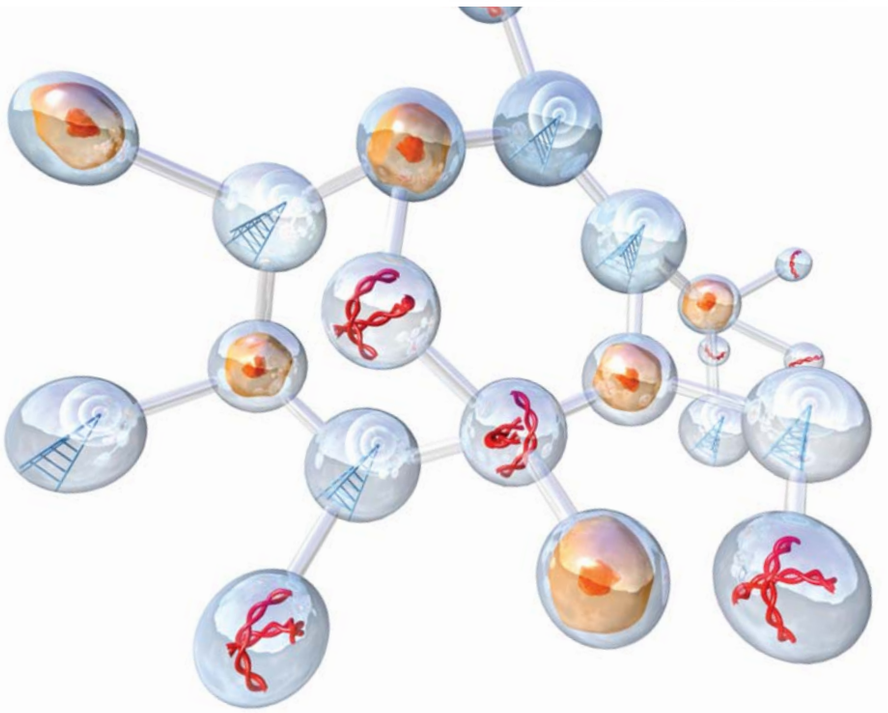

TechnologyReview

10 Emerging Technologies

EACH YEAR, *Technology Review* identifies 10 technologies that are worth keeping an eye on. This year's list spans a broad range of disciplines, from life sciences to nanotechnology to the Internet, but the technologies have one thing in common: they will soon have a significant impact on business, medicine, or culture. *Nanomedicine* and *nanobiomechanics* both illustrate nanotechnology's increasing contribution to the understanding and treatment of diseases. In biology, *epigenetics* is part of an exploding effort to understand the ways that chemical compounds can influence DNA, while *comparative interactomics* is a compelling example of how researchers are beginning to visualize the body's remarkable complexity. *Diffusion tensor imaging* is the most recent in a series of astonishing breakthroughs in imaging the brain. Meanwhile, *cognitive radio*, *pervasive wireless*, and *universal authentication* reflect the continuing struggle to keep the digital world accessible and secure. There is also controversy on the list: *nuclear reprogramming* describes the contentious hunt for an "ethical stem cell." Finally, some of the technologies, such as *stretchable silicon*, are just cool.

BRYAN CHRISTIE DESIGN

DRUG DISCOVERY

Comparative Interactomics

By creating maps of the body's complex molecular interactions, Trey Ideker is providing new ways to find drugs.

BIOMEDICAL RESEARCH THESE DAYS seems to be all about the "omes": genomes, proteomes, metabolomes. Beyond all these lies the mother of all omes—or maybe just the ome du jour: the interactome. Every cell hosts a vast array of interactions among genes, RNA, metabolites, and proteins. The impossibly complex map of all these interactions is, in the language of systems biology, the interactome.

Trey Ideker, a molecular biotechnologist by way of electrical engineering, has recently begun comparing what he calls the "circuitry" of the interactomes of different species. "It's really an incremental step in terms of the concepts, but it's a major leap forward in that we can gather and analyze completely new types of information to characterize biological systems," says Ideker, who runs the Laboratory for Integrative Network Biology at the University of California, San Diego. "I think it's going to be cool to map out the circuitry of all these cells."

