

The Runners-Up >>

2 REPROGRAMMING CELLS. The riddle of Dolly the Sheep has puzzled biologists for more than a decade: What is it about the oocyte that rejuvenates the nucleus of a differentiated cell, prompting the genome to return to the embryonic state and form a new individual? This year, scientists came closer to solving that riddle. In a series of papers, researchers showed that by adding just a handful of genes to skin cells, they could reprogram those cells to look and act like embryonic stem (ES) cells. ES cells are famous for their potential to become any kind of cell in the body. But because researchers derive them from early embryos, they are also infamous for the political and ethical debates that they have sparked.

The new work is both a scientific and a political breakthrough, shedding light on the molecular basis of reprogramming and, perhaps, promising a way out of the political storm that has surrounded the stem cell field.

The work grows out of a breakthrough a decade ago. In 1997, Dolly, the first mammal cloned from an adult cell, demonstrated that unknown factors in the oocyte can turn back the developmental clock in a differentiated cell, allowing the genome to go back to its embryonic state.

Various experiments have shown how readily this talent is evoked. A few years ago, researchers discovered that fusing ES cells with differentiated cells could also reprogram the nucleus, producing ES-like cells but with twice the normal number of chromosomes.

Recently, they also showed that a fertilized mouse egg, or zygote, with its nucleus removed could also reprogram a somatic cell.

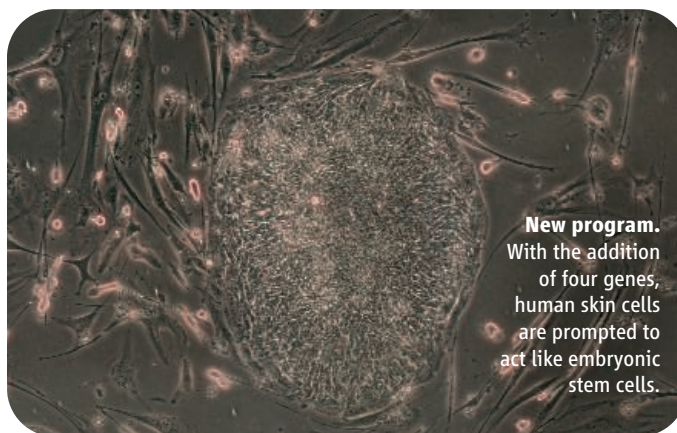
Meanwhile, the identity of the reprogramming factors continued to puzzle and tantalize biologists. In 2006, Japanese researchers announced that they were close to at least part of the answer. By adding just four genes to mouse tail cells, they produced what they call induced pluripotent stem (iPS) cells: cells that looked and acted like ES cells.

This year, in two announcements that electrified the stem cell field, scientists closed the deal. In a series of papers in June, the same Japanese group, along with two American groups, showed that the iPS cells made from mouse skin could, like ES cells, contribute to chimeric embryos and produce all the body's cells, including eggs and sperm. The

work convinced most observers that iPS cells were indeed equivalent to ES cells, at least in mice.

Then in November came a triumph no one had expected this soon: Not one, but two teams repeated the feat in human cells. The Japanese team showed that their mouse recipe could work in human cells, and an American team found that a slightly different recipe would do the job as well.

The advance seems set to transform both the science and the politics of stem cell research. Scientists say the work demonstrates that the riddle of Dolly may be simpler than they had dared to hope: Just four genes can make all the difference. Now they can get down to the business of understanding how to guide the development of these high-potential cells in the laboratory. In December, scientists reported that



New program. With the addition of four genes, human skin cells are prompted to act like embryonic stem cells.

CREDITS (TOP TO BOTTOM): UNIVERSITY OF WISCONSIN, MADISON; TERRY SMITH (CRYSTAL BALLS)

Downloaded from www.sciencemag.org on December 21, 2007



HOW'D WE DO?

Rating the predictions we made last year in "Areas to Watch"

World-weary? Hardly. Four spacecraft returned torrents of data from around the solar system. The Venus Express orbiter probed the vicious atmosphere of Earth's near-twin. On its way to Pluto, New Horizons snapped pictures of Jupiter. The Mars Reconnaissance Orbiter revealed unforeseen hazards for future landers. And Europe's Earth-orbiting COROT discovered its first planet orbiting another star, showing that COROT can detect exoplanets as small as Earth.



