a 58-year-old woman who had been unable to speak or move her limbs for 15 years manipulated a robotic arm with her thoughts, reaching out to grasp a bottle and take a sip of coffee. A tetraplegic man, 66, also learned to touch and grasp objects.

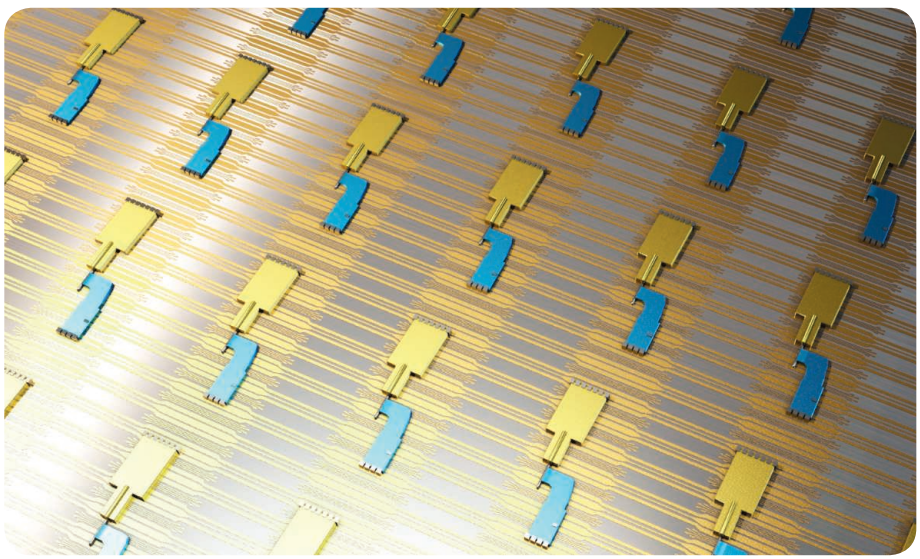
All of this work builds on more than a decade of research with monkeys and other animals. And that work continues to advance. In 2011, researchers described a prosthetic system that provides tactile feedback by stimulating the somatosensory cortex, the brain region responsible for the perception of touch. And in April of this year, a team used signals from electrodes implanted in the motor cortex of the brain to stimulate muscles in the temporarily paralyzed arms of two monkeys, enabling the animals to pick up rubber balls and place them in a chute. Such

CREDIT: KAROL NASS, CFEL

Published by AAAS

MAJORANA FERMIONS, QUASI-HERE AT LAST

Nanoscience is more than just a fashionable buzzword. It's already paid off in billions of dollars worth of products including better batteries and baseball bats. This year, researchers in the field delivered a different type of value: their first-ever likely particle discovery, known as Majorana fermions.



Particle detectors. At the heart of each device in this array is an indium antimonide nanowire, one end is gold-coated and the other is a superconductor (blue). Majorana fermions are produced at the ends of the nanowires.

Speculation about the existence of Majorana particles dates back more than 7 decades, when a young Italian physicist named Ettore Majorana crunched some equations in the emerging field of quantum mechanics. His mathematics united the quantum understanding of fermions, particles such as electrons that show a type of angular momentum known as spin, with Albert Einstein's equations of relativity that impact particles traveling near the speed of light. Majorana's insights implied the existence of a new type of fermion that could act as their own antimatter and annihilate themselves.

Physicists have long suspected that neutrinos are Majorana fermions. Thus far, they've been unable to nail down the case. And prospects for finding other Majorana fermions long seemed remote. But a few years ago, theorists suggested that the collective motion of electrons in nanoscale wires adjacent to a superconductor may form "quasiparticles" that for all intents and purposes behave as if they were a fundamental Majorana particle themselves. The race was on. This year, a team of physicists and chemists in the Netherlands crossed the line showing compelling evidence that the Majorana quasiparticles exist.

