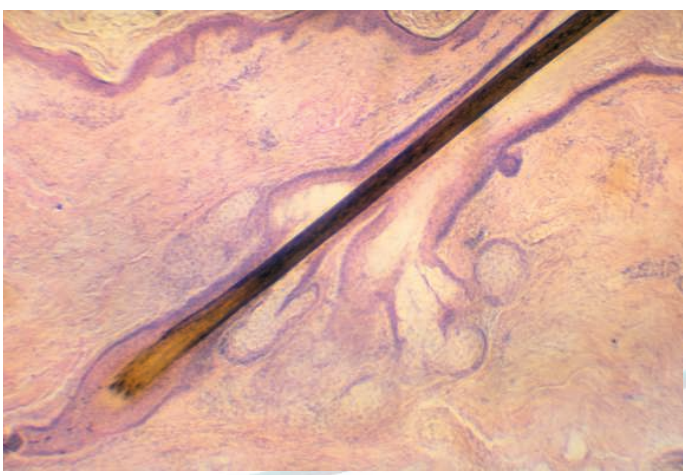
Breakthrough of the Year

Reprogramming Cells

By inserting genes that turn back a cell's developmental clock, researchers are gaining insights into disease and the biology of how a cell decides its fate

THIS YEAR, SCIENTISTS ACHIEVED A LONG-SOUGHT FEAT OF CELLULAR alchemy. They took skin cells from patients suffering from a variety of diseases and reprogrammed them into stem cells. The transformed cells grow and divide in the laboratory, giving researchers new tools to study the cellular processes that underlie the patients' diseases. The achievement could also be an important step on a long path to treating diseases with a patient's own cells.

The feat rests on a genetic trick, first developed in mice and described 2 years ago, in which scientists wipe out a cell's developmental "memory," causing it to return to its pristine embryonic state and then regrow into something else. In 2008, researchers achieved another milestone in cell reprogramming. In an elegant study in live mice, they prompted cells to make the leap directly from one mature cell into another—flouting the usual rule that development of cells is a one-way street. These and other advances in tweaking cells to assume new identities add up to make the now flourishing field of cellular reprogramming *Science*'s Breakthrough of the Year.



This year's breakthroughs have done much to wipe out memories of a major scandal that erupted 3 years ago, after scientists in South Korea fraudulently claimed to have used somatic cell nuclear transfer—the technique used to clone Dolly the sheep—to generate stem cells from patients suffering from type 1 diabetes, spinal cord injury, and a congenital immune disease. The debacle dealt the field a huge setback; patient-specific stem cells seemed like a distant prospect.

Breakthrough Online

For an expanded version of this section, with references, links, and multimedia, see www.sciencemag.org/btoy2008.

The new developments build on two previous breakthroughs. Ten years ago last month, scientists in Wisconsin announced that they had cultured human embryonic stem (hES) cells—cells with the potential to form any cell type in the body. That power, known as pluripotency, opened up a world of possibilities in developmental biology and medical research, but it came with baggage: Because isolating the cells typically destroys the embryo, the research sparked fierce debates over bioethics. In many countries, including the United States, political decisions limited the work scientists could do with hES cells.

In 2006, Japanese researchers reported that they had found a possible way around the practical and ethical questions surrounding hES cells. By introducing just four genes into mouse tail cells growing in a lab dish, they could produce cells that looked and acted very much like ES cells. They called these cells induced pluripotent stem (iPS) cells. Last year, in a development recognized as the first runner-up in *Science*'s 2007 Breakthrough of the Year issue, the same team and two others in the United States extended the reprogramming technique to human cells. That result opened the floodgates to new research.

Cells, made to order

For nearly a decade, stem cell biologists have sought a way to make long-lived cell lines from patients suffering from hard-to-study diseases. (Most adult cells do not survive culture conditions in the lab, so taking cells of interest directly from patients doesn't work.) This year, two groups achieved that goal. One team derived iPS cell lines from the skin cells of an 82-year-old woman suffering from amyotrophic lateral sclerosis (Lou Gehrig's disease), a degenerative disease that attacks the motor neurons, causing gradual paralysis. The scientists then directed the cells to form neurons and glia, the cells that are most affected by the disease (photos, p. 1767).

Just a week later, another group reported making patient-specific iPS cell lines for 10 different diseases (see table), among them muscular dystrophy, type 1 diabetes, and Down syndrome. Many of these diseases are difficult or impossible to study in animal models; the reprogrammed cells give scientists a new tool for studying the molecular underpinnings of disease. They may also prove useful in screens for potential drugs. Eventually, such techniques might allow scientists to correct genetic defects in the lab dish and then treat patients with their own repaired cells.

Another paper published this year suggests that the reprogramming exit ramp does not have to lead back to an embryonic state but can take a cell directly to a new mature fate. American researchers, working in mice, reprogrammed mature pancreas cells called exocrine cells into beta cells, the cells in the pancreas that produce insulin and are destroyed by type 1 diabetes. The team injected a cocktail of three viruses into the pancreases of adult mice. The viruses primarily infected the exocrine cells, and each one carried a different gene known to play a role in beta cell development. Within days, the treated mice formed insulin-producing cells that looked and acted like bona fide beta cells.

The results are surprising because in living creatures, specialized cells almost never change course, changing, say, from a muscle cell into a lung cell. Such direct reprogramming, however, might be simpler and safer than using pluripotent cells to treat some diseases. The technique might also enable scientists to speed up the lab production of desired cell types, using defined factors to change one type of cultured cell directly into another.