Beyond the cool factor, Ideker and other leaders in the nascent field of interactomics hope that their work may help uncover new drugs, improve existing drugs by providing a better understanding of how they work, and even lead to computerized models of toxicity that could replace studies now conducted on animals. "Disease and drugs are about pathways," Ideker says.

Ideker made a big splash in the field in 2001 while still a graduate student with Leroy Hood at the Institute for Systems Biology in Seattle. In a paper for *Science*, Ideker, Hood, and coworkers described in startling detail how yeast cells use sugar. They presented a wiring-like diagram illustrating everything from the suite of genes involved, to the protein-protein interactions, to how perturbing the system altered different biochemical pathways. "His contribution was really special," says geneticist Marc Vidal of the Dana-Farber Cancer Institute in Boston, who introduced the concept that interactomes can be conserved between species. "He came up with one of the first good visualization tools."

Last November, Ideker's team turned heads by reporting in *Nature* that it had aggregated in one database all the available protein-protein interactomes of yeast, the fruit fly, the nematode worm, and the malaria-causing parasite *Plasmodium falciparum*. Though there's nothing particularly novel about comparing proteins across species, Ideker's lab is one of the few that has begun hunting for similarities and differences between the protein-protein *interactions* of widely different creatures. It turns out that the interactomes of yeast, fly, and worm include interactions called protein complexes that have some similarities between them. This conservation across species indicates that the interactions may serve some vital purpose. But *Plasmodium*, oddly, shares no protein complexes with worm or fly and only three with yeast. "For a while, we struggled to figure out what was going wrong with our analysis," says Ideker. After rechecking their data, Ideker and his team concluded that *Plasmodium* probably just had a somewhat different interactome.

For pharmaceutical makers, the discovery of unique biological pathways, such as those found in the malaria parasite, suggests new drug targets. Theoretically, a drug that can interrupt such a pathway will have limited, if any, impact on circuits in human cells, reducing the likelihood of toxic side effects. Theoretically. In reality, pharmaceutical companies aren't exactly tripping over themselves to make new drugs for malaria—a disease that strikes mainly in poor countries. But the general idea has great promise, says Ideker, who now plans to compare the interactomes of different HIV strains to see whether any chinks in that virus's armor come to light.

George Church, who directs the Lipper Center for Computational Genetics at Harvard Medical School, has high respect for Ideker but adds another caveat: existing interactome data comes from fast, automated tests that simply aren't that accurate yet. "The way I divide the omes is by asking, Are these data permanent, or are they going to be replaced by something better?" says Church. Data on the DNA sequences of genomes, Church says, is permanent. But interactome data? "There's a 50-50 chance that this will be true or accepted in two years," says Church. "That's not Trey's fault. He's one of the people who is trying to make it more rigorous."

Ideker agrees that "there's a lot of noise in the system," but he says the continuing flood of interactome data is making what happens inside different cells ever more clear. "Within five years, we hope to take these interaction data and build models of cellular circuitry to predict actions of drugs before they're in human trials. That's the billion-dollar application." **JON COHEN**

OTHER PLAYERS

Comparative Interactomics

Researcher	Project
James Collins *Boston University*	Synthetic gene networks
Bernhard Palsson *University of California, San Diego*	Metabolic networks
Marc Vidal *Dana-Farber Cancer Institute, Boston, MA*	Comparison of interactomes among species