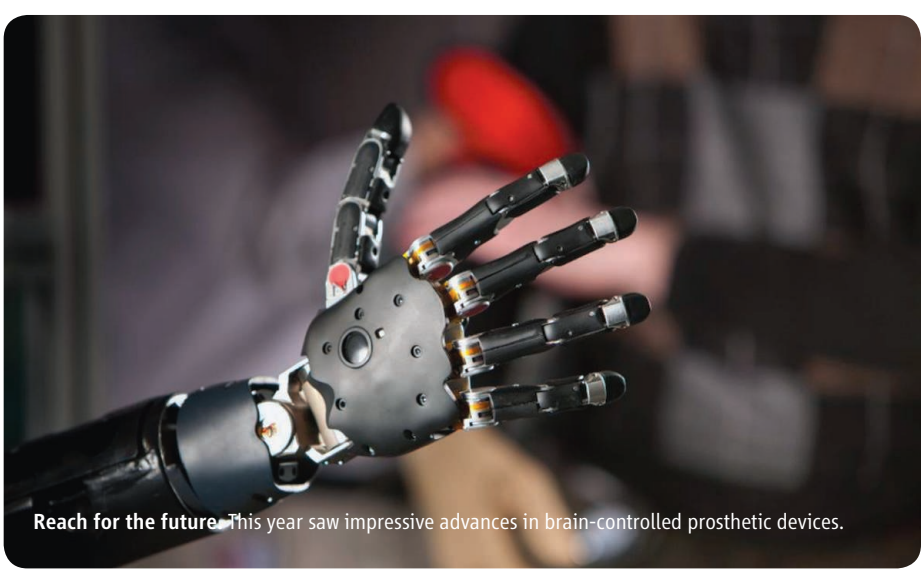
RUNNER-UP

The discovery has already prompted efforts to use the new particles to build a stable quantum computer. Such computers operate on quantum bits, or qubits. Unlike regular bits of digital information represented as 0s and 1s in calculations, qubits can be virtually any combination of a 0 and 1—say, 57% 0 and 43% 1, or 12% 0 and 88% 1. As a result, quantum computers have the potential to store and process information in ways that conventional digital machines can't hope to match. For some types of calculations, crunching just 300 qubits could generate an answer that today's best supercomputers would struggle to solve.

However, current qubit technology is far too fussy for practical computing. The slightest bump in temperature or other outside influence typically wipes out the information stored in a standard qubit. Theoretical calculations show that Majorana fermions should be able to "remember" their quantum state even when buffeted by outside forces. So now the Dutch team and others are hot on the trail to see whether that is the case. If it is, nanoscience may soon be able to add to its bragging rights.

findings hint at the tantalizing possibility that it may one day be possible to reanimate paralyzed limbs in people.

As hopeful as these developments are, it will be years before large numbers of people can benefit from BMIs. The robotic arms are experimental and extraordinarily expensive, and patients use them only in the lab, aided by a team of technicians. And the movements enabled by BMIs aren't nearly as fast and graceful as the movements made by uninjured individuals. Advances in the algorithms that decode neural signals and convert them into commands a computer or prosthetic limb can understand should help with that. Progress in that area continues apace, but for hundreds of thousands of patients paralyzed by strokes, spinal injuries, and other conditions, it can't come quickly enough.



Reach for the future. This year saw impressive advances in brain-controlled prosthetic devices.

CREDITS (TOP TO BOTTOM): TU DELFT 2012; THE JOHNS HOPKINS UNIVERSITY APPLIED PHYSICS LABORATORY (JHU/APL)

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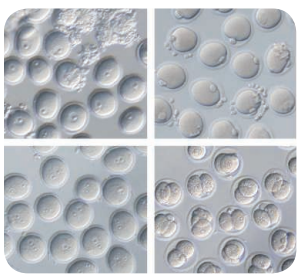
MAKING EGGS FROM STEM CELLS

Researchers have been trying for more than a decade to make egg cells in the laboratory. This year, they took an important step toward that goal, as lab mice gave birth to the first live pups born of eggs derived from mouse embryonic stem (ES) cells. The technique, developed by researchers in Japan, still requires a mouse to host the developing eggs during a key part of their maturation, so it doesn't achieve the big prize: deriving egg cells entirely in vitro. But it does demonstrate that ES cells can give rise to fertile oocytes, and it gives scientists a way to learn more about how these complex and powerful cells develop.