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Published by AAAS

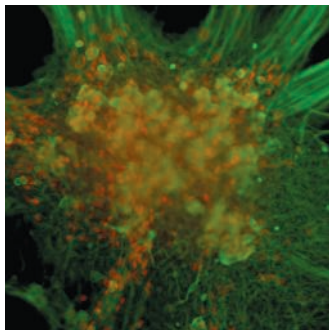
Wanted: more breakthroughs

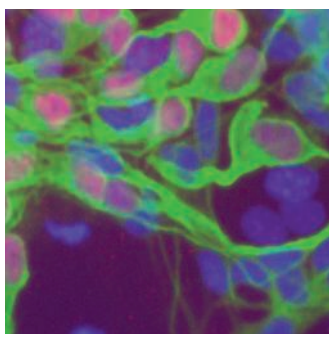
Although researchers made impressive progress in 2008, several more breakthroughs are needed before cellular reprogramming yields its first cure for disease. For reprogramming to be safe enough to use in cell therapy, researchers must find an efficient, reliable way to trigger it. They also want to understand exactly how the process works. Although dozens of labs have used the technique, what is happening inside the reprogrammed cell remains a mystery, and a combination of chance events seems to determine which rare cells end up being reprogrammed. A leading theory is that some of the reprogramming factors first help to loosen up the DNA in a cell's nucleus, making it easier to reactivate turned-off genes. Then the other factors help to set off a cascade of protein signals that give a cell its new identity (see the Review by Gurdon and Melton on p. 1811).

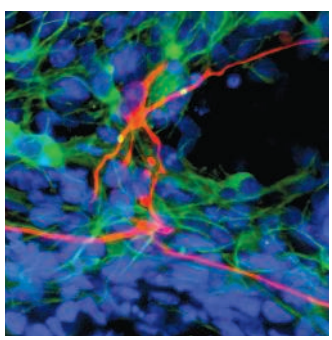
The original reprogramming recipe relies on viruses to insert the reprogramming genes into the infected cell's genome, altering the DNA permanently. Scientists are wary of that approach for a couple of reasons. First, the inserted DNA could interrupt existing genes—for example, those that guard against cancer, leaving the cells likely to form tumors. And although the inserted genes seem to turn off after reprogramming is finished, allowing the cell's own genes to take over, scientists worry that the inserted genes could be reactivated or could have other subtle effects on the cell.

For that reason, labs around the world are working on other ways to trigger reprogramming. This year, they made rapid progress. Several groups found that they could substitute chemicals for some of the inserted genes. Another found that adenoviruses could also do the trick, at least in mouse cells. Adenoviruses, which cause the common cold, do not insert themselves into the genome. The viruses express their genes long enough to reprogram the cells, but as the cells divide, the viruses are diluted down to undetectable levels, leaving reprogrammed cells with their original genomes unchanged. Researchers in Japan showed that rings of DNA called plasmids could also carry the required genes into the cell. The alternatives are much less efficient than the original recipe, however, and most have not yet worked in human cells, which are harder to reprogram than mouse cells.

To be useful, reprogramming also needs to become much more efficient. Most experiments have managed to reprogram fewer than one in 10,000 cells. In what seems to be a lucky break for the field, however, two groups showed this year that the skin cells called keratinocytes are particularly easy to reprogram. Researchers can reprogram roughly 1% of the keratinocytes they treat, and the process takes only 10 days instead of the several weeks that other cells require. Hair follicles (photo, p. 1766) are a rich source of keratinocytes, and researchers in California and Spain showed that they could efficiently derive personalized cell lines from cells taken from a single human hair plucked from the scalp—an even easier source of cells than cutting out a piece of skin.

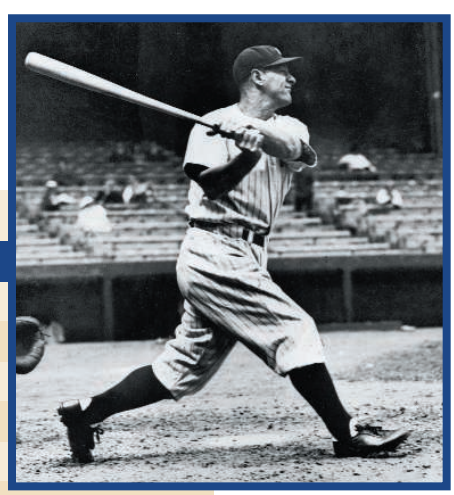






Finally, reprogramming needs better quality control. This year, an American group took a major step in that direction by making cells in which the reprogramming genes could be turned on by the addition of the antibiotic doxycycline. They then used the reprogrammed cells to generate "second generation" iPS cells that are genetically identical—each contains the same viral inserts. These cells will allow scientists to study the process of reprogramming for the first time under standardized conditions and should help to reveal the biochemical processes that enable an adult cell to take an exit ramp from its one-way path of development.