Skulls and bones. In 2007, paleoanthropologists unveiled the long-awaited postcranial bones of a 1.7-million-year-old *Homo erectus* from Dmanisi, Georgia, bits of a putative gorilla ancestor, and new early *Homo* specimens from Africa. But the world still waits for publication of the skeleton of the enigmatic *Ardipithecus ramidus*, a 4.4-million-year-old Ethiopian hominid that may shed light on the murky roots of the human family tree.

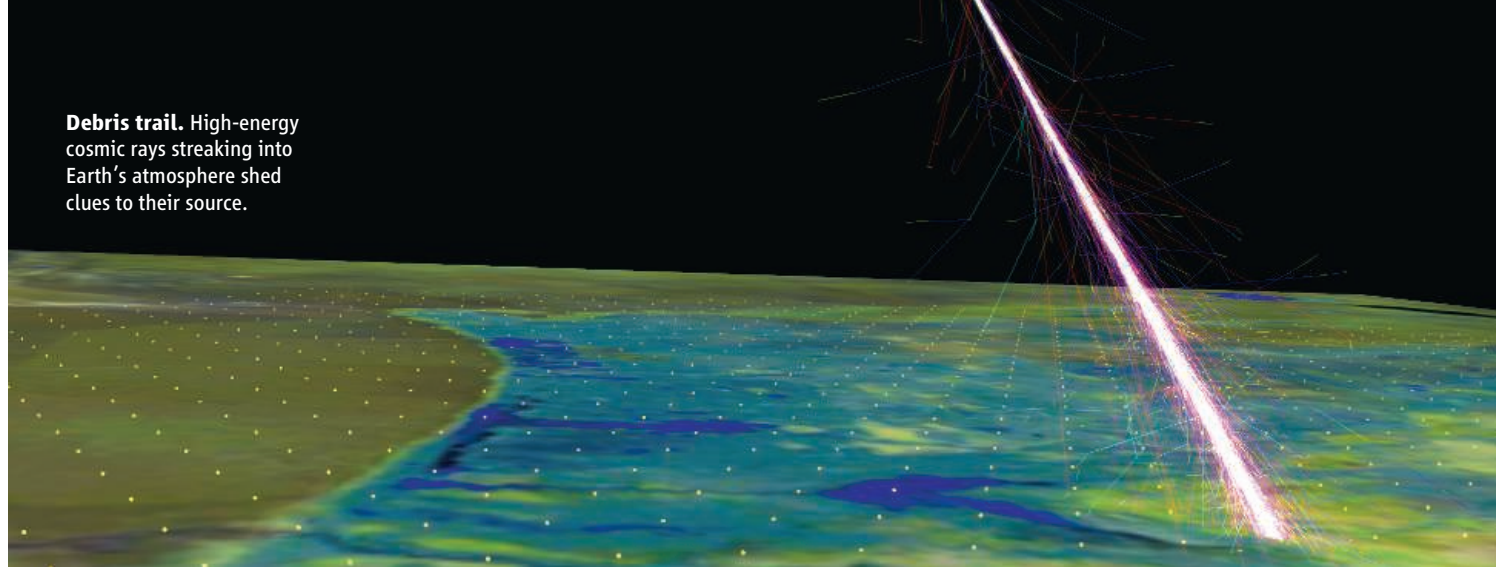


Loads of new primate genes. The published genome sequence of the rhesus macaque did help clarify genetic changes that led to humans, but the analyses of the genomes of the gorilla, orangutan, marmoset, gibbon, galago, tree shrew, and mouse lemur have yet to appear. Eventually, though, these sequence maps will bring a host of evolutionary insights.



A climate of change? High-profile reports, an agenda-setting meeting in Bali, Indonesia, and a

Debris trail. High-energy cosmic rays streaking into Earth's atmosphere shed clues to their source.



CREDIT: M. SUBBARAO, D. SURENDRAN, AND R. LANDSBERG/KICP/ADLER PLANETARIUM AND ASTRONOMY MUSEUM/UNIVERSITY OF CHICAGO

they had already used mouse iPS cells to successfully treat a mouse model of sickle cell anemia. The next big challenge will be finding a way to reprogram human cells without using possible cancer-causing viruses to insert the genes.