RUNNER-UP

Egg and sperm cells, also known as germ cells, have a particularly complicated development. They undergo meiosis, a special kind of cell division that leaves them with half the normal number of chromosomes. They also reset the genomic imprinting that helps determine which genes are turned on and which are turned off. Although pluripotent cells—including ES cells—are capable of becoming any kind of cell in the body, turning them into germ cells in the lab has proved difficult.

In 2011, the same lab in Japan reported that it had turned ES cells into fertile sperm. In 2012, researchers there showed that a similar process can produce eggs. First, they treated the stem cells with a cocktail of growth factors and proteins to form what they call primordial germ cell-like cells, which resemble the precursors of egg and sperm cells found in early embryos. They then mixed the cells with ovarian tissue. The cells formed clusters that resemble miniature ovaries. The scientists implanted those clusters in the ovaries or kidneys of host mice, and several weeks later they were able to extract mature oocytes.



Growing potential. Fertilized lab-derived egg cells yielded embryos—and live mice.

The scientists used normal mouse sperm to fertilize the oocytes in vitro and then implanted the resulting embryos into foster mothers. The foster mothers gave birth to normal mice, which were then able to go on and have offspring of their own. (The recipe also works with induced pluripotent stem cells, which are derived from adult cells that have been reprogrammed to behave like embryonic cells.)

The technique doesn't yet work with human cells—and the requirement for ovarian tissue and a live host for part of the development makes it impractical and ethically problematic to try. But having a better way to study the genes and other factors that influence egg cell development could already help researchers understand some kinds of infertility—and could lead to better ways to make these elusive but powerful cells in the lab.

SCORECARD

RATING LAST YEAR'S AREAS TO WATCH

THE HIGGS BOSON

We said that at the rate physicists were collecting data with the world's biggest atom smasher, the Large Hadron Collider, it was "all but a mathematical certainty" that they would either find the long-sought Higgs boson or rule out its existence. It appears that physicists have bagged their prize (see p. 1524). Nature was generous. Math works.

FASTER-THAN-LIGHT NEUTRINOS

As suggested, last year's claim that particles called neutrinos travel faster than light fell apart—but in an unexpectedly spectacular way. Physicists had reported that neutrinos were making the 730-kilometer trip from CERN in Switzerland to the OPERA particle detector in Italy 60 nanoseconds faster than they should at light speed. This February, however, they found that the time discrepancy had been caused by a loose cable connection. In March, two leaders of the 200-member OPERA team stepped down after a vote of no confidence.

STEM-CELL METABOLISM

Scientists made progress this year in understanding the way stem cells use energy and the molecules needed for cell function as they differentiate into various tissues. They uncovered more details about how metabolism influences the reprogramming of mature cells into embryolike ones. It's also increasingly clear that the metabolism of embryolike stem cells resembles that of cancer cells. However, there's plenty more to discover about the complicated pathways and their influence on aging, disease, and regenerative medicine. Keep watching.

GENOMIC EPIDEMIOLOGY

This year has shown that whole-genome sequencing of infectious bacteria can help scientists understand and even control disease outbreaks. Researchers used the technique to discover how *Clostridium difficile* spread went on a rampage in hospitals around the world and to track outbreaks of resistant *Staphylococcus aureus* and *Klebsiella pneumoniae* bacteria within a single hospital; in the last two cases, they think their genomic sleuthing may have saved lives.