GREGG SEGAL

Trey Ideker

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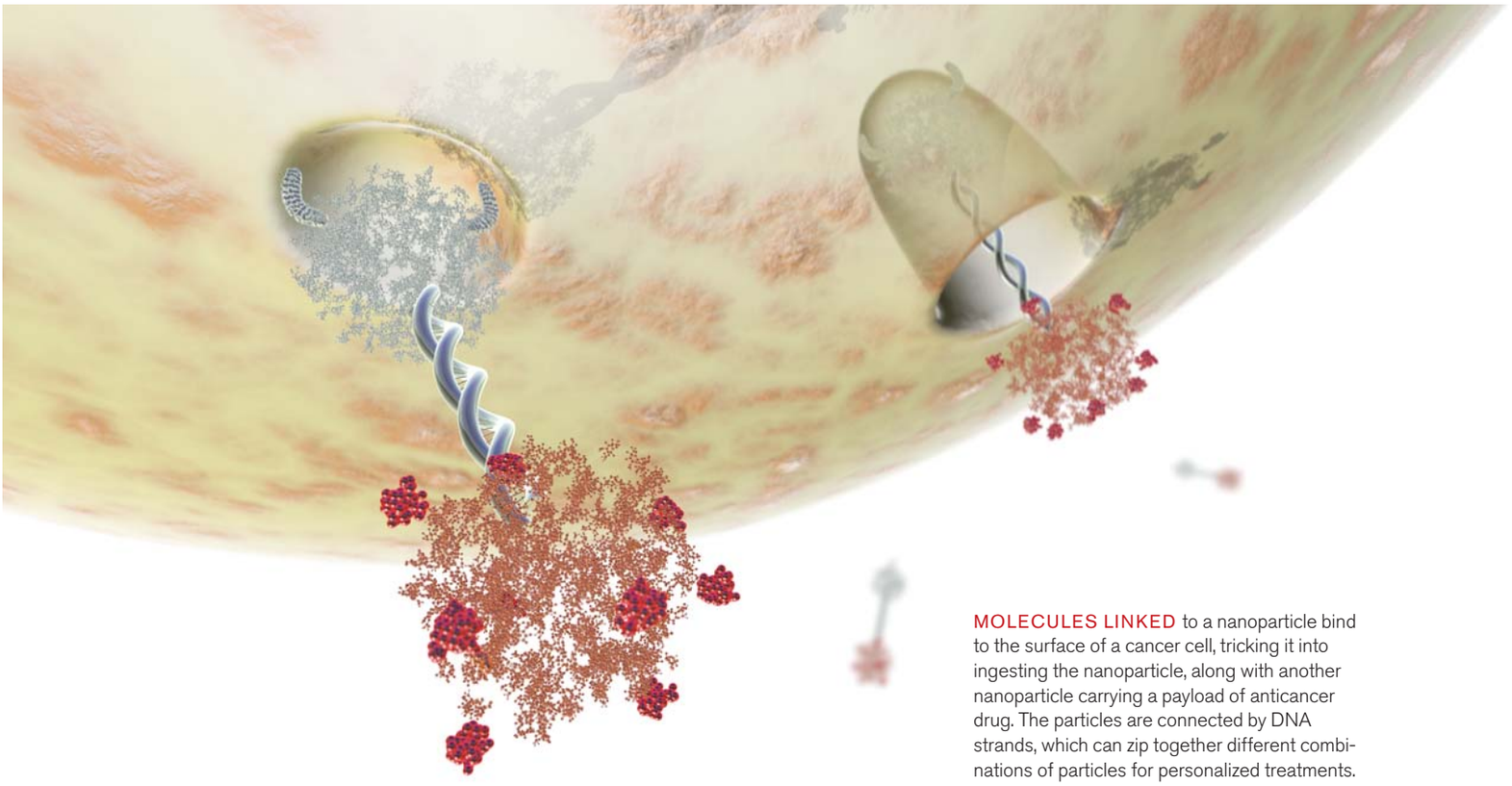


MOLECULES LINKED to a nanoparticle bind to the surface of a cancer cell, tricking it into ingesting the nanoparticle, along with another nanoparticle carrying a payload of anticancer drug. The particles are connected by DNA strands, which can zip together different combinations of particles for personalized treatments.

THERAPEUTICS

Nanomedicine

James Baker designs nanoparticles to guide drugs directly into cancer cells, which could lead to far safer treatments.