Politicians and ethicists on both sides of the debate about embryo research are jubilant. Supporters hope the new technique will enable them to conduct research without political restrictions, and opponents hope it will eventually render embryo research unnecessary. Indeed, several scientists said the new work prompted them to abandon their plans for further research on human cloning.

Officials at the National Institutes of Health said there was no reason work with iPS cells would not be eligible for federal funding, enabling scientists in the United States to sidestep restrictions imposed by the Bush Administration. And President George W. Bush himself greeted the announcement by saying that he welcomed the scientific solution to the ethical problem.

But it's much too early to predict an end to the political controversies about stem cell research. Some researchers say they still need to be able to do research cloning to find out just what proteins the egg uses for its reprogramming magic. And now that science has come a step closer to the long-term goal of stem cell therapy, mouse models won't be adequate for animal studies. Rather, researchers will need to test cell transplantation approaches with primates, a move that will inevitably stir up resistance from animal-rights activists.

3 TRACING COSMIC BULLETS. What's smaller than an atom but crashes into Earth with as much energy as a golf ball hitting a fairway? Since the 1960s, that riddle has tantalized physicists studying the highest energy cosmic rays, particles from space that strike the atmosphere with energies 100 million times higher than particle accelerators have reached. This year, the Pierre Auger Observatory in Argentina supplied key clues to determine where in space the interlopers come from.

Many physicists had assumed the extremely rare rays were protons from distant galaxies. That notion took a hit in the 1990s, when researchers with the Akeno Giant Air Shower Array (AGASA) near Tokyo reported 11 rays with energies above 100 exa-electron volts (EeV)—about 10 times more than expected. The abundance was tantalizing. On their long trips, protons ought to interact with radiation lingering from the big bang in a way that saps their energy and leaves few with more than 60 EeV. So the excess suggested that the rays might be born in our galactic neighborhood, perhaps in the decays of super-massive particles forged in the big bang. But researchers with the Hi-Res detector in Dugway, Utah, saw only two 100-EeV rays, about as many as expected from far-off sources.

The Auger team set out to beat AGASA and Hi-Res at their own games. When a cosmic ray strikes the atmosphere, it sets off an avalanche of particles. AGASA used 111 detectors spread over 100 square kilometers to sample the particles and infer the ray's energy and direction; Auger comprises nearly 1500 detectors spread over 3000 square kilometers. The avalanche also causes the air to fluoresce. Hi-Res used two batteries of telescopes to see the light; Auger boasts four. In July, the Auger team reported its first big result: no excess of rays above 60 EeV.

Auger still sees a couple of dozen rays above that level, however. Last month, the team reported that they seem to emanate from active galactic nuclei (AGNs): enormous black holes in the middles of some galaxies. The AGNs lie within 250 million light-years of Earth, close enough that cosmic radiation would not have drained the particles' energy en route. Auger researchers haven't yet proved that AGNs are the sources of the rays, and no one knows how an AGN might accelerate a proton to such stupendous energies.

Expect the controversy to continue. Hi-Res researchers say that they see no correlation with AGNs. With Japanese colleagues, they are completing the 740-square-kilometer Telescope Array in Millard County, Utah, which has 512 detectors and three telescope batteries. But with a much bigger array, the Auger team will surely be first to test its own claims.



Nobel Peace Prize placed global climate squarely in the public eye, but policy-makers in the United

States, China, and India haven't passed mandatory limits on greenhouse gas emissions that scientists say are needed. (See "Global Warming, Hotter Than Ever," p. 1846.)

Whole-genome association studies. In work that made up part of this year's Breakthrough of the Year (see p. 1842), more than a dozen large-scale comparative studies of human DNA showed the technique's enormous promise for

tracking down genes linked to disease.



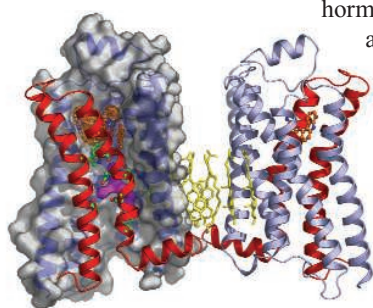
Light crystals.

Physicists hope to explore high-temperature superconductivity and other bizarre properties of solids by emulating them in optical lattices, artificial "crystals" based on corrugated patterns of laser light.