TREATING INTELLECTUAL DISABILITY

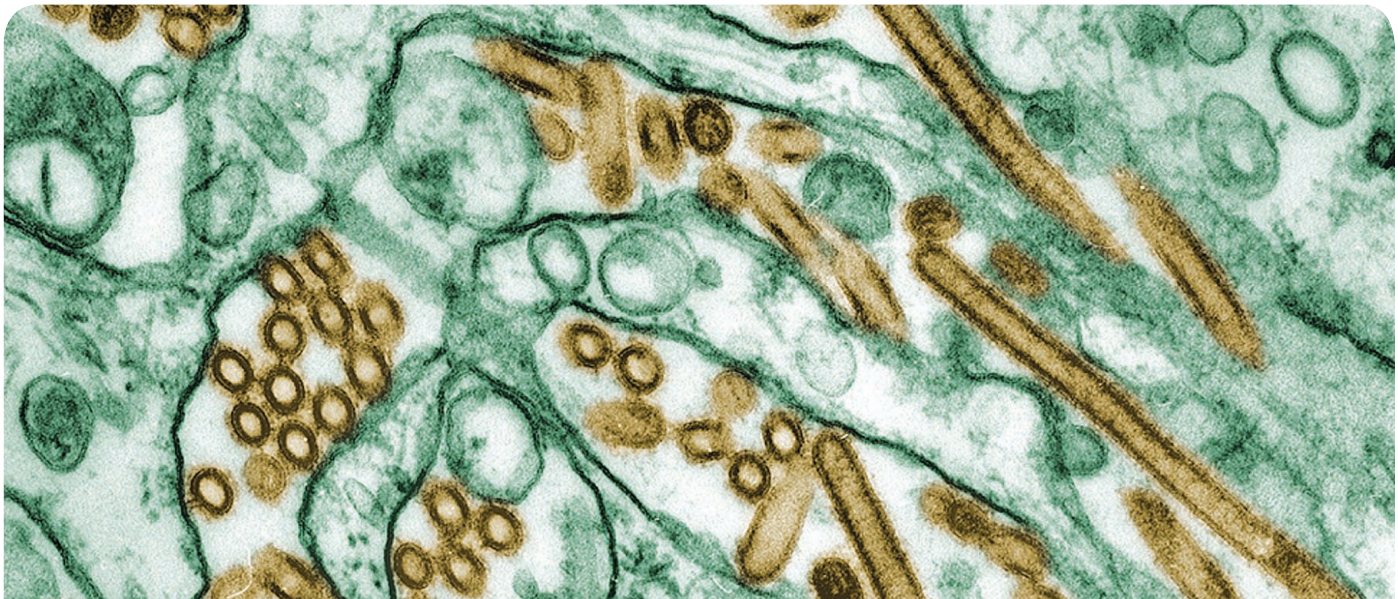
As we predicted, in 2012 animal studies turned up more potential targets for reversing cognitive and behavioral symptoms in autism and related disorders. And clinical trials continued, with researchers reporting encouraging findings with arbaclofen and bumetanide, drugs that enhance certain effects of the neurotransmitter GABA, in people with fragile X syndrome and autism, respectively. Closely watched clinical trials for fragile X with mGluR5 antagonists, which inhibit a receptor for glutamate, another neurotransmitter, should release findings in 2013.

CURIOSITY TO MARS

The Mars Science Laboratory has indeed proved worth watching. Its "7 minutes of terror" descent through the martian atmosphere ended in a safe, spot-on landing (see p. 1529) followed by—so far—months of productive scientific work by the Mini Cooper–sized Curiosity rover. Who could ask for more?

CREDIT: HAYASHI *ET AL.*, *SCIENCE*, 338 (6109)

Published by AAAS



CREDIT: CDC

A YEAR ON, THE H5N1 DEBATE REMAINS INFECTIOUS, WITH NO END IN SIGHT

Fiasco. Essential. Inevitable.