A thorough understanding of reprogramming is not enough, however. Ten years after the discovery of human ES cells, scientists are still working on standardizing procedures for coaxing pluripotent cells to become mature tissue. It's a critical problem: Stray pluripotent cells used in therapies could trigger dangerous tumors. And even though scientists can easily prompt pluripotent cells to become beating heart cells in a lab dish, no one has yet perfected a way to get such cells to integrate into the body's tissues to replace or repair their diseased counterparts. But researchers are moving faster down the highway of discovery than many had expected or dared to hope. **–GRETCHEN VOGEL**



Diseases With Patient-Specific iPS Cell Lines

Amyotrophic Lateral Sclerosis (Lou Gehrig's disease)
ADA-SCID
Gaucher disease type III
Duchenne muscular dystrophy
Becker muscular dystrophy
Down syndrome
Parkinson's disease
Juvenile diabetes mellitus
Shwachman-Bodian-Diamond syndrome
Huntington disease
Lesch-Nyhan syndrome (carrier)

CREDITS (TOP TO BOTTOM): DIMOS *ET AL.* (GROUP OF THREE); C. BICKEL/*SCIENCE*; JERRY COOKE/SPORTS ILLUSTRATED/GETTY IMAGES

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Seeing Exoplanets

SEEING MIGHT BE BELIEVING, BUT FOR SCIENTISTS BELIEF RARELY depends on seeing. The right squiggles coming out of an instrument are usually enough to confirm that they have caught their quarry, however infinitesimal, insubstantial, or bizarre. Astronomers searching for planets circling other stars, however, may have been getting just a tad impatient with their progress toward their ultimate goal: recognizing a habitable, even an inhabited, planet beyond our own solar system. For that, they'll need to see their target. But all exoplanet detections had been of the squiggly variety.

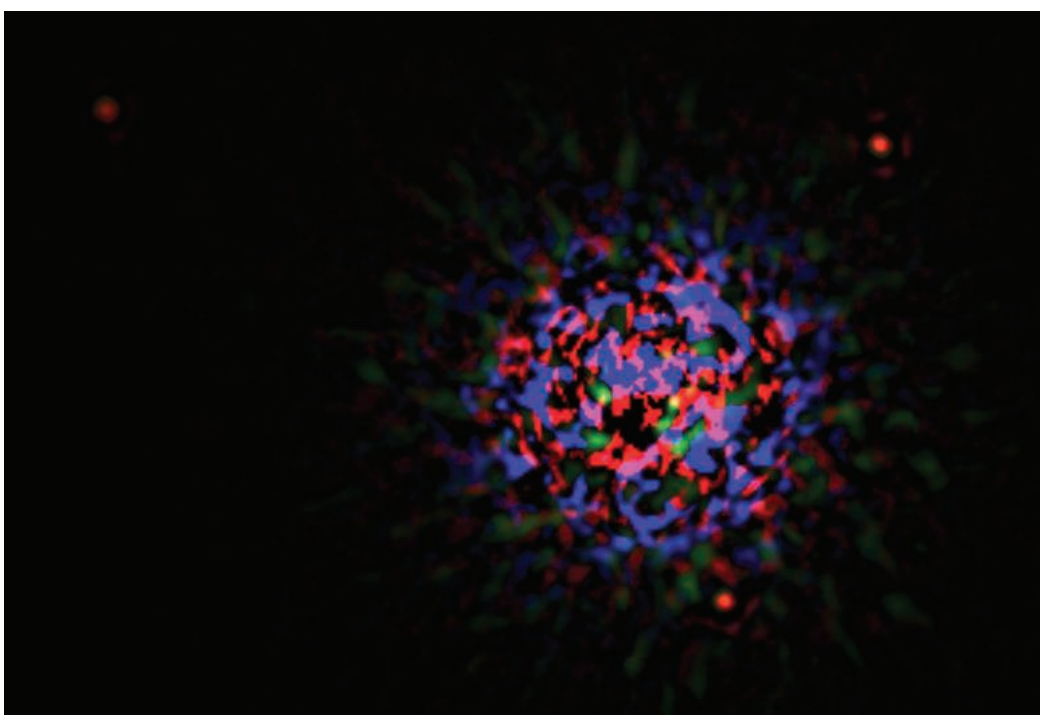
Now, astronomers have seen exoplanets for the first time—a half-dozen candidates have been announced in the past few months. To some, the new observations may simply have replaced squiggles with dots. But the faint pinpricks of light from far-off worlds have captured the public's imagination and will give astronomers new clues to what those distant planets are made of and how they were formed. Key to these direct detections have been big telescopes and the latest technology to pick out a vanishingly faint planet from its host star's overwhelming glare.

Previous, indirect detections of more than 300 exoplanets had provided breakthroughs of their own. For 13 years, astronomers have been finding exoplanets using ground-based telescopes to monitor the subtle wobble a planet gravitationally induces in its star. This workhorse radial-velocity technique is especially useful for finding massive "hot Jupiters" searingly close to their star. No light is seen from the planet, however. Another method, called microlensing—in which a planet's gravity momentarily brightens a background star by bending its passing light—is particularly good for detecting planets more distant from their stars and in principle could spot lightweights with masses down to that of Earth. But microlensing is a one-off event; once the fleeting alignment with the star is over, no sign of the planet will ever be seen again.

If a planet happens to orbit across the face of its star as viewed from Earth, however, the repeated tiny dimming of the total light of the star plus the planet can reveal the presence of the planet. At the same time, starlight passing through the outer planetary atmosphere can reveal clues about composition. Already, water, methane, and—just last month—carbon dioxide have been detected in transiting exoplanets. Those compounds, plus molecular oxygen, are the key markers of an inhabited planet. But only hot Jupiters—unlikely abodes of life—are liable to transit their stars and be detected using current technology.