The year's hundreds of papers on optical lattices did not include a super-conductor stand-in, but a grand entrance can't be far off.



4 RECEPTOR VISIONS. Just when some crystallographers were fretting that the task was impossible, researchers nabbed a close-up of adrenaline's target, the β_2 -adrenergic receptor. Its structure has long been on the to-do list, but the feat also got pulses racing because of the molecule's family connections. The receptor is one of roughly 1000 membrane-spanning molecules called G protein-coupled receptors (GPCRs). By detecting light, odors, and tastes, the receptors clue us in to our surroundings. GPCRs also help manage our internal conditions by relaying messages from



Gotcha! Researchers have worked out the architecture of the adrenaline receptor.

hormones, the neurotransmitter serotonin, and myriad other molecules. From antihistamines to beta blockers, the pharmacopoeia brims with medicines aimed at GPCRs—all of which researchers discovered without the benefit of high-resolution structures. A clear picture of, say, a receptor's binding site might spur development of more potent, safer drugs. But scientists had cracked only one "easy" GPCR structure, for the visual pigment rhodopsin.

Getting a look at the β_2 -adrenergic receptor took the leaders of two overlapping crystallographic teams almost 2 decades. The effort paid off this fall with four papers published in the journals *Science*, *Nature*, and *Nature Methods*. The lab ingenuity that other experts call a technical tour de force shows in the way the teams restrained the molecule's flexible third loop. They either replaced it with the stolid enzyme lysozyme or tacked it down with an antibody.

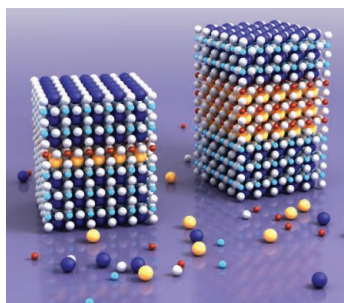
But this snapshot of the receptor is just the beginning. Before researchers can design compounds to jam the molecule, they need to picture it in its different "on" states. And the other GPCRs awaiting analysis mean that for crystallographers, it's two down and 1000 to go.

5 BEYOND SILICON? Sixty years ago, semiconductors were a scientific curiosity. Then researchers tried putting one type of semiconductor up against another, and suddenly we had diodes, transistors, microprocessors, and the whole electronic age. Startling results this year may herald a similar burst of discoveries at the interfaces of a different class of materials: transition metal oxides.

Transition metal oxides first made headlines in 1986 with the Nobel Prize-winning discovery of high-temperature superconductors. Since then, solid-state physicists keep finding unexpected properties in these materials—including colossal magnetoresistance, in which small changes in applied magnetic fields cause huge changes in electrical resistance. But the fun should really start when one oxide rubs shoulders with another.

If different oxide crystals are grown in layers with sharp interfaces, the effect of one crystal structure on another can shift the positions of atoms at the interface, alter the population of electrons, and even change how

Tunable sandwich. In lanthanum aluminate sandwiched between layers of strontium titanate, a thick middle layer (*right*) produces conduction at the lower interface; a thin one does not.



GLOBAL WARMING, HOTTER THAN EVER

Climate change, a perennial runner-up for Breakthrough of the Year, broke from the pack this year—both in the pages of this section and in the public arena.

In 2007, the debate about the reality of global warming ended, at least in the political and public realms in the United States. After 6 years of silence, the United Nations' Intergovernmental Panel on Climate Change (IPCC) drew heavy and wholly positive media coverage for a series of wide-ranging reports. The world is warming, IPCC declared; human activity is behind most of it, and if it keeps up we'll pay a price. But the panel also said that much of the climate pain might be avoided if the world agrees to begin sharing the economic pain. Impressed with that performance, the Nobel committee anointed IPCC, as well as climate campaigner Al Gore, with its Peace Prize.

Other reminders also drove home the gravity of the climate change situation. Scientists now worry that the record melt-back of sea ice during the summer might indicate that feedbacks are ampli-

fying the effects of global warming. A steady stream of media reports this year noted record melting of Greenland ice, record-high temperatures in the United States, and surging Antarctic glaciers. And the energy crisis deepened as oil prices increased to \$100 a barrel, boosting anxieties about the future of fossil fuels.