Those are just a few of the words that scientists and national security experts have used to describe the global controversy that engulfed influenza researchers this year. The drama began in late 2011 after two science teams showed how to make the H5N1 avian influenza virus—which typically kills birds—transmissible among mammals, potentially opening the door to a deadly human pandemic. Some say the storm—which is still far from over—has exposed long-standing flaws in efforts to prevent dangerous agents from escaping from unsafe laboratories or falling into the hands of terrorists, and highlighted the need for tighter oversight of "dual-use" research that can be used for good and evil. But others fear the episode is fueling a regulatory overreaction that could harm international collaboration and put an end to U.S. funding for potentially valuable science.

There's one thing that all sides appear to agree on: Nobody wants to repeat the highly publicized meltdown that sowed confusion and contention among scientists, government officials, the media, and the public. "In many ways, it's been a debacle," Anthony Fauci, head of the U.S. National Institute of Allergy and Infectious Diseases, told *Science* earlier this year.

Fauci should know. His agency funded the two controversial studies, which raised dual-use concerns after the results were submitted to *Nature* and *Science*. As word leaked out, researchers helped fan the flames when an author of one the studies—virologist Ron Fouchier of Erasmus MC in Rotterdam—told reporters from *Science* and other outlets that his team had engineered a virus that might kill millions. Such suggestions ultimately helped persuade the U.S. National Science Advisory Board for Biosecurity (NSABB), which advises the government on the security risks associated with biological research, to recommend against fully publishing the studies.

That recommendation did little to quell the debate, however, with some scientists calling it misguided while others argued that it didn't go far enough. ***The New York Times*** even called on the government to destroy the "doomsday" virus and halt funding for similar research. To help ease fears, in January influenza researchers announced a voluntary, temporary moratorium on H5N1 experiments that might make the virus more dangerous to humans. And some asked NSABB to reconsider its recommendation. In March, it did—and a majority of the members changed their minds, in part because they learned that Fouchier's virus was less lethal than originally believed. Some were also encouraged by the release of a new U.S. policy designed to help funders and scientists spot problematic dual-use studies before they begin—potentially heading off future conflicts. With NSABB's blessing in hand, *Science* and *Nature* finally published the studies.

The end of story, however, isn't settled. The voluntary moratorium on H5N1 research—which was originally planned to last just 60 days—is still in place with no end in sight. A long-promised follow-up to the March dual-use policy, designed to help U.S. university officials implement the rules, has yet to appear. And this month, U.S. officials introduced a new plot line, unveiling draft guidelines that would bar government funding for H5N1 studies that would enable the virus to gain functions, such as the ability to easily infect humans, which might not naturally evolve. The rules could also require such "gain-of-function" studies to be kept secret.

Not surprisingly, that draft is getting a mixed reception from researchers, with some worrying that it will end U.S. funding for a whole subset of possibly useful studies. Meanwhile, even supporters of such controls say they'll have only a limited effect if other nations don't adopt similar rules. "This is a global issue—lots of laboratories can do this type of research, and the U.S. can't be effective acting alone," says microbiologist and biosecurity expert Ronald Atlas of the University of Louisville in Kentucky.

The end result: More than a year after the H5N1 controversy erupted, there is still no clear international consensus on which kinds of studies are worth the risk, or how potentially dangerous results should be reviewed or safely communicated to the public and public health experts. Until the confusion clears, experts warn, more messy public battles over finding the right balance between science and security are probably, well, inevitable.

–DAVID MALAKOFF

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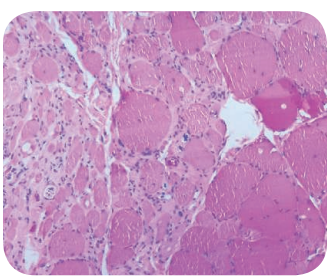
THE YEAR IN NEWS

Here are some of the people, places, and events that helped shape the world of science in 2012

JANUARY

Baikonur Cosmodrome, Kazakhstan: Russia's Fobos-Grunt sampling mission fails to escape Earth's orbit on way to martian moon.