That leaves direct detection. The chore is simple enough: Separate the light from a planet from the light of its nearby star. The hitch is that the star is millions of times brighter than any planet, and Earth's turbulent atmosphere churns the light of star and planet together. To solve the latter problem, astronomers can move their telescopes above the atmosphere to Earth orbit. Or they can correct the incoming telescopic image using so-called adaptive optics, in which precisely controlled warping of a mirror many times a second straightens out distorted light. Coping with the vast difference in brightness between planet and star requires a coronagraph in the telescope to physically block out the star or "virtual coronagraph" software to remove starlight from the image. It also helps to search for very young and therefore still hot planets at infrared wavelengths, in which case the star-planet contrast will be much smaller.

With more than 5 years of observations using the latest technology, astronomers are suddenly busting down the doors to announce candidates for directly detected exoplanets. Published last month, the most secure—and surely the most stunning—are three objects orbiting a star called HR 8799, 128 light-years from Earth. Judged to have five to 10 times the mass of Jupiter, they orbit at least 24 to 68 times farther from their star than Earth orbits from the sun. That makes them among the most massive exoplanets discovered and by far the most distant from their star. New detection techniques typically start by finding such oddballs. These are giving theorists fits; they don't see how planets could have formed that far out.



Other direct detections came one per star. Last month, another group also reported detecting a planet of roughly three Jupiter masses orbiting the star Fomalhaut, one of the brightest stars in the sky. A third group announced a single candidate exoplanet last September but must await confirmation that it is orbiting the star rather than just passing through. And a fourth group announced late last month what would be—at eight times the sun-Earth distance from its star—the imaged planet closest to its star.

Astronomers are already starting to analyze the light of some of the new finds for clues to their physical and chemical nature. That should keep planetary formation theorists busy. The chance to directly study potentially inhabited planets is further off. Imaging Earth-like exoplanets in Earth-like orbits is probably still decades and certainly billions of dollars away.

CREDIT: CHRISTIAN MAROIS/NRC HERZBERG INSTITUTE OF ASTROPHYSICS

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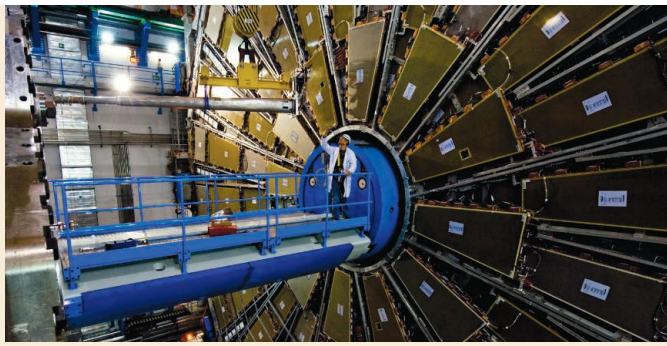
PHENOMENON OF THE YEAR:
EUROPEAN BIG SCIENCE



IN SEPTEMBER, WHEN THE FIRST BEAMS circulated through the Large Hadron Collider (LHC), Europe's giant particle accelerator near Geneva, Switzerland, media outlets were quick to name a winner. "Europe leaps ahead on physics frontier" ran a story on MSNBC.com, and a blog trumpeted "LHC a sure sign that Europe is the center of physics." The electrical fault that put the LHC out of action just days after its inauguration didn't change the overall picture.

That success was bittersweet for U.S. particle physicists, whose own machine, the Superconducting Super Collider, was canceled in 1993. By most objective measures, U.S. research still leads the world, but in their ability to pool resources in the pursuit of "big science," European nations are showing increasing ambition and success.

CERN is the model of a pan-European laboratory. Formed in 1953 to help rebuild postwar European science and encourage international cooperation, the facility became a guiding light for European particle physics and spurred other fields to follow suit. The next few decades saw the creation of the Institut Laue-Langevin neutron source, the European Molecular Biology Laboratory, the European Space Agency, the European Southern Observatory, the Joint European Torus, and the European Synchrotron Radiation Facility (ESRF). But after the agreement to build ESRF in 1984, the enthusiasm for joint European ventures faded.

That situation has changed this decade, however. First off, the European Union (E.U.) decided that it wanted to host ITER, the worldwide reactor project that aims to prove nuclear fusion as a viable power source. During much of 2004 and 2005, the E.U. was locked in a staring match with Japan over whose site should take the honor. Determined shuttle diplomacy and a face-saving formula put together by E.U. officials finally paid off, and ITER is now under construction at Cadarache in southern France. Such is Europe's confidence in the project that when Congress zeroed out the U.S. contribution to ITER from its 2008 budget, managers in Cadarache barely broke step.

The E.U. didn't stop there. In 2002, it created the European Strategy Forum on Research Infrastructures (ESFRI), which set about drawing up a list of projects worthy of E.U. support. The ESFRI Roadmap, published in October 2006, lists 35 projects, which include a database on population aging and a neutrino observatory on the Mediterranean seabed. The E.U. didn't have money to build the projects. But it did have money to support design studies and asked all the Roadmap's nominated projects to apply—and nearly all of them did. The aim of the cash is to "get the projects to a point where a political decision can be made" on whether to build, says materials scientist John Wood of Imperial College London, who was chair of ESFRI at the time.

The ESFRI Roadmap and E.U. infrastructure funding have given a number of projects a major push toward becoming reality. This year, the European XFEL, an x-ray light source, and the Facility for Antiproton and Ion Research, both in Germany, have enlisted international partners for construction, and both expect to sign conventions by early next year. The European Spallation Source, proposed in the early 1990s, now has three sites vying to host it, and a decision—in part brokered by ESFRI—is expected this month. A final design for the *Aurora Borealis*, a groundbreaking polar research ship, was also released this month. And this autumn, groups of European astronomers and astroparticle physicists have published their own road maps, listing potentially world-leading instruments such as the European Extremely Large Telescope and the Cherenkov Telescope Array. "I'm absolutely staggered at how influential [the Roadmap] has been," says Wood.