THE TREATMENT BEGINS WITH AN injection of an unremarkable-looking clear fluid. Invisible inside, however, are particles precisely engineered to slip past barriers such as blood vessel walls, latch onto cancer cells, and trick the cells into engulfing them as if they were food. These Trojan particles flag the cells with a fluorescent dye and simultaneously destroy them with a drug.

Developed by University of Michigan physician and researcher James Baker, these multipurpose nanoparticles—which should be ready for patient trials later this year—are at the leading edge of a nanotechnology-based medical revolution. Such methodically designed nanoparticles have the potential to transfigure the diagnosis and treatment of not only cancer but virtually any disease. Already, researchers are working on inexpensive tests that could distinguish a case of the sniffles from the early symptoms of a bioterror attack, as well as treatments for disorders ranging from rheumatoid arthritis to cystic fibrosis. The molecular finesse of nanotechnology, Baker says, makes it possible to "find things like tumor cells or inflammatory cells and get into them and change them directly."

Cancer therapies may be the first nanomedicines to take off. Treatments that deliver drugs to the neighborhood of cancer cells in nanoscale capsules have recently become available for breast and ovarian cancers and for Kaposi's sarcoma. The next generation of treatments, not yet approved, improves the drugs by delivering them inside individual cancer cells. This generation also boasts multifunction particles such as Baker's; in experiments reported last June, Baker's particles slowed and even killed human tumors grown in mice far more efficiently than conventional chemotherapy.

"The field is dramatically expanding," says Piotr Grodzinski, program director of the National Cancer Institute's Alliance for Nanotechnology in Cancer. "It's not an evolutionary technology; it's a disruptive technology that can address the problems which former approaches couldn't."

The heart of Baker's approach is a highly branched molecule called a dendrimer. Each dendrimer has more than a hundred molecular "hooks" on its surface. To five or six of these, Baker connects folic-acid molecules. Because folic acid is a vitamin, most cells in the body have proteins on their surfaces that bind to it. But many cancer cells have significantly more of these receptors than normal cells. Baker links an anticancer drug to other branches of the dendrimer; when cancer cells ingest the folic acid, they consume the deadly drugs as well.

The approach is versatile. Baker has laden the dendrimers with molecules that glow under MRI scans, which can reveal the location of a cancer. And he can hook different targeting molecules and drugs to the dendrimers to treat a variety of tumors. He plans to begin human trials later this year, potentially on ovarian or head and neck cancer.

BRYAN CHRISTIE DESIGN

Mauro Ferrari, a professor of internal medicine, engineering, and materials science at Ohio State University, is hopeful about what Baker's work could mean for cancer patients. "What Jim is doing is very important," he says. "It is part of the second wave of approaches to targeted therapeutics, which I think will have tremendous acceleration of progress in the years to come."

To hasten development of nano-based therapies, the NCI alliance has committed $144.3 million to nanotech-related projects, funding seven centers of excellence for cancer nanotechnology and 12 projects to develop diagnostics and treatments, including Baker's.

Baker has already begun work on a modular system in which dendrimers adorned with different drugs, imaging agents, or cancer-targeting molecules could be "zipped together." Ultimately, doctors might be able to create personalized combinations of nanomedicines by simply mixing the contents of vials of dendrimers.

Such a system is at least 10 years away from routine use, but Baker's basic design could be approved for use in patients in as little as five years. That kind of rapid progress is a huge part of what excites doctors and researchers about nanotechnology's medical potential. "It will completely revolutionize large branches of medicine," says Ferrari. **KEVIN BULLIS**

OTHER PLAYERS

Nanomedicine

Researcher	Project
Raoul Kopelman *University of Michigan*	Nanoparticles for cancer imaging and therapy
Robert Langer *MIT*	Nanoparticle drug delivery for prostate cancer
Charles Lieber *Harvard University*	Nanowire devices for virus detection and cancer screening
Ralph Weissleder *Harvard University*	Magnetic nanoparticles for cancer imaging

GUNTER KLOETZER/LAIF/REDUX

HUMAN GENETICS

Epigenetics

Alexander Olek has developed tests to detect cancer early by measuring its subtle DNA changes.