Washington, D.C.: Obama administration proposes dismantling Commerce Department and scattering its scientific components across the federal government.



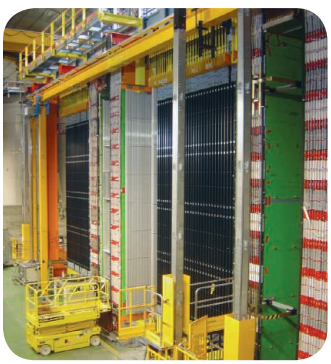
New Delhi: India celebrates going 1 year without a case of polio; no new cases reported in 2012.

London and Washington, D.C.: Flu researchers announce a 60-day moratorium on risky H5N1 studies in a letter to *Nature* and *Science*. The moratorium remains in effect.

FEBRUARY

Antarctica: A team of Russian scientists finishes drilling 3770 meters through the Antarctic ice to reach the surface of buried Lake Vostok.

Bethesda, Maryland: The National Institutes of Health decides to revise the original design for the National Children's Study after spending nearly $800 million to plan the monitoring of 100,000 children.

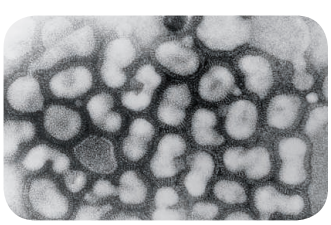


Gran Sasso, Italy: Faulty wiring is found to have caused the anomalous faster-than-light neutrino results announced in September 2011 by scientists in Italy.

MARCH

Mariana Trench, Pacific Ocean: Filmmaker James Cameron's one-man sub dives to the bottom of Challenger Deep, the first solo visit to Earth's deepest domain.

Washington, D.C.: U.S. Department of Energy shelves $1.5 billion Long Baseline Neutrino Experiment, asks Fermilab for cheaper alternatives.



Bethesda: Reversing an earlier decision, the National Science Advisory Board for Biosecurity approves publication of two controversial papers on H5N1's ability to trigger a pandemic.

Washington, D.C.: U.S. government announces rules designed to reduce risk of harmful consequences from experiments using 15 pathogens and toxins.

APRIL

Paris: Contact is lost with Europe's 10-year-old Earth-observing satellite Envisat.

Washington, D.C.: Jim Yong Kim elected as first scientist/physician to lead the World Bank.

MAY

Amsterdam: Australia and South Africa chosen as co-hosts for the $2 billion Square Kilometre Array.

Mongstad, Norway: Work begins on $1 billion carbon capture and storage facility, the largest such test site in the world.

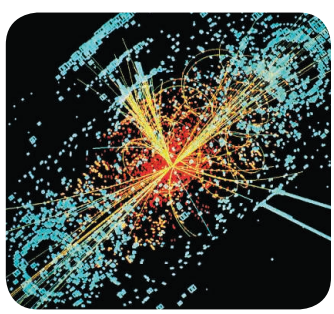
Boston: Autopsies of four military veterans find signs of the same neurodegenerative disease found previously in U.S. football players.

JUNE

Galapagos Islands: Centenarian Lonesome George, the last giant tortoise in the Galapagos Islands, succumbs to apparent heart failure.

Rio de Janeiro, Brazil: Lack of major commitments dooms Rio+20 conference on sustainable development.

JULY



Meyrin, Switzerland: Physicists at CERN report they've probably found the Higgs boson, the particle that conveys mass to other fundamental particles.

London: U.K. government expects to spend more than $100 million to subsidize publication in open access journals of research it funds.

Northeastern U.S.: One species of North American bats infected with white-nose syndrome fights the disease by hibernating alone.

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Washington, D.C.: New U.S. law is expected to funnel up to $20 billion in BP civil fines from the 2010 Gulf oil spill to restoration and research.