Politicians weren't idle, although U.S. climate policymakers still have little to show for their concern. Since gaining control of Congress in January, Democrats have transformed the debate from "if to when for mandatory limits on U.S. emissions," says Paul Bledsoe of the National Commission on Energy Policy in Washington, D.C. But hundreds of hearings and reams of legislative proposals have not translated into legislation.

The status of the most prominent Senate proposal, offered by senators Joseph Lieberman (I-CT) and John Warner (R-VA), illustrates the pitfalls that lie ahead for Democrats. Introduced in October after months of negotiations with corporate lobbyists and environmental groups, the bill would cut U.S. emissions by roughly 15% of 2005 levels by 2020 with innovative proposals for emissions credits to spur new technologies. But the debate at a 5 December markup exposed some of the hurdles that the legislation will face in what experts expect will be a multiyear

electrons' charges are distributed around an atom. Teams have grown together two insulating oxides to produce an interface that conducts like a metal or, in another example, a superconductor. Other combinations have shown magnetic properties more familiar in metals, as well as the quantum Hall effect, in which conductance becomes quantized into discrete values in a magnetic field. Researchers are optimistic that they may be able to make combinations of oxides that outperform semiconductor structures.

With almost limitless variation in these complex oxides, properties not yet dreamed of may be found where they meet.

6 ELECTRONS TAKE A NEW SPIN. Chalk one up for the theorists. Theoretical physicists in California recently predicted that semiconductor sandwiches with thin layers of mercury telluride (HgTe) in the middle should exhibit an unusual behavior of their electrons called the quantum spin Hall effect (QSHE). This year, they teamed up with experimental physicists in Germany and found just what they were looking for.

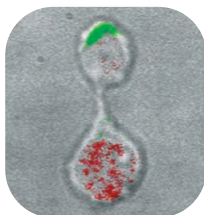
Breakthrough of the Year

7 DIVIDE TO CONQUER. Fresh evidence illuminating how immune cells specialize for immediate or long-term protection had researchers a little feverish this year. When a pathogen attacks, some CD8 T cells become short-lived soldiers, while others morph into memory cells that loiter for decades in case the same interloper tries again. The new work demonstrates how one cell can spawn both cell types.

A T cell remains passive until it meets a dendritic cell carrying specific pathogen molecules. The liaison between the two lasts for hours. As the cells dally, receptors and other molecules congregate at each end of the T cell. A U.S.-based team tested the proposal that if the T cell then divided, its progeny would inherit different molecules that might steer them onto distinct paths. Such asymmetric divisions are a common method for cell diversification during development.

In March, the team reported experiments showing that different specialization-controlling proteins amassed at each pole of a T cell during its dance with a dendritic cell. When the researchers nabbed newly divided T cells, they found that progeny that had been adjacent to the dendritic cell carried receptors typical of soldiers, whereas their counterparts showed the molecular signature of memory cells.

Unequal divisions could also help generate diversity among CD4 T cells, immune regulators that differentiate into three types. Practical applications of the discovery will have to wait until researchers know more about memory-cell specialization, but eventually they might be able to tweak the process to give vaccines more kick.



Separate and unequal. As a T cell divides, the upper and lower cells sort distinct molecules.

8 DOING MORE WITH LESS. Society may finally be embracing energy efficiency and waste reduction, but these attributes have always been prized among synthetic chemists. Extra plaudits and stature go to chemists who carry out

desired reactions in the simplest and most elegant ways. One reason: Fewer synthetic steps almost always saves cash. And although such economizing is a perennial goal, this year an impressive array of synthetic successes showed that chemists are gaining a new level of control over the molecules they make and how they make them.