SEQUENCING THE HUMAN GENOME was far from the last step in explaining human genetics. Researchers still need to figure out which of the 20,000-plus human genes are active in any one cell at a given moment. Chemical modifications can interfere with the machinery of protein manufacture, shutting genes down directly or making chromosomes hard to unwind. Such chemical interactions constitute a second order of genetics known as *epigenetics*.

In the last five years, researchers have developed the first practical tools for identifying epigenetic interactions, and German biochemist Alexander Olek is one of the trailblazers. In 1998, Olek founded Berlin-based Epigenomics to create a rapid and sensitive test for gene methylation, a common DNA modification linked to cancer. The company's forthcoming tests will determine not only whether a patient has a certain cancer but also, in some cases, the severity of the cancer and the likelihood that it will respond to a particular treatment. "Alex has opened up a whole new way of doing diagnostics," says Stephan Beck, a researcher at the Wellcome Trust Sanger Institute in Cambridge, England, and an epigenetics pioneer.

Methylation adds four atoms to cytosine, one of the four DNA "letters," or nucleotides. The body naturally uses methylation to turn genes on and off: the additional atoms block the proteins that transcribe genes. But when something goes awry, methylation can unleash a tumor by silencing a gene that normally keeps cell growth in check. Removing a gene's natural methylation can also render a cell can-

Alexander Olek


Heather Zheng

cerous by activating a gene that is typically "off" in a particular tissue.

The problem is that methylated genes are hard to recognize in their native state. But Olek says Epigenomics has developed a method to detect as little as three picograms of methylated DNA; it will spot as few as three cancer cells in a tissue sample.

To create a practical diagnostic test for a given cancer, Epigenomics compares several thousand genes from cancerous and healthy cells, identifying changes in the methylation of one or more genes that correlate with the disease. Ultimately, the test examines the methylation states of only the relevant genes. The researchers go even further through a sort of epigenetic archeology: by examining the DNA in tissues from past clinical trials, they can identify the epigenetic signals in the patients who responded best or worst to a given treatment.

Philip Avner, an epigenetics pioneer at the Pasteur Institute in Paris, says that Epigenomics' test is a powerful tool for accurately diagnosing and understanding cancers at their earliest stages. "If we can't prevent cancer, at least we can treat it better," says Avner.

Roche Diagnostics expects to bring Epigenomics' first product, a screening test for colon cancer, to market in 2008. The test is several times more likely to spot a tumor than the current test, which measures the amount of blood in a stool sample. And thanks to the sensitivity of its process, Epigenomics can detect the tiny amounts of methylated DNA such tumors shed into the bloodstream, so only a standard blood sample is required. The company is working on diagnostics for three more cancers: non-Hodgkin's lymphoma, breast cancer, and prostate cancer.

Olek believes that epigenetics could also have applications in helping explain how lifestyle affects the aging process. It might reveal, for example, why some individuals have a propensity toward diabetes or heart disease.

Olek's goal is a human-epigenome mapping project that would identify the full range of epigenetic variation possible in the human genome. Such a map, Olek believes, could reveal the missing links between genetics, disease, and the environment. Today, progress on the methylation catalogue is accelerating, thanks to Epigenomics and the Wellcome Trust Sanger Institute, which predict that the methylation status of 10 percent of human genes will be mapped by the end of this year. **PETER FAIRLEY**

OTHER PLAYERS
Epigenetics

Researcher	Project
Stephan Beck *Wellcome Trust Sanger Institute, Cambridge, England*	Epigenetics of the immune system
Joseph Bigley *OncoMethylome Sciences, Durham, NC*	Cancer diagnosis and drug development
Thomas Gingeras *Affymetrix, Santa Clara, CA*	Gene chips for epigenetics

GREGG SEGAL

WIRELESS

Cognitive Radio

To avoid future wireless traffic jams, Heather "Haitao" Zheng is finding ways to exploit unused radio spectrum.