Washington, D.C.: Two studies published in *Science* failed to find arsenic in bacterial DNA, refuting controversial work reported in 2010.

Phnom Penh: A mysterious syndrome that killed dozens of children is identified as hand, foot, and mouth disease after patients test positive for Enterovirus 71.

Tokyo: Panel finds that anesthesiologist Yoshitaka Fujii fabricated a record-setting 172 papers.

AUGUST

Bethesda: The National Heart, Lung, and Blood Institute launches massive clinical trial to test whether blocking inflammation can prevent heart disease.

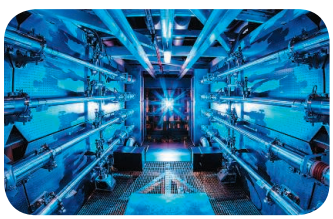
Pasadena, California: NASA's Curiosity rover lands safely on Mars and begins 2-year mission.

Indianapolis and New York: Long-awaited clinical trial results for bapineuzumab and solanezumab fail to show cognitive benefits for Alzheimer's disease patients.

Kyoto, Japan: Mathematician Shinichi Mochizuki invites colleagues to poke holes in his proof of the abc conjecture.

SEPTEMBER

Hinxton, U.K.: Results from the Encyclopedia of DNA elements (ENCODE) project identifying a high percentage of human DNA with some functionality generate praise and controversy.



Livermore, California: National Ignition Facility fails to meet its own deadline for achieving a self-sustaining fusion reaction.

Saudi Arabia and Qatar: Two cases, one fatal, of a new coronavirus related to SARS triggers worries about a wider outbreak.

Hunan province, China: In a nationwide uproar, critics say that a U.S.-funded study involving genetically modified (GM) golden rice used Chinese children as guinea pigs.

Caen, France: Study claiming that GM maize causes tumors and early death in rats generates headlines—and widespread criticism from food safety agencies.

Alaska: Shell begins exploratory oil drilling in Alaska's Chukchi Sea, the first in more than 2 decades. But technical problems cut the project short.

OCTOBER

L'Aquila, Italy: Six scientists and a government official are found guilty of manslaughter and sentenced to 6 years in prison for making reassuring statements before a deadly April 2009 earthquake.

Hyderabad, India: The U.N. Convention on Biological Diversity announces a doubling, to $10 billion a year, of aid to developing countries by 2015.

Cambridge, U.K.: First articles appear in *eLife*, a new open access journal backed by the Howard Hughes Medical Institute, the Wellcome Trust, and the Max Planck Society.

Austin: Nobelist Alfred Gilman resigns from $3 billion Cancer Prevention and Research Institute of Texas along with dozens of peer reviewers to protest agency's peer review practices.

NOVEMBER

Sacramento: California's cap-and-trade program, the broadest in the nation, began auctioning permits to businesses in an effort to regulate release of greenhouse gases.

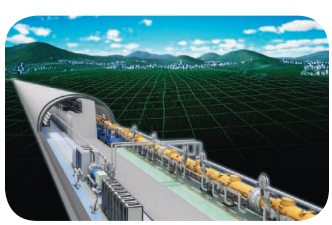
Washington, D.C.: BP to pay $2.5 billion for research and restoration efforts as part of guilty plea in criminal case from oil spill.

Brussels: The European Commission's approval to market Glybera to treat a rare disease called lipoprotein lipase deficiency makes it the first gene therapy drug in the Western world.

Tilburg, the Netherlands: Investigators say social psychologist Diederik Stapel has committed fraud in at least 55 of his 137 papers.

Cape Town: Disappointing results from first phase III trial of a malaria vaccine dim prospects for RTS,S vaccine.

DECEMBER



Tokyo: Scientists complete technical design for proposed International Linear Collider, a $10 billion facility that Japan hopes to host.

Brussels: E.U. officials endorse a unified patent system that they hope will take effect in 25 countries in 2014.

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