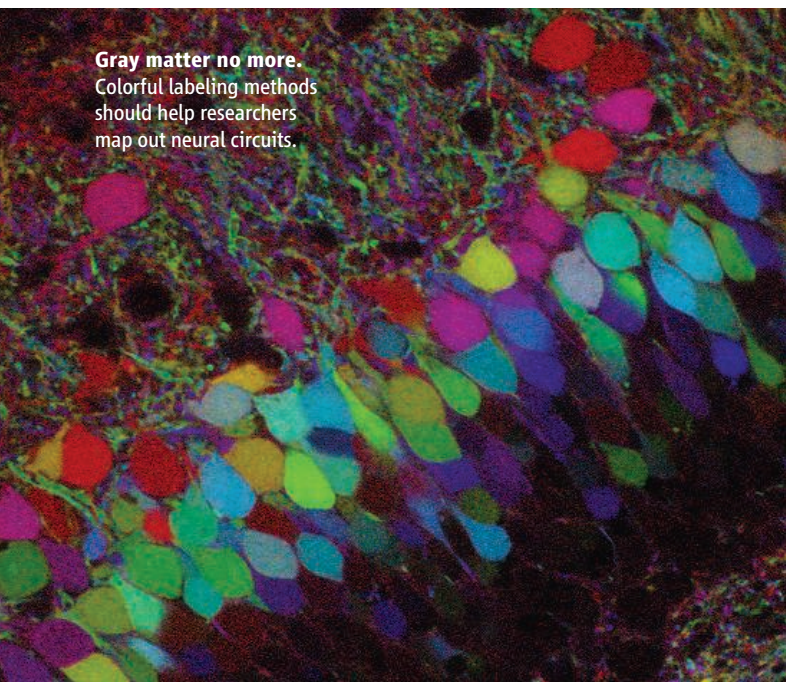
Achieving this control has not been easy. Many desired molecules, such as pharmaceutical and electronic compounds, consist of a backbone of carbon atoms with hydrogen atoms or other more complex functional groups dangling off the sides. When chemists convert a starting compound into one they really want, they typically aim to modify just one of those appendages but not the others. They normally do so either by adorning the starting material with chemical “activators” that prompt the molecule to react only at the tagged site or by slapping “protecting” groups on the sites they want left untouched.

This year, researchers around the globe made major strides in doing away with these accessories. One group in Israel used a ruthenium-based catalyst to convert starting compounds called amines and alcohols directly into another class of widely useful compounds called amides. A related approach enabled researchers in Canada to link pairs of ring-shaped compounds together. Another minimized the use of protecting groups to make large druglike organic compounds. Yet another did much the same in mimicking the way microbes synthesize large ladder-shaped toxins. And those are just a few examples. For chemists, it was an efficient year.

9 BACK TO THE FUTURE. In Greek mythology, the goddess of memory, Mnemosyne, gave birth to the Muses, spirits who inspire imagination. Some modern scientists have seen the kinship as both literal and practical. Remembering the past, they propose, helps us picture—and pre-



Gray matter no more. Colorful labeling methods should help researchers map out neural circuits.



AREAS TO WATCH

A smashing start? Next summer, physicists will start up the Large Hadron Collider (LHC) at the European particle physics lab, CERN, outside Geneva, Switzerland. Researchers hope this highest-energy collider will reveal plenty of new particles and puzzles, but the immediate question is how fast will it come on? The ultracomplex machine runs at a frigid 1.9 kelvin, and if for some reason researchers have to warm part of it up, it will take months to cool it again. Still, CERN has a record of bringing new machines on line smoothly. Call it a major

success if the LHC produces even a little data next year.

Micromanagers. Research on small RNA molecules that control gene expression continues at a rapid clip, and microRNAs are surging to the front of the pack. Roughly 800 papers on the tiny molecules were published in 2007, tying them to a slew of cancers, heart ailments, a healthy immune system, stem cell differentiation, and more. But it's still early days. In 2008, researchers will start using microRNAs to unveil disease mechanisms and will make inroads into solving fundamental puzzles about how they function.

Cell to order. It's hard to separate the hype from the hard science, but

CREDITS (TOP TO BOTTOM): JOHN T. CHANG; LIVET ET AL., NATURE 450, 7166 (2007)

Downloaded from www.sciencemag.org on December 21, 2007



Something to Muse on.
In the brain as in Greek mythology, memory and imagination may be related.

pare for—the future. The notion got a boost this year from several studies hinting at common neural mechanisms for memory and imagination.

In January, researchers in the United Kingdom reported that five people with amnesia caused by damage to the hippocampus, a crucial memory center in the brain, were less adept than healthy volunteers at envisioning hypothetical situations such as a day at the beach or a shopping trip. Whereas healthy subjects described such imagined events vividly, the amnesic patients could muster only a few loosely connected details, suggesting that their hippocampal damage had impaired imagination as well as memory.