As this issue went to press, ESFRI was about to release a revised road map, updating its original effort and including some fields that were omitted before. European scientists are eager to see where it leads.

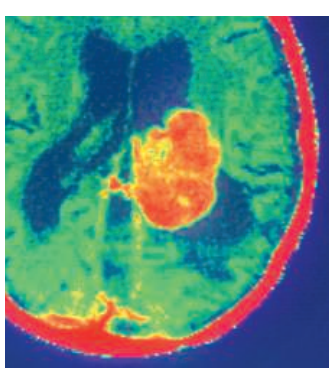
–DANIEL CLERY

Cancer Genes

RESEARCHERS THIS YEAR TURNED A SEARCHLIGHT ON THE ERRANT DNA that leads tumor cells to grow out of control. These studies are revealing the entire genetic landscape of specific human cancers, providing new avenues for diagnosis and treatment.

Tumor cells are typically riddled with genetic mistakes that disrupt key cell pathways, removing the brakes on cell division. Thanks to the completion of the human genome and cheaper sequencing, researchers can now systematically survey many genes in cancer cells for changes that earlier methods missed. Results from the first of these so-called cancer genome projects came out 2 years ago, and the output ramped up in 2008.

Leading the list were reports on pancreatic cancer and glioblastoma, the deadliest cancers. By sequencing hundreds or thousands of genes, researchers fingered dozens of mutations, both known and new. For example, a new cancer gene called *IDH1* appeared in a sizable 12% of samples from glioma brain tumors. A separate glioma study revealed hints as to why some patients' tumors develop drug resistance. Other studies winnowed out abnormal DNA in lung adenocarcinoma tumors and acute myeloid leukemia.



The expanding catalog of cancer genes reveals an exciting but sobering complexity, suggesting that treatments that target biological pathways are a better bet than "silver bullet" drugs aimed at a single gene. Genome projects for at least 10 more cancers are in the works.

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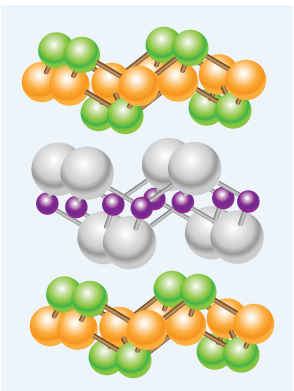
New High-Temperature Superconductors

4

PHYSICISTS DISCOVERED A SECOND FAMILY OF HIGH-TEMPERATURE superconductors, materials that carry electricity without resistance at temperatures inexplicably far above absolute zero. The advance deepened the biggest mystery in condensed-matter physics.

In February, a group in Japan reported the first material, fluorine-doped lanthanum iron arsenic oxide ($LaFeAsO_{(1-x)}F_x$), which is superconducting up to a "critical temperature" of 26 kelvin. Within 3 months, four groups in China had replaced the lanthanum with elements such as praseodymium and samarium and driven the temperature for resistance-free flow up to 55 kelvin. Others have since found compounds with different crystal structures and have bumped the critical temperature up to 56 kelvin.

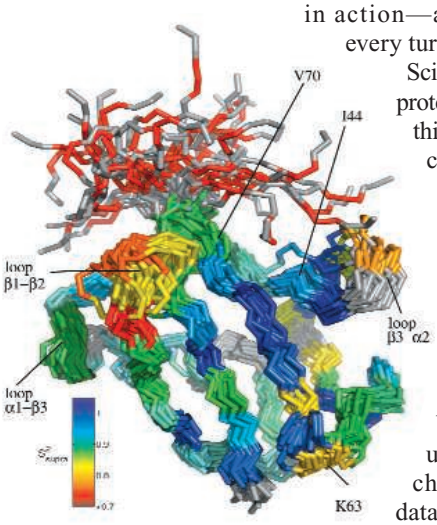


For a critical temperature, that's not so hot. The record is 138 kelvin for members of the other family of high-temperature superconductors, the copper-and-oxygen, or "cuprate," compounds discovered in 1986. Still, the iron-based materials have created a stir, in part because they might help solve the enduring mystery of how the cuprates work. The $64,000 question is whether the two families work the same way. So far, evidence points in both directions.

Watching Proteins at Work

5

AFTER STUDYING PROTEINS FOR MORE THAN A CENTURY, BIOCHEMISTS pushed the boundaries of watching the molecules in action—and received surprises at every turn.



Scientists have long debated how proteins bind to their targets. Most think the shape of a target molecule forces a protein to wiggle into a complementary profile. But it's also possible that proteins in solution wiggle among many slightly different conformations until one finds its target. Computational biologists in Germany and the United States offered bold new support for that upstart idea when they crunched extensive experimental data and showed how one long-studied protein seems to dance among dozens of conformations. In another surprise, a U.S. team tracked individual proteins and found that a single random molecular event can switch a bacterial cell from one metabolic state to another.

Zooming out to the large scale, proteomics researchers in Germany simultaneously monitored the abundance of up to 6000 proteins in yeast cells and quantified how the expression of individual proteins differed between two different cell types. Their technique could lead to new insights into development and disease. Finally, proteomics researchers in Sweden revealed that different tissues in the body likely get their unique characteristics by controlling not which proteins are expressed but how much of each gets made.