GROWING NUMBERS OF PEOPLE ARE making a habit of toting their laptops into Starbuck's, ordering half-caf skim lattes, and plunking down in chairs to surf the Web wirelessly. That means more people are also getting used to being kicked off the Net as computers competing for bandwidth interfere with one another. It's a local effect—within 30 to 60 meters of a transceiver—but there's just no more space in the part of the radio spectrum designated for Wi-Fi.

Imagine, then, what happens as more devices go wireless—not just laptops, or cell phones and BlackBerrys, but sensor networks that monitor everything from temperature in office buildings to moisture in cornfields, radio frequency ID tags that track merchandise at the local Wal-Mart, devices that monitor nursing-home patients. All these gadgets have to share a finite—and increasingly crowded—amount of radio spectrum.

Heather Zheng, an assistant professor of computer science at the University of California, Santa Barbara, is working on ways to allow wireless devices to more efficiently share the airwaves. The problem, she says, is not a dearth of radio spectrum; it's the way that spectrum is used. The Federal Communications Commission in the United States, and its counterparts around the world, allocate the radio spectrum in swaths of frequency of varying widths. One band covers AM radio, another VHF television, still others cell phones, citizen's-band radio, pagers, and so on; now, just as wireless devices have begun proliferating, there's little left over to dole out. But as anyone who has twirled a radio dial knows, not every channel in every band is always in use. In fact, the FCC has determined that, in some locations or at some times of day, 70 percent of the allocated spectrum may be sitting idle, even though it's officially spoken for.

Zheng thinks the solution lies with cognitive radios, devices that figure out which frequencies are quiet and pick one or more over which to transmit and receive data. Without careful planning, however, certain bands could still end up jammed. Zheng's answer

is to teach cognitive radios to negotiate with other devices in their vicinity. In Zheng's scheme, the FCC-designated owner of the spectrum gets priority, but other devices can divvy up unused spectrum among themselves.

But negotiation between devices uses bandwidth in itself, so Zheng simplified the process. She selected a set of rules based on "game theory"—a type of mathematical modeling often used to find the optimal solutions to economics problems—and designed software that made the devices follow those rules. Instead of each radio's having to tell its neighbor what it's doing, it simply observes its neighbors to see if they are transmitting and makes its own decisions.

Zheng compares the scheme to a driver's reacting to what she sees other drivers doing. "If I'm in a traffic lane that is heavy, maybe it's time for me to shift to another lane that is not so busy," she says. When shifting lanes, however, a driver needs to follow rules that prevent her from bumping into others.

Zheng has demonstrated her approach in computer simulations and is working toward testing it on actual hardware. But putting spectrum-sharing theory into practice will take engineering work, from designing the right antennas to writing the software that will run the cognitive radios, Zheng acknowledges. "This is just a starting phase," she says.

Nonetheless, cognitive radios are already making headway in the real world. Intel has plans to build reconfigurable chips that will use software to analyze their environments and select the best protocols and frequencies for data transmission. The FCC has made special allowances so that new types of wireless networks can test these ideas on unused television channels, and the Institute of Electrical and Electronics Engineers, which sets many of the technical standards that continue to drive the Internet revolution, has begun considering cognitive-radio standards. It may be 10 years before all the issues get sorted out, Zheng says, but as the airwaves become more crowded, all wireless devices will need more efficient ways to share the spectrum. **NEIL SAVAGE**

OTHER PLAYERS
Cognitive Radio

Researcher	Project
Bob Broderson *University of California, Berkeley*	Advanced communication algorithms and low-power devices
John Chapin *Vanu, Cambridge, MA*	Software-defined radios
Michael Honig *Northwestern University*	Pricing algorithm for spectrum sharing
Joseph Mitola III *Mitre, McLean, VA*	Cognitive radios
Adam Wolisz *Technical University of Berlin, Germany*	Protocols for communications networks