In April, a brain-imaging study with healthy young volunteers found that recalling past life experiences and imagining future experiences activated a similar network of brain regions, including the hippocampus. Even studies with rats suggested that the hippocampus may have a role in envisioning the future: One team reported in November that when a rat faces a fork in a familiar maze, neurons in the hippocampus that encode specific locations fire in sequence as if the rat were weighing its options by mentally running down one path and then the other.

On the basis of such findings, some researchers propose that the brain's memory systems may splice together remembered fragments of past events to construct possible futures. The idea is far from proven, but if future experiments bear it out, memory may indeed turn out to be the mother of imagination.

synthetic biologists say humanmade microbes are in reach. By this time next year, one group hopes to put a synthesized genome into DNA-less bacteria; another is incrementally replacing natural DNA with synthetic DNA. The point is to make biofuels—perhaps even microbe-derived gasoline—or pharmaceuticals.

Paleogenomics. Expect a very rough draft of the Neandertal genome by the end of 2008 and more comparisons between the genes of Neandertals and *Homo sapiens* that will continue to flesh out those fossil bones, filling out many features of this extinct human. Thanks to cheaper, faster technologies, there will be more genomes, from more extinct

species, rolling out of the sequencing pipelines.

Multiferroics. Relatives of ceramic oxide superconductors, the compounds called multiferroics form a group in which single materials display multiple electronic, magnetic, and structural behaviors. Physicists recently used electric fields to manipulate magnetic domains in a multiferroic. Now, they are racing to better control this switching and shape the materials into novel computer chip devices. Success could pave the way for chips that combine the logic functions normally handled by semiconductors with the memory functions now carried out by magnetic materials.

10

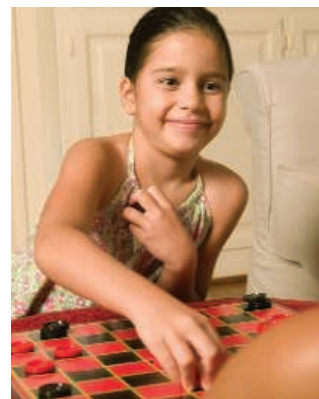
GAME OVER. Computer scientists finally took some of the fun out of the game of checkers. After 18 years of trying, a Canadian team proved that if neither player makes a mistake, a game of checkers will inevitably end in a draw. The proof makes checkers—also known as draughts—the most complicated game ever “solved.” It marks another victory for machines over humans: A mistake-prone person will surely lose to the team's computer program.

Proving that flawless checkers will end in a stalemate was hardly child's play. In the United States, the game is played on an eight-by-eight grid of red and black squares. The 12 red and 12 black checkers slide diagonally from black square to black square, and one player can capture the other's checker by hopping over it into an empty space just beyond. All told, there are about 500 billion billion arrangements of the pieces, enough to overwhelm even today's best computers.

So the researchers compiled a database of the mere 39,000 billion arrangements of 10 or fewer pieces and determined which ones led to a win for red, a win for black, or a draw. They then considered a specific opening move and used a search algorithm to show that players with perfect foresight would invariably guide the game to a configuration that yields a draw.

Reported in July, the advance exemplifies an emerging trend in artificial intelligence. Human thinking relies on a modest amount of memory and a larger capacity to process information. In contrast, the checkers program employs relatively less processing and a whole lot of memory—the 39,000-billion-configuration database. The algorithms the team developed could find broad applications, others say, such as deciphering the information encoded in DNA.

—THE NEWS STAFF



Megamicrobes. Featured in both the U.S. National Institutes of Health and the European Union plans for 2008, the human microbiome will go under the microscope this year in many labs around the world. Expect the genomes of 200 of the bacteria that call humans home to be sequenced, as well as the first steps toward extensive surveys of gut, skin, mouth, and reproductive-tract microbial communities. Meanwhile, researchers are mapping the distribution of microbes in other environments, including icebergs and hot ash.

New light on neural circuits. Exciting new methods are poised to start revealing how circuits of

neurons process information and mediate behavior. Recently, neuroscientists mapped neural connections in mice by genetically tagging neurons with nearly 100 fluorescent hues. Others have been using lasers to control the electrical activity of individual neurons in the brains of rodents, thanks to light-sensitive ion channels introduced by genetic engineering. Meanwhile, a magnetic resonance method called diffusion tensor imaging is providing new detail about connections between regions of the human brain. These techniques should yield important insights into how neural circuits work—and how they break down in brain disorders.