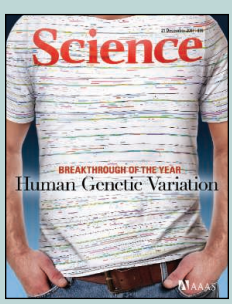
Water to Burn

6

RENEWABLE ENERGY SOURCES, SUCH AS WIND AND SOLAR POWER, have plenty going for them. They're abundant and carbon-free, and their prices are dropping. But they're part-timers. Even when the sun is shining and the wind is blowing, there is no good way to store excess electricity on an industrial scale. Researchers in the United States reported this year that they've developed a new catalyst that could begin to change that picture.

The catalyst, a mixture of cobalt and phosphorus, uses electricity to split water into hydrogen and oxygen. Hydrogen can then be burned or fed to fuel cells that recombine it with oxygen to produce electricity. Researchers have known for decades that precious metals such as platinum will split water. But platinum's rarity and high cost make it impractical for large-scale use. The cobalt version isn't all the way there yet, either—it still works too slowly for industrial use—but just getting a cheap and abundant metal to do the job is a key step. Now, if researchers can speed it up, on-again-off-again renewables could have a future as fuels that can be used anywhere at any time.

SCORECARD



Rating last year's Areas to Watch

(For this year's predictions, see page 1773.)

A smashing start

The Large Hadron Collider came on smoothly in just a few hours, in keeping with *Science*'s observation that the European particle physics lab, CERN, has a knack for getting new machines running quickly. Nine days later, the enormous particle smasher wrecked so bad that it will be down until summer, fulfilling *Science*'s warning that a mishap could take the machine out of action for months.

Micromanagers

MicroRNA work surged in 2008, as efforts to use the molecules to understand and modify disease edged forward. The first successful microRNA manipulation in primates lowered cholesterol in African green monkeys, and the molecules slowed virus replication in ailing mice. Companies are rushing to

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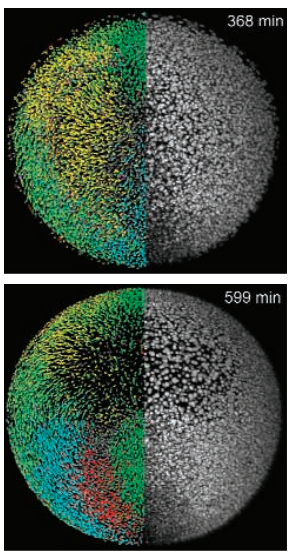
Published by AAAS

The Video Embryo

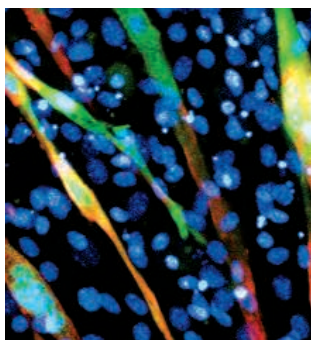
THE DANCE OF CELLS AS A FERTILIZED EGG BECOMES AN ORGANISM IS at the center of developmental biology. But most microscopes allow only partial glimpses of the process. This year, scientists observed the ballet in unprecedented detail, recording and analyzing movies that traced the movements of the roughly 16,000 cells that make up the zebrafish embryo by the end of its first day of development.

Researchers in Germany made the movies with a new microscope they designed. It uses a laser beam to scan through a living specimen, capturing real-time images and avoiding the bleaching and light damage that have usually limited such videos to just a few hours. The researchers then used massive computing power to analyze and visualize the recorded movements. They also ran the movies backward to trace the origin of cells that form specific tissues, such as the retina. A movie of a well-known mutant strain of fish revealed for the first time exactly what goes wrong as the embryo develops.



The zebrafish movies are freely available on the Internet, and the developers say they hope the Web site will develop into a full-blown virtual embryo—a sort of developmental biology YouTube with contributions from labs around the world.

Fat of a Different Color



THIS YEAR, RESEARCHERS FINALLY UNCOVERED the mysterious roots of so-called brown fat. Hardly blubber, the energy-using tissue turns out to be one step away from muscle.

Anatomists first noted the distinction between our two fat types more than 400 years ago. White fat is the energy-caching padding that vexes doctors and dieters. If white fat is a quilt, brown fat is an electric blanket. Thanks to plentiful mitochondria, it burns fat molecules to generate heat that warms the body.

Scientists long assumed that both fat varieties developed from the same kind of progenitor cell. Then a team led by U.S. scientists discovered that they could morph brown fat into muscle and vice versa. The researchers knew that the gene *PRDM16* spurs specialization of brown fat. So when they turned down *PRDM16* in brown-fat precursor cells, they expected white fat cells to result.

Instead, the cells stretched out into tube-shaped muscle cells that could even twitch. Reflecting their altered identity, the cells switched off a raft of genes characteristic of brown fat and switched on genes typical of muscle. Coercing cells that had already begun differentiating into muscle to fashion *PRDM16* triggered the reverse transformation, yielding brown fat. Using a technique called lineage tracing, the researchers identified the descendants of the muscle cell clan in mice. They included muscle and brown fat cells but not white fat cells.

The discoveries could mark a step toward antiobesity treatments that melt away bad white fat, either by firing up existing fat-burning brown cells in the body or by transplanting new ones.

develop microRNA-based therapies—but coaxing microRNAs to combat disease is slow going, and safety concerns remain.