STEM CELLS

Nuclear Reprogramming

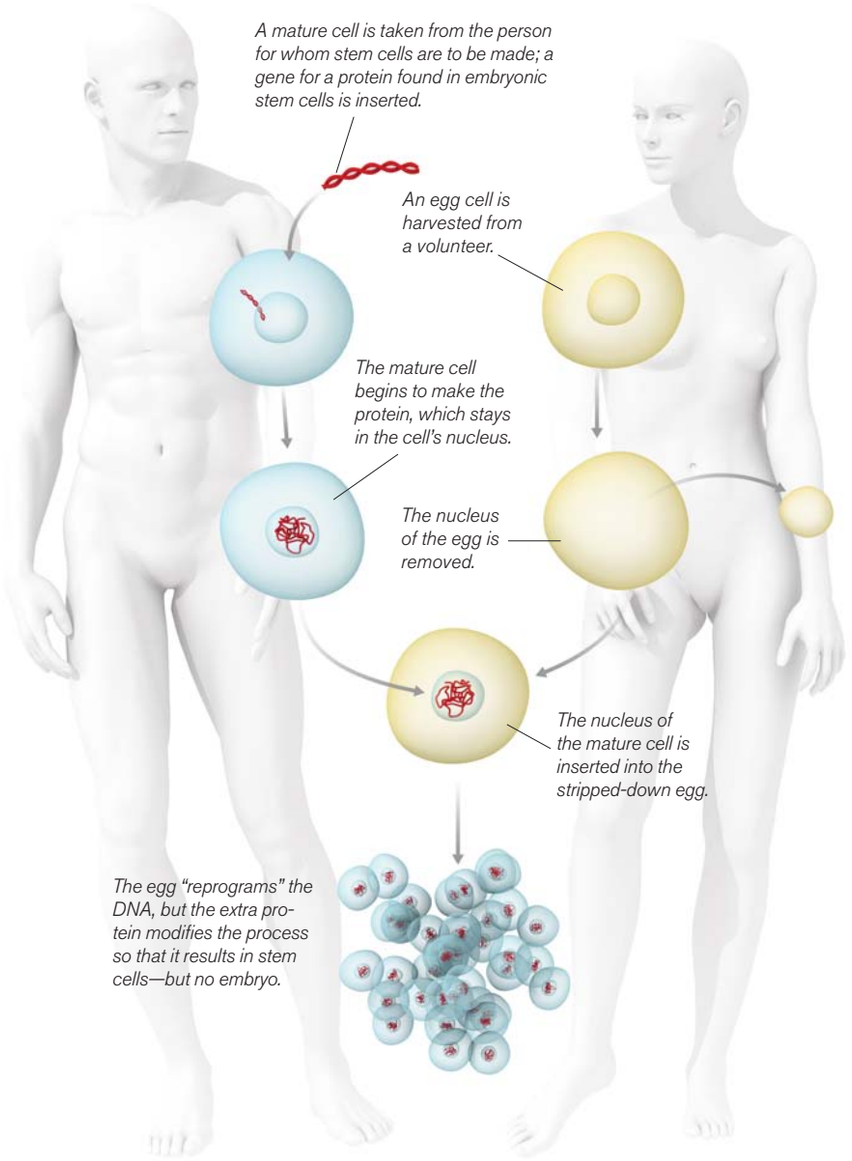
Hoping to resolve the embryonic-stem-cell debate, Markus Grompe envisions a more ethical way to derive the cells.

EMBRYONIC STEM CELLS MAY SPARK more vitriolic argument than any other topic in modern science. Conservative Christians aver that the cells' genesis, which requires destroying embryos, should make any research using them taboo. Many biologists believe that the cells will help unlock the secrets of devastating diseases such as Parkinson's and multiple sclerosis, providing benefits that far outweigh any perceived ethical harm.