Cell to order

Despite high hopes, humanmade microbes are not yet in reach. Researchers did customize cell-signaling circuits in live cells and are exploring new ways of building genomes from scratch. One research group synthesized an entire bacterial genome but has yet to incorporate it into a cell. And designing microbes to make biofuels remains a pipe dream.

Paleogenomics

It was a scramble to get enough sequence done, but a very rough genome of the Neandertal is almost in hand. Along the way, the sequencing team has obtained the complete sequence of Neandertal mitochondrial DNA, finding a few key differences between us and them. Two groups unraveled the mitochondrial genome of extinct cave bears. And sequencing 70% of the woolly mammoth genome prompted speculation about cloning this beast to bring it back to life.

Multiferroics

Multiple electronic, magnetic, and structural behaviors give these materials the potential to carry out both logic and memory functions, now handled separately by semiconductors and metals. Researchers reported steady improvements in performance. Novel multiferroics can change their stripes near room temperature and in low magnetic fields, both important developments for real-world applications. But progress remains muted in turning these materials into complex circuitry.

Megamicrobes

Metagenomics is in full swing, with several key surveys of microbial and viral diversity completed this year in environments as varied as microbial mats, subsurface ecosystems, and the mammalian gut. In addition, DNA sequences from nearly 200 genomes of bacteria associated with humans are finished, and hundreds more are in the pipeline. In October, groups from around the world formed the International Human Microbiome Consortium to study the role the human microbiome plays in health and disease.

New light on neural circuits

This year's Nobel Prize in chemistry honored scientists who turned a luminescent protein from jellyfish into a powerful tool for imaging cells. Building on that work, neuroscientists can now tag neurons with myriad colors to study their connections. And light-sensitive proteins from algae have made it possible to control neural firing with laser pulses. Such methods have great potential for unraveling the function of neural circuits. This year saw steady progress, and the bigger breakthroughs we predicted can't be far off.

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BREAKDOWN OF THE YEAR: **FINANCIAL MELTDOWN**

THE SALES SLUMP THAT BECAME A CREDIT crunch and then a global financial crisis this fall will leave a big smudge in the economics record for 2008. Panic hit the stock market in October, engulfed investment companies, and even threatened to pull down the giant General Motors Co. The full scope of the breakdown isn't clear yet.

Luckily, scientific research did not take a direct hit, but scientists are feeling the consequences like everyone else, and research budgets could get caught in the fallout next year. In the United States, the drop in stock values deflated private endowments—some by 15% to 25% over a few months. Retirement accounts withered. Meanwhile, programs funded by endowments began to cut back (*Science*, 7 November, p. 841). The Smithsonian Institution acknowledged in its first public board meeting in November that its endowment was down 21% over a 4-month period and that it would need to tighten its $1 billion budget. Like many, it has delayed announcing hard cuts.

Companies that need capital to advance new technologies will be pinched, and some will go under. New energy projects seem likely to be delayed. In the biomedical area, a recent report by the Biotechnology Industry Organization in Washington, D.C., noted that 38% of its smaller public companies are on track to burn through their cash reserves in a year.

State-funded hospitals and universities are cutting employees and putting off new facilities as state revenues decline. The California state university system, responding to the governor's budget, has threatened to cut student enrollment by 10,000, or 2.1%, next year. Private schools are being affected, too. President Drew Faust announced a 22% drop in Harvard's endowment, along with potential delays in the new Allston campus and research area. The Massachusetts Institute of Technology plans to reduce spending by 10% to 15%, said MIT President Susan Hockfield. Federal spending on research has not changed, but President-elect Barack Obama and Congress have not yet tackled the 2009 budget.

In this murky landscape, there is at least one fixed point: the official starting date of the crisis. According to Federal Reserve Board Chairman Ben Bernanke, the cascade began in August 2007 with a general price collapse in U.S. real estate. Houses went unsold; owners walked away from mortgages; companies holding the mortgages began to default on obligations; a huge firm that insured against such defaults, AIG, ran out of funds and was saved by the government. Five high-flying U.S. investment banks with mortgage-related investments quit the investment field—four to become ordinary commercial banks and one to disappear (Lehman Brothers). Governments in North America, Europe, and Asia are now pumping hundreds of billions of dollars into private companies in an attempt to restore the economy's pulse.

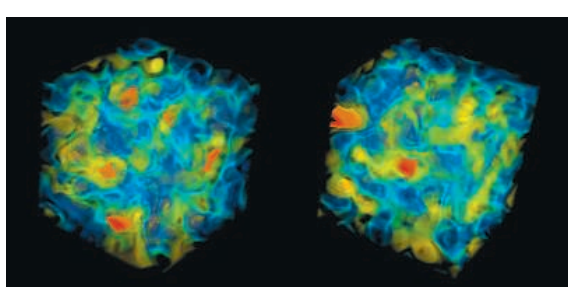
What caused the crash? Bernanke and other Fed economists describe it as the natural end of an "asset bubble," an irrational run-up in values. Whether it's labeled as optimism or greed, the appetite for growth got out of hand, and the financial models that underpinned some investment strategies broke down. Some say the remedy is to increase controls on finance and enable more scrutiny of private funds. One school of economists argues that the solution is to create models that steer investors away from bad risks by relying less on "rational" economic principles and more on observed human behavior (*Science*, 12 December, p. 1624). The debates are just warming up and will occupy analysts of the 2008 crash for years to come. **–ELIOT MARSHALL**

Proton's Mass 'Predicted'

STARTING FROM A THEORETICAL DESCRIPTION OF ITS INNARDS, physicists precisely calculated the mass of the proton and other particles made of quarks and gluons. The numbers aren't new; experimenters have been able to weigh the proton for nearly a century. But the new results show that physicists can at last make accurate calculations of the ultracomplex strong force that binds quarks.

In simplest terms, the proton comprises three quarks with gluons zipping between them to convey the strong force. Thanks to the uncertainties of quantum mechanics, however, myriad gluons and quark-antiquark pairs flit into and out of existence within a proton in a frenzy that's nearly impossible to analyze but that produces 95% of the particle's mass.

To simplify matters, theorists from France, Germany, and Hungary took an approach known as "lattice quantum chromodynamics." They modeled continuous space and time as a four-dimensional array of points—the lattice—and confined the quarks to the points and the gluons to the links between them. Using supercomputers, they reckoned the masses of



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the proton and other particles to a precision of about 2%—a tenth of the uncertainties a decade ago—as they reported in November.

In 2003, others reported equally precise calculations of more-esoteric quantities. But by calculating the familiar proton mass, the new work signals more broadly that physicists finally have a handle on the strong force.

10 Sequencing Bonanza

NEW GENOME-SEQUENCING TECHNOLOGIES that are much faster and cheaper than the approach used to decipher the first human genome are driving a boom in sequencing.

This year, using "sequencing by synthesis" technology from 454 Sequencing, which "grows" fluorescently labeled DNA on microscopic beads, researchers produced the mitochondrial genomes of extinct cave bears and of a Neandertal, and 70% of the genome of a woolly mammoth.

A preliminary draft of the full Neandertal genome is in the works. Another new technology, developed by Solexa (now part of Illumina), made its debut in the scientific literature with the descriptions of the first genomes of an Asian, an African, and a cancer patient, shedding new light on early human migrations and candidate genes that may underlie malignancies. Illumina's technology sequences DNA in massively parallel reactions on glass plates. A proof-of-concept paper by Pacific Biosciences, a company that sequences single DNA molecules, provided an exciting glimpse of even faster sequencing. Now the goal is to make it more accurate.

Costs continue to drop; at least one company boasts that genomes for $5000 are in reach. **–THE NEWS STAFF**

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AREAS TO WATCH

Plant genomics. Maize got the U.S. government behind deciphering plant DNA. In 2009, expect to see the analysis of its genome published, along with a bumper harvest of DNA sequences from other plants: crops such as soybean and foxtail millet; biofuels plants; monkey flower, much studied by ecologists; and a primitive plant called a lycopod. Several fruits are in the works, and other projects are gaining momentum. And to understand genetic variation, hundreds of strains of the model plant *Arabidopsis* are being sequenced.

Ocean fizz. Acidification of the oceans driven by rising atmospheric carbon dioxide continues apace. The falling pH is bad news for sea creatures, from coral reefs to microscopic plankton. But the looming threat has yet to gain a poster child the likes of global warming's polar bear. Look for a rising tide of studies confirming the pervasive detrimental effects of ocean acidification, although whether more science will grab the public's attention is problematic.

Neuroscience in court. Scientists and legal scholars cringed this year when an Indian court convicted a woman of murdering her fiancé, citing electroencephalograms that purportedly revealed neural activity indicating "experiential knowledge" of the crime. Although images of anatomical abnormalities in the brain have previously been introduced as mitigating evidence during sentencing, the use of methods that measure brain activity is far more controversial. Even so, at least two companies now offer lie-detection services based on functional magnetic resonance imaging. Ready or not, neuroscience appears poised to have its day in court.

Road to Copenhagen. A 12-day international climate summit in November 2009 marks the deadline for countries to set a successor for the Kyoto treaty, which expires in 2012. Can the United States, China, and India agree to binding targets tough enough to mitigate global warming? Will the agreement include funding for developing nations to adopt Western energy technologies and adapt to a warming world? President-elect Barack Obama has pledged that the United States will take a leading role in the talks and will push for a mandatory system. But with the world economy reeling and oil prices low, he'll face a tough crowd in the U.S. Senate, where lawmakers from coal and car states will want to block any deal that doesn't provide maximum leeway.

Darkness visible. Are particles of exotic dark matter annihilating each other in the heavens to produce high-energy cosmic rays? This year, the orbiting PAMELA particle detector and the ATIC balloon experiment reported possible signs of such annihilations. Next year, PAMELA should test the consistency of its result and ATIC's, and NASA's Fermi Gamma-ray Space Telescope, launched this June, will look for photons from dark-matter annihilations. Still, don't expect the stuff to be lured into the light by next December.

Defining species. In the 200th anniversary of Darwin's birth and the 150th of his *On the Origin of Species*, expect more clues about genes that split species into two. In 2008, researchers discovered several sources of genetic incompatibilities that prevent successful reproduction in animals as varied as nematodes and mice. Thanks to advances in genetics, gene sequencing, and protein surveying, they expect to find more and more of such "speciation genes" in coming months.

Tevatron's triumph. Researchers in Switzerland will be scrambling to get the gargantuan Large Hadron Collider up and smashing particles. But the real drama should unfold at the Fermi National Accelerator Laboratory in Batavia, Illinois, where next year the Tevatron Collider should have produced just enough data to reveal signs of the Higgs boson—if its mass is as low as indirect evidence suggests. Don't be surprised to hear shouts of "Eureka!" if not next year then in 2010, when all of next year's data are analyzed.

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