Markus Grompe, director of the Oregon Stem Cell Center at Oregon Health and Science University in Portland, hopes to find a way around the debate by producing cloned cells that have all the properties of embryonic stem cells—but don't come from embryos. His plan involves a variation on the cloning procedure that produced Dolly the sheep. In the original procedure, scientists transferred the genetic material from an adult cell into an egg stripped of its own DNA. The egg's proteins reprogrammed the adult DNA, creating an embryo genetically identical to the adult donor. Grompe believes that by forcing the donor cell to produce a protein called nanog, which is found only in embryonic stem cells, before its nucleus is transferred into the egg, he can alter the reprogramming process so that it never results in an embryo but instead yields a cell resembling an embryonic stem cell.

Grompe's work is part of a growing effort to find alternative ways to create cells with the versatility of embryonic stem cells. Many scientists hope to use proteins to directly reprogram, say, skin cells to behave like stem cells. Others think smaller molecules may do the trick; Scripps Research Institute chemist Peter Schultz has found a chemical that turns mouse muscle cells into cells able to form fat and bone cells. And Harvard University biologist Kevin Eggan believes it may be possible to create stem cells whose DNA matches a specific patient's by using existing stem cells stripped of their DNA to reprogram adult cells.

Meanwhile, researchers have tested methods for extracting stem cells without destroying viable embryos. Last fall, MIT biologist Rudolf Jaenisch and graduate student Alexander Meissner showed that by turning off a gene called *CDX2* in the nucleus of an adult cell



BRYAN CHRISTIE DESIGN

before transferring it into a nucleus-free egg cell, they could create a biological entity unable to develop into an embryo—but from which they could still derive normal embryonic stem cells.

Also last fall, researchers at Advanced Cell Technology in Worcester, MA, grew embryonic stem cells using a technique that resembles something called preimplantation genetic diagnosis (PGD). PGD is used to detect genetic abnormalities in embryos created through in vitro fertilization; doctors remove a single cell from an eight-cell embryo for testing. Lanza's team separated single cells from eight-cell mouse embryos, but instead of testing them, they put each in a separate petri dish, along with embryonic stem cells. Unidentified factors caused the single cells to divide and develop some of the characteristics of stem cells. When the remaining seven-cell embryos were implanted into female mice, they developed into normal mice.

Such methods, however, are unlikely to resolve the ethical debate because, in the eyes of some, they still endanger embryos. Grompe's approach holds out the promise of unraveling the moral dilemma. If it works, no embryo will have been produced—so no potential life will be harmed. As a result, some conservative ethicists have endorsed Grompe's proposal.

Whether it is actually a feasible way to harvest embryonic stem cells remains uncertain. Some are skeptical. "There's really no evidence it would work," says Jaenisch. "I doubt it would." But the experiments Grompe proposes, Jaenisch says, would still be scientifically valuable in helping explain how to reprogram cells to create stem cells. Harvard Stem Cell Institute scientist George Daley agrees. In fact, Daley's lab is also studying nanog's ability to reprogram adult cells.

Still, many biologists and bioethicists have mixed feelings about efforts to reprogram adult cells to become pluripotent. While they agree the research is important, they worry that framing it as a search for a stem cell compromise may slow funding—private and public—for embryonic-stem-cell research, hampering efforts to decipher or even cure diseases that affect thousands of desperate people. Such delays, they argue, are a greater moral wrong than the loss of cells that hold only the potential for life. Many ethicists—and the majority of Americans—seem to agree. "We've already decided as a society that it's perfectly okay to create and destroy embryos to help infertile couples to have babies. It seems incredible to me that we could say that that's a legitimate thing to do, but we can't do the same thing to help fight diseases that kill children," says David Magnus, director of the Stanford Center for Biomedical Ethics. **ERIKA JONIETZ**

OTHER PLAYERS

Nuclear Reprogramming

Researcher	Project
George Daley *Harvard Medical School*	Studying nanog's ability to reprogram nuclei
Kevin Eggan *Harvard University*	Reprogramming adult cells using stem cells
Rudolf Jaenisch *MIT*	Creating tailored stem cells using altered nuclear transfer (*CDX